C O N T E N T S

Journal, Indian Academy of Clinical Medicine • Vol. 11, Number 2, April – June, 2010

Contains pages from 81 to 160 inclusive of all advertisements

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JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

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for the

Indian Association of Clinical Medicine

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Tel.: (011) 2642 9099, 2352 5740 E-mail: iacmjournal@gmail.com

Typesetting by: Initials, Tel.: 2354 7929 E-mail: sanjeev.initials@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Elsevier's Bibliographic Databases

Indexed in IndMED (http://indmed.nic.in)

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

Indexed Internationally on Elsevier's Bibliographic Databases (a leading indexing service) from January 2005. These databases include EMBASE, Compendex, Geobase and Scopus (Science Direct Navigator).

Printed by Dr. B.B. Rewari, Published by Dr. B.B. Rewari
on behalf of Indian Association of Clinical Medicine
and printed at Tan Prints, A-47, Mangolpuri Industrial Area, Phase II, Delhi,
and published from D II/65, Kaka Nagar, Dr. Zakir Hussain Marg, New Delhi – 110 003. Editor: Dr. B.B. Rewari

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VIEWPOINT

JIACM 2010; 11(2): 92-5

Homo Economicus Masquerading as Homo Altruisticus

*BM Hegde**

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

– Bertrand Russell (1872 – 1969).

"The globe is warming at an alarming speed thanks to man's greed," is the new slogan of these nouveau altruistics like the nouveau riche do-gooders. This cliché has caught the imagination of the world, thanks to our trumpeters, the electronic and the print media. Has mankind become suddenly altruistic to be so much bothered about the common good of others in society? Have their social conscience and consciousness been aroused so much by a mirage like global warming while they do not even think of the millions who are dying due to malnutrition and hunger with illnesses, right under their nose here and now? Nearly one-third of the world population gets less than a meal a day. Does that not worry the media and the altruists? The Pulitzers, the Nobels, and the Bookers bend over backwards to honour these altruists daily. Every one seems to have forgotten history and even philosophy. Instead of worrying about tomorrow which is yet to be born why are we forgetting our present misery? If one ponders over this question the truth will be unearthed.

Unless the imaginary danger is exaggerated, maybe by making a movie or forming an organisation, one cannot draw the attention of the society to attain greatness. Hunger, illness, and deaths among the poorest of the poor do not excite any such reaction from society. History is studded with many such examples. Good people like Edward Teller, Edward Calabrese, and many like them had to suffer because they went against the above tenets of masked altruism. Most of these altruists who are fighting for saving the globe, belong to the common species of homo economicus. They all have a hidden agenda. The west, which had it all good for so long to attain the positions they have attained at the cost of the third world, is now threatened by the growth and industrialisation of the third world. Unless they do act now they might be left behind in this race for power. One cannot overtly start any movement to curb the growth of the third world as it will not look altruistic. So they have to create newer imaginary monsters to push the third world to stop their growth indirectly. Global warming threat is one such. There are many other areas where the rich and the powerful take the poor for a joy ride. For a change, India stood its ground this time round in Copenhagen.

The globe was threatening to cool down too much in the 1950s to even up to the mid- 1970s. At one point in the 1960s, England was so cool that winter got prolonged by a month reducing the crops so much that there was widespread fear of food production going down to dangerous levels in the future. James Lovelock, who at the age of 90, is the champion of saving this world, does not think that carbon is going to send the global temperatures soaring to the skies! "Not a hope in hell. Most of the 'green' stuff is verging on a gigantic scam. Carbon trading, with its huge government subsidies, is just what finance and industry wanted. It's not going to do a damn thing about climate change, but it'll make a lot of money for a lot of people (and the Nobel for a few) and postpone the moment of reckoning. I am not against renewable energy, but to spoil all the decent countryside in the UK with wind farms is driving me mad. It's absolutely unnecessary, and it takes 2,500 square kilometres to produce a Giga watt – that's an awful lot of countryside", he wrote. James could have predicted

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the unusually cool winters of 2009 – 2010! If linear reductionism is true, this winter might be a sign of global cooling!

"The people who will be hit first and hardest by climate change are, by and large, already among the poorest on the planet. For example, the panel concluded with 'medium confidence' that, because of the effects on crop yields, climate change will increase the number of hungry and malnourished people in the 21st century by 80 or 90 million. The consequences of extreme weather differ vastly, according to populations' ability to cope. For example, cyclones in Bangladesh in 1970 and 1991 caused an estimated 3,00,000 and 1,39,000 deaths, respectively. In contrast Hurricane Andrew caused 55 deaths when it struck the United States in 1992", wrote Cathy Read in the *British Medical Journal* recently[1]. Even if the world does not disappear as is being predicted, weather changes do affect human health. Nobody seems to be worried. This is true for any major change in the weather – not just global warming. Even under these circumstances please note that it is the poorest of the poor that suffer most.

We had been brought-up in school with the good feeling about carbon dioxide being our saviour. The carbon dioxide in our expired air is taken by the green leaves to be converted using the water vapour into the base of all energy for food as chlorophyll, in addition to giving us the life-sustaining oxygen. Now that the media is demonising carbon dioxide, the next generation might grow up hating that life-saving stuff. In fact, the most important aspect of global heating is the water vapour which can never be stopped unless we dry up our oceans! All vegetarian animals, except the Kangaroo, introduce so much methane into the atmosphere both in their farts and excreta that it would outnumber the carbon dioxide from all industries. It is estimated that the methane produced by a single cow's fart would be equivalent to the amount of carbon dioxide from a small industrial unit. Methane, the main gas in the cow's fart, is nearly fifty times more dangerous in elevating the global temperature compared to carbon dioxide. Every single milk dairy would be equal to many big factories' output of carbon dioxide[2]. All that we have to do is to convert methane into Gobar gas for energy in every village.

The green brigade, most of the time patronised covertly by the industry in the developed countries, is also against the sulphur dioxide coming from coal-based plants. We could use the same sulphur dioxide to cool this globe. All that we have to do is to find a cheap technology to send those hot sulphur fumes directly to the stratosphere where it will form a nice blanket filtering the hot rays from the sun. Some scientists have already come up with very cheap and simple technology to do just that. This blanket of sulphur dioxide does not matter in most of the third world countries as sunshine is plenty in the tropical climate. Even if we were to believe the doomsday predictions of the green brigade, in the worst scenario, the sea rising would be about a foot and a half which the high tide brings about even now. A small addition could easily be managed. The spectre of the smaller islands disappearing is all about scaring the common man to get more people to support their homo economicus agenda in the guise of homo altruisticus. Many economists in the last century did laboratory experiments to see if humans are basically altruistic or not. The results in the laboratories did show that most of us are altruistic. This research, the Dictator studies, did get the Nobel prize. However, some crazy economists like John List did further studies in real life situations to see if this was true? Their studies *did not* support the conclusion that most of us are born with the altruistic bent of mind. The latter is the truth, but no Nobels for that!

"The World Renowned Scientists Who Stood Up Against Global Warming Hysteria, Political Persecution, and Fraud, and those who are too fearful to do so" are all in a new book, *The Deniers*, by Lawrence Solomon who wrote a series of articles in Canada's *National Post* about eminent "deniers" of Climate Alarmism, and then discovered there were so many such individuals that he had to write a book to document them all. *This is the one book that PROVES the science is NOT settled. The scientists profiled are too eminent and their research too devastating to allow simplistic views of global warming to survive.* Those scientists who dispute the alarmist view on global warming are corrupt crackpots and "deniers", comparable to neo-Nazis who deny the Holocaust, says a prominent politician in the US[3]. There seems to be a new definition of *peace* according to two recent speeches by the latest

Peace Nobel, Barak Obama, which were paraphrased by the famous Australian playwright John Pilger thus: He affirmed that peace was no longer peace, but rather a permanent war that "extends well beyond Afghanistan and Pakistan" to "disorderly regions and diffuse enemies". He called this "global security" and invited people's gratitude. To the people of Afghanistan, which America has invaded and occupied, he said wittily: "We have no interest in occupying your country"[4].

Come to the field of medicine. When kidney transplant was shown to be useful in the early 1960s many altruistic people, mainly relatives, came forward to donate their healthy kidneys. But that was not enough and there were not enough cadaver kidneys to go around either. A brilliant US doctor, Barry Jacobs, came up with a very altruistic scheme. His *International Kidney Exchange Inc.* would get poor people from the East, paying their expenses, and removing one of their kidneys for a price, to be transplanted into American patients in need! It was thought to be a very humane thing to do as it killed two birds with one stone. American patients got their kidneys and the poor man got some money for his family! While many lauded his efforts, soon it was shown that this is a dangerous game. The company closed shop. Recent Indian experience in the larger metropolises to "steal" kidneys comes to mind. Even today this lucrative business goes on behind the scenes. In one country prisoners on death role were being used to do just that – they were going to die in prison anyway. Why not make a quick business in their kidneys? Altruistic indeed! However, all these people from Barry Jacobs to the present ones are all clever homo economicus', wanting to make money out of human misery.

The biggest industry, netting trillions of dollars out of human misery, is the drug and medical devices industry. Despite all that, a recent audit in the USA has clearly shown that the present modern medical hi-tech has become a curse on mankind with the former as the leading cause of death. However, for the common man, the hi-tech modern medicine is made out to be his saviour, thanks to the media blitz and professional brainwashing, using very sophisticated statistical methods, to take the gullible doctors for a ride. Majority of them collude with the industry for personal gains as humankind is hard wired to be homo economicus in the first place. It takes Herculean efforts to keep your head above the water under such circumstances. Long-term (lifelong) treatment strategies are the biggest money spinners. In the late 1950s and early 60s there was a craze for selling drugs to lower one's blood pressure, although we do not have a scientific definition of "normal" pressure for a given individual. This continues with greater alacrity now.

In Germany they created beautiful vans in the 1950s, called *Wellness Vans* with a small clinic inside with a charming nurse. The van would get parked outside shopping malls, theatres and church yards on holidays inviting people to come for a "free" check-up! Lo and behold, many were labelled as hypertensives to take drugs for life. Similar efforts are on in India now to label people as diabetics. Obliging medical "scientists" produce studies to show that lowering blood pressures help. They coined a new term "silent killers" and added another very lucrative business of lowering a ghost called cholesterol, another very big business. German doctor Jerg Blech has written a very good book *Disease Inventors* where he graphically details their tricks of the trade[5]. In England, a great blood pressure researcher, Professor Sir George Pickering, had this to say about blood pressure business: "More people make a living OFF hypertension than dying OF it." Another great researcher, Professor Sir Michael Oliver, wrote about a Trans-Atlantic Consensus Conference which he chaired. While on his flight back home he saw a huge newspaper headline. Consensus conference decides to lower every one's cholesterol with drugs!! He was so distressed that he wrote an article in *the Lancet* after coming home in Scotland entitled *Consensus or Nonsensus Conference*[6]*?*

Cancer is another area where trillions of dollars business has been going on with no sign of cancer being defeated. Many of these exorbitantly expensive drugs have not even gone through the FDA scrutiny. Recent revelations that FDA gets funding from the industry makes the homo economicus activity very clear. I am told that 80% of the budget of even the WHO comes from the industry. Which industry will fund any organisation if the latter breaks their rice bowl? Recent audits and studies by Gary Null and colleagues show the medical establishment as the

leading cause of death and disability! This does not seem to make any impact on our profession. We need to seriously deschool society about their present beliefs vis-à-vis modern medical hi-tech. Any bondage, including scientific bondage, shackles and debilitates the mind and unfits it for every noble enterprise.

Douglas C Wallace, in his elegant studies, using his new microchip MITCHIP, has been able to show that almost all the chemical molecules designed to attack a particular target in the human body (pharmacodynamics), have but damaged the cell itself while the thousands of years of observational research in Asian herbal drugs seems to have shown that those drugs are safe and useful in therapeutics. His study, 'Mitochondria as Chi', appeared in the prestigious journal *Genetics* in the year 2008[7]. In the year 1944 George Orwell described a super state called Oceania, whose language of war inverted lies that "passed into history and became truth. 'Who controls the past', ran the Party slogan, 'controls the future: who controls the present controls the past'." This war slogan seems to be the business slogan of the century. Whatever is good for business (homo economicus) seems to be sold as good for humankind (homo altruisticus). This world is a wonderful wonder where what we say does not mean what we think. In this business, truth becomes the first casualty and is only relative. Philosophers and spiritualists were all wrong one hundred per cent! In the New Year 2010 let us all mourn the sad demise of truth.

It is better to end this article with a quote from George Orwell in *Nineteen Eighty-four*, "It was curious to think that the sky was the same for everybody, in Eurasia or Eastasia as well as here. And the people under the sky were also very much the same, everywhere, all over the world – people ignorant of one another's existence, *held apart by walls of hatred and lies*, and yet almost exactly the same people who were storing-up in their hearts and bellies and muscles the power that would one day overturn the world"[8]. Steven Levitt and Stephen Dubner, in their recent book *Super Freakonomics* have done a great service to mankind in exposing many of the falsehoods masquerading as fashionable truths[2]. Life goes on all the same. I had borrowed liberally from them about global warming and economic studies, including the terms economicus and altruisticus.

"The pessimist complains about the wind;
the optimist expects it to change;
the realist adjusts the sails."

–William Arthur.

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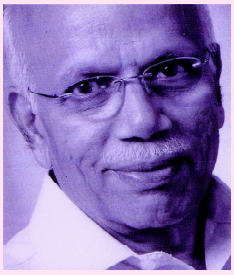
CONGRATULATIONS... PROFESSOR HEGDE !



The Journal, Indian Academy of Clinical Medicine congratulates Professor Belle Monappa Hegde on being conferred the coveted National honour – Padma Bhushan, by the President of India. The *Journal* has had the unique distinction and privilege of publishing his VIEWPOINT regularly in its pages since the last ten years!

Needless to say, his writings scratch our cerebral cortex and inspire us all to think afresh on innumerable issues and challenges facing the world of medical science and technology. We look forward to splashing his profound wisdom on our pages in future issues too!

– The Editors.

TRIBUTE

JIACM 2010; 11(2): 96-8

Dr. G. B. Jain – *Purusha Shreshta* and a Rare Physician

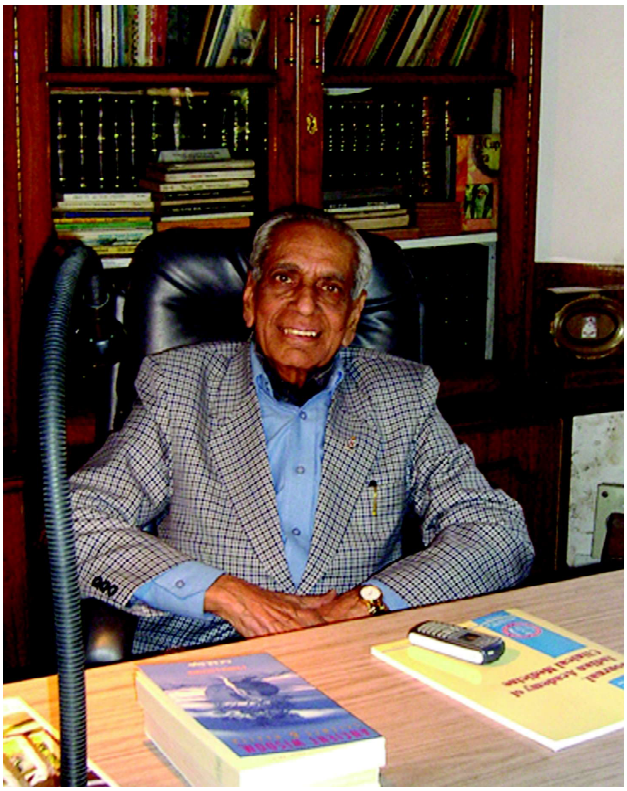
*BM Hegde**

"The good physician treats the disease;
the great physician treats the patient who has the disease."

– Sir William Osler.

It was four in the afternoon on a pleasant Delhi spring evening, decades ago, when I had to deliver a lecture on some aspect of hypertension – I do not remember the exact title now – where I met a diminutive, fatherly, kind hearted, elderly gentleman with a very broad natural smile, chairing my talk. His very presence and smile made me feel so tranquil that I immediately felt at ease although I was to lecture to the "great" Delhi doctors! Our chemistries gelled so well that we became the greatest of friends till the day Dr. Guninder Bahadur Jain met his maker in Heaven, recently at the age of 80 at his own home, Barnala House, in the comfort of his loving children and their spouses. Thanks to his physician son, Dinesh, death was made dignified for him without the usual tubes stuck in all orifices in the *so called* ICU which, most of the time, is the most expensive – but, useless – route to heaven.

I think my lecture went down well with all sections of the audience and the President, in his concluding remarks, used such superlatives about me that I was dumbfounded! I left Delhi and when I reached home I had such a sweet handwritten letter waiting for me, the like of which I never had in my life, which told me what I was. We kept meeting every time I went to Delhi and Late Dr. G. B. Jain sahib came down to my University – Manipal – in December 2000, as Chief Guest for delivering the Convocation address when I was the Vice-Chancellor. He is the other name for true philanthropy. He donated a substantial sum for scholarships in our University on that very occasion. I would like him to have a title, a longish one at that, of a true *infracaninophile!*



Dr. Guninder Bahadur Jain (26-03-1930 – 31-12-2009).

Dr. G. B. Jain was born 26th March, in the spring of 1930, at Barnala (Punjab), then a small town of the erstwhile Patiala State. He was barely 18 months old when he lost his mother. After a brilliant schooling at Barnala, he joined the Government Medical College, Amritsar, Punjab. Throughout his academic career, Dr. Jain received several distinctions and awards – be it games, scouting, NCC, or studies. After graduating from Amritsar, he had the best of medical training in Liverpool and Edinburgh in the mid-1950s under some of the great brains of that time and took his MRCP (Edinburgh) examinations with credit in 1957 at the young age of 27! But just before that, in 1956, he qualified the DTM and H with the coveted Milne Medal from the famed Liverpool School of Tropical Medicine. His teachers included such giants of medicine like Sir Stanley Davidson, Sir John Crofton, Professor K. L. Wig – who went

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

on to become the first Dean of the All India Institute of Medical Sciences. He was elected a Fellow of the Royal College of Physicians of Edinburgh in 1973 and was one of the most respected Fellows even by the local Fellows of the College. He kept in touch with his Scottish and English colleagues to his last days. Luckily, his son Dr. D. G. Jain, a physician-pulmonologist, also became a Fellow of three Royal Colleges, which gave the old man supreme happiness. Dinesh, who is also a distinguished medical journalist, is a true chip of the old block, following on his father's footsteps like his shadow.

As a physician, Dr. G.B. Jain was peerless; as a doctor he was the friend, philosopher, and guide to his ailing patients; as a father he was the best that God ever created; as a friend he was genuinely sincere; as a husband, I was told, he was an icon; as a scientist he was curious; as a teacher he was a role model; and as a citizen he was the most committed to his fellow human beings – altruistic to the core. The unique part of him was as a literary man. In the year 2001 he penned his memoirs *Spring Through Autumn – An Indian Physician's Reminiscences and Reflections* published by the College of Physicians and Surgeons, Delhi. In his address at the book release function, Dr. Jain said that, "based on my personal experiences and happenings, the thread that I have chosen to embroider the tapestry on the rose-brown pages of my book is the thread of friendship with my colleagues, patients, and near and dear ones – a friendship based on mutual trust and tolerance. And this forms the theme of my book..." When he invited me to write a 'Foreword' to his book, I decided to include a poem I had written on him when he came visiting Manipal. It goes thus:

'Having been what all
doctors should be but few are,
And even when most
difficult, Dr. G.B. Jain,
You deserve our
unbiased affection,
and objective praise.'

Thereafter came his English poetry translation of the Srimad Bhagavad Gita – *A Timeless Melody*, which stands out like the *Geetanjali* of Tagore. It is a scholarly and passionate rendering of the Bhagawad Gita from Hindi *Chowpayee* into the English verse form. This bilingual book was published by the Indian publishing giant Rupa in 2005, and has received much acclaim.

He treated me like his own son, and I had the privilege of addressing him as "daddyji". In 2003, he sponsored the publication of a collection of my articles, written over the years. Contributing more than two hundred thousand Indian Rupees from his own pocket, he donated copies of the book to all medical institutions. I don't remember a parallel to that act of kindness to date. This book – *Ancient Wisdom, Science and Health* – also has a beautiful 'Foreword' written by him.

He literally built a few good hospitals in Delhi nurturing them in every respect. He was the much adored Medical Trustee of the Tirath Ram Shah Charitable Hospital – one of the premier hospitals of Delhi. He walked like a medical colossus over the Indian medical stage for more than five decades. People of all hues liked and respected him. He instituted a number of prestigious orations and awards: Dr. G. B. Jain Oration (Indian Association of Clinical Medicine), Smt. Pawan Kumari Jain Oration (Association of Physicians of India), Dr. G. B. Jain Oration (Delhi Medical Association), and many others. He was a Founder-Fellow of the National College of Chest Physicians at the V. P. Chest Institute, University of Delhi; and a Founder-Director of the Asthma, Bronchitis and Cancer Lung Foundation of India. He was fascinated with the history of medicine and had even studied the *Charak Samhita* in his leisure hours. He was deeply impressed with the life and work of the unparalleled physician Sir William Osler and had even published an article on him in one of the earlier issues of *JIACM*. He had no enemies as he hated none but loved all. Medical students, practitioners, teachers, law makers and bureaucrats sought his valuable and unparalleled advice, opinion, and guidance on difficult issues and challenges. He excelled in making balanced and practical decisions quickly. His infective sense of humour was as well known as his clinical acumen and skills, and there was never a sad moment in his presence. Always serene and tranquil, 'daddyji' preferred to keep a low profile all his life.

Dr. Jain was a homely family man enjoying the company of his children, grandchildren, and in-laws. His only sorrow was his wife Pawan's precocious death from lung cancer, which he used to repent to his last day. While Dinesh is a physician like his father, Naresh the next son,

is a worthy and able medical administrator, and his only daughter Sunita, a paediatrician of repute in Jaipur. Her husband Kamal is a well-known physician-diabetologist there. Of his six grandchildren, four are already doctors pursuing post-graduate studies, and two are in the medical pipeline! His family garden is full of flowers that blossomed well to serve the society like the gardener himself. He was a firm believer in vegetarianism from the scientific point of view. He could easily convince anybody that a well-balanced vegetarian diet is much more superior to any non-vegetarian diet. May Dr. G. B. Jain's soul rest in eternal peace. May he guide us – all doctors – as to how an authentic doctor could live well even in these days of medical commercialisation.

The best memorial for the Late Dr. Jain would be for all doctors to live like him. Rudyard Kipling would have written about him thus: "This earth belonged to him – and, More – he was a MAN."

"A few can touch the magic string, and noisy fame is proud to win them:
Alas for those that never sing, but die with all their music in them!"

– Oliver Wendell Holmes.

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LEAD ARTICLE

JIACM 2010; 11(2) : 99-106

Rheumatic Fever: A Reappraisal

Pulin Gupta, Sarit Chatterjee**, AK Agarwal***, Vivek Pal Singh****, Vivek Arya***

Introduction

Rheumatic fever (RF) and rheumatic heart disease (RHD) are non-suppurative complications of group A beta haemolytic streptococcal (GABHS) pharyngitis due to a delayed immune response.

Despite a decrease in the incidence and prevalence of acute rheumatic fever (RF) and rheumatic heart disease (RHD) in industrialised countries, these conditions remain significant causes of cardiac disease in the developing world.

Patients with RHD are probably not getting as much attention as is their due, as today's clinician is overwhelmed by coronary artery disease related advances. Therefore, there is a need to re-focus on the early diagnosis, treatment and prophylaxis of RF and RHD; particularly recurrences.

Epidemiology

The overall mean incidence of first attack of RF is 5 – 51/ 100,000 population across the world[1]. In one report from a developing nation, rheumatic carditis comprised 6.6% of all cardiovascular admissions[2].

The prevalence of RHD has declined in the West, but continues to be an important cause of cardiac morbidity and mortality in India. It varies from 1.0 to 5.4/1,000 school children (mean 2.1). The incidence of rheumatic fever (RF) varies from 0.2 to 0.75/1,000/year (mean 0.54) in school children 5 – 15 years of age. On an average, one-third of patients with a possible first attack of RF develop chronic valvular lesions[3].

Socioeconomic and environmental factors play an indirect, but important role in the magnitude and severity of RF and RHD. Factors such as a shortage of resources for providing quality health-care, inadequate expertise of health-care providers, and a low level of awareness of the disease in the community can all impact the expression of the disease in populations. Crowding adversely affects rheumatic fever incidence.

Cardiac sequelae of rheumatic fever appear relatively earlier in the tropics. A combination of poor socioeconomic conditions, lack of proper medical care infrastructure, delay in treatment and overcrowding are held responsible.

Pathogenesis of rheumatic fever

Initial streptococcal infection, in a genetically predisposed host and in a susceptible environment leads to the activation of T-cell and B-cell lymphocytes. This is due to streptococcal antigens and superantigens, which results in the production of cytokines and antibodies directed against streptococcal carbohydrate and myosin, an up-regulation of VCAM1 and other adhesion molecules heralding cellular infiltration[4]. A break in the endothelial continuity of a heart valve would expose subendothelial structures (vimentin, laminin and valvular interstitial cells) and lead to a "chain reaction" of valvular destruction. Once valve leaflets are inflamed through the valvular surface endothelium and new vascularisation occurs, the newly formed microvasculature allows T-cells to infiltrate and perpetuate the cycle of valvular damage.

Diagnosis of rheumatic fever: An evolution through time

The Jones' criteria

The Jones' criteria (1944) included major manifestations – carditis, joint symptoms, subcutaneous nodules and chorea and minor manifestations comprised of fever, erythema marginatum, abdominal pain, epistaxis and pulmonary findings. Laboratory markers of acute inflammation, such as leukocytosis (WBC), and elevated

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erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) were also included as minor criteria.

A history of RF or pre-existing rheumatic heart disease (RHD) was considered to be a major criterion since RF tends to recur. It was proposed that the presence of two major, or one major and two minor manifestations offered reasonable clinical evidence of rheumatic activity. Since a previous history of definite RF or RHD was considered a major criterion, diagnosis of a recurrence of RF did not require strict application of these guidelines, and minor manifestations were considered sufficient for the diagnosis. Fig. 1 shows the evolution of the diagnostic criteria with time.

Although the inclusion of a preceding streptococcal infection as a criterion helped to improve diagnostic specificity, it impaired sensitivity[6]. Therefore, late manifestations of RF were subsequently exempted from the requirement to demonstrate streptococcal aetiology[7,8]. The 2003 WHO criteria for the diagnosis of RF and RHD are shown in Tables I and II.

Diagnosis of rheumatic carditis

Pancarditis is the most serious manifestation and second most common complication of RF (50%). Although the endocardium, myocardium and pericardium are all affected to varying degrees, rheumatic carditis is almost always associated with a murmur of valvulitis.

Valvulitis/endocarditis

Carditis should be suspected in a patient who develops a new apical systolic murmur of mitral regurgitation (with or without an apical mid-diastolic murmur), and/or the basal early diastolic murmur of aortic regurgitation. On the other hand, in an individual with previous RHD, a definite change in the character of any of these murmurs or the appearance of a new significant murmur indicates the presence of carditis. In a large retrospective study, mitral valve regurgitation alone or in combination with other valvular lesions was the commonest echocardiographic diagnosis present in 59.7% patients. Mixed mitral valve disease was present in 13.7% of patients, 23.7% had mixed aortic and mitral valve disease, 25% had pure mitral stenosis and 15.3% had pure aortic regurgitation[10].

Myocarditis

Myocarditis in the absence of valvulitis is unlikely to be rheumatic. It should always be associated with an apical systolic or basal diastolic murmur. An unexplained worsening of CHF in a suspected case of recurrent RF indicates presence of active carditis, if supported by adequate minor manifestations and evidence of a preceding streptococcal infection.

Pericarditis

Isolated pericarditis is not sufficient to diagnose rheumatic activity. Large effusions and tamponade are rare[11].

Diagnosis of extra cardiac manifestations of RF

Major manifestations

Arthritis

Arthritis is the most frequent and early major manifestation of RF, occurring in up to 75% of patients during the first attack[12]. Joint involvement may vary from arthralgia to disabling arthritis. It typically presents as migratory polyarthritis, most often in the larger joints. Inflamed joints are characteristically warm, red and swollen, and an aspirated sample of synovial fluid may reveal a high average leukocyte count (29,000/mm^3, range 2,000 - 96,0000/mm^3).

Differential diagnosis of arthritis in RF

Polyarthritis unaccompanied by other major manifestations of RF deserves differential diagnosis from septic arthritis which may be ruled out by microbiological studies. Gonococcal arthritis can be excluded by an epidemiological history and characteristic skin lesions (if present), in addition to gonococcal cultures of urethra, cervix, rectum and pharynx.

Arthritis may also occur in infective endocarditis, and it may be difficult to differentiate this disease from RF, particularly when the endocarditis occurs in a patient with known RHD. The epidemiological features, history, physical examination, results of blood cultures, echocardiographic studies, and antistreptococcal antibody assays may all help to differentiate between infective endocarditis and RF. Lyme disease, which presents with arthritis, cardiac involvement, and skin lesions, may at times suggest RF;

Fig. 1: *Changes in Jones' criteria following reviews by American Heart Association (AHA) and World Health Organisation (WHO).*

even the skin lesions of erythema chronicum migrans may resemble erythema marginatum. The diagnosis can be confirmed by serological studies and the response to antimicrobial therapy.

Table I: WHO criteria (2003) for the diagnosis of rheumatic fever and rheumatic heart disease (based on the revised Jones' criteria)[7,9].

Diagnostic category	Criteria
Primary episode of RF.	Two major* or one major and two minor** manifestations plus evidence of a preceding group A streptococcal infection***.
Recurrent attack of RF in a patient without established rheumatic heart disease.	Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection.
Recurrent attack of RF in a patient with established rheumatic heart disease.	Two minor manifestations plus evidence of a preceding group A streptococcal infection.
Rheumatic chorea, insidious onset rheumatic carditis.	Other major manifestations or evidence of group A streptococcal infection not required.
Chronic valve lesions of RHD (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease).	Do not require any other criteria to be diagnosed as having rheumatic heart disease.

Table II: Definition of WHO criteria.

*Major manifestations	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules
**Minor manifestations	Clinical fever polyarthralgia Laboratory elevated acute phase reactants (erythrocyte sedimentation rate or leukocyte count) electrocardiogram: prolonged P-R interval
***Supporting evidence of preceding streptococcal infection within the last 45 days	Elevated or rising antistreptolysin-O or other streptococcal antibody, or Rapid antigen test for group A streptococci, or Recent scarlet fever.

Viraemias, including hepatitis B and C, rubella, serum sickness and finally, collagen vascular diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE) may, at their onset, mimic RF. In juvenile rheumatoid arthritis certain associated findings, such as rash, lymphadenopathy and splenomegaly, may suggest the diagnosis. Henoch-Schönlein purpura, sickle-cell anaemia, acute leukaemia and gout at times mimic the arthritis of RF.

The arthritis of RF heals completely, unlike carditis, and leaves no pathological or functional residua. The one possible exception is Jaccoud's chronic postrheumatic arthritis. This rare condition is not a true synovitis, but rather is a periarticular fibrosis of the metacarpophalangeal joints. It usually occurs in patients with severe RHD, but is not associated with evidence of RF.

Sydenham's chorea

Chorea occurs primarily in children and is rare after the age of 20 years. It occurs primarily in females, and almost never occurs in postpubertal males. The prevalence of chorea in RF patients varied from 5 – 36% in different reports[13].

Sydenham's chorea is characterised by emotional lability, uncoordinated movements, and muscular weakness[14, 15]. Neither sensory deficits nor pyramidal tract involvement are present.

Chorea has a latent period of 1 – 7 months. As a result, polyarthritis and Sydenham's chorea do not occur together; and the onset of chorea often calls attention to subclinical carditis. Streptococcal antibody titres and laboratory measures of inflammation may have resolved by the time choreiform movements appear.

Subcutaneous nodules

The incidence of subcutaneous nodules in acute RF has been reported in up to 20% of cases[16]. The subcutaneous nodules are round, firm, freely moveable, painless lesions varying in size from 0.5 – 2.0 cm. They occur in crops over bony prominences or extensor tendons. Common locations are the elbows, wrists, knees, ankles and Achilles tendons, occiput, and spinous process of the vertebrae. In most cases, they are associated with the presence of severe carditis[17].

Erythema marginatum

Erythema marginatum occurs in up to 15% of RF patients. The lesions of erythema marginatum appear first as a bright pink macule or papule that spreads outward in a circular or serpiginous pattern. They are better identified in fair complexioned individuals and are transient in nature. The lesions are multiple, nonpruritic and painless, occur early in the disease, may persist or recur and are associated with carditis.

Minor manifestations

Arthralgia and fever are termed "minor" manifestations because they lack diagnostic specificity. Fever occurs in almost all rheumatic attacks at the onset, usually ranging from 101° F to 104° F (38.4 – 40.0° C). Arthralgia without objective findings is common in RF. The pain usually involves large joints, may be mild or incapacitating, and may be present for days to weeks, often varying in severity.

New diagnostic techniques for rheumatic carditis

Echocardiography

There are significant advantages in using echocardiography to detect vulvulitis.

The use of 2D echo-Doppler and colour flow Doppler echocardiography may prevent the over diagnosis of a functional murmur as valvular heart disease[18]. Similarly, the over interpretation of physiological or trivial valvular regurgitation may result in a misdiagnosis of iatrogenic valvular disease[19, 20]. Although several researchers have recommended the use of echocardiography as a major criterion[21, 22] at present the role of echocardiography in the diagnosis of rheumatic carditis remains supportive[23].

Endomyocardial biopsy

Current data suggest that endomyocardial biopsy may not provide additional diagnostic information for patients with clinical carditis during a primary episode of RF.

Radionuclide imaging

As rheumatic carditis is predominantly infiltrative, rather than degenerative in nature, radionuclide imaging is not a tool which can be used in usual clinical settings and may be reserved for research purposes.

Diagnosis of streptococcal infection

The gold standard for detecting the causative organism remains a throat swab on blood agar culture. Cultures negative for *S. pyogenes* after an overnight incubation should be incubated for another 24 hours. Only 11% patients have positive throat cultures for group A streptococcus[24].

Laboratory tests that support a diagnosis of RF

The diagnosis of RF requires evidence of prior streptococcal infections. The most commonly performed and commercially available tests are antistreptolysin-O test, and the antideoxyribonuclease B test. The blood titres of antistreptolysin-O, antideoxyribonuclease B reach a peak 3 – 4 weeks after the acute infection, and usually are maintained for 2 – 3 months before declining. The mean periods of time to normalisation for these serological tests were 4 months for ASO and 35 months for ADNase-B. For the determination of streptococcal infection, it is necessary to test 3 antibodies, i.e., ASO, antistreptokinase antibody (ASK) and ADN-B at a time, and if 2 of the 3 titers are positive one can make diagnosis of fairly recent

streptococcal infection. If only one of the 3 titers is positive, previous or non-specific causes should be considered[25]. In studies from India the upper limit of ASO titers was found to be 239 IU and that of ADN B to be 100 u/ml[26].

Medical management of rheumatic fever

General measures

All patients with acute RF should be placed on bed rest and monitored closely for the onset of carditis. In patients with carditis, a rest period of at least four weeks is recommended. Patients with chorea must be placed in a protective environment so they do not injure themselves.

Antimicrobial therapy

Ideally, two throat cultures should be performed before starting antibiotics. However, antibiotic therapy is warranted even if the throat cultures are negative. Penicillin is the drug of choice and can be given orally (as penicillin, 500 mg PO twice daily for 10 days) or as a single dose of 1.2 million units IM benzathine penicillin G. Erythromycin, 250 mg qid for 7 to 10 days, may be used for patients with penicillin allergy. Antibiotic therapy does not alter the course, frequency and severity of cardiac involvement[27].

Suppression of the inflammatory process

Aspirin, 100 mg/kg/day divided into 4 – 5 doses, is the first line of therapy and is generally adequate for achieving a clinical response. In children, the dose may be increased to 125 mg/kg/day, and to 6 – 8 g/day in adults[28]. In a recent meta-analysis of the use of salicylates or steroids, no differences were observed in the long-term outcomes of these treatments for decreasing the frequency of late rheumatic valvular disease[29]. However, since one large study in the meta-analysis favoured the use of steroids, it remains unclear whether one treatment is superior to the other. Patients with pericarditis or heart failure respond favourably to corticosteroids; corticosteroids are also advisable in patients who do not respond to salicylates and who continue to worsen and develop heart failure despite anti-inflammatory therapy[30]. The use of steroids is not indicated solely for the treatment of arthritis in RF. Therapy may be initiated with prednisone (1 – 2 mg/kg/day, to a maximum of 80 mg/day) or intravenous methyl prednisolone given once daily[31]. Since there is no evidence that aspirin or corticosteroid therapy affects the course of carditis or reduces the incidence of subsequent heart disease, the duration of anti-inflammatory therapy is based upon the clinical response to therapy and normalisation of acute phase reactants. Salicylates may be given for 4 – 6 weeks and gradually tapered so as to prevent a rebound.

Management of heart failure

Heart failure in RF generally responds to bed rest and steroids, but in patients with severe symptoms, diuretics, angiotensin converting enzyme inhibitors, and digoxin may be used.

Management of chorea

Chorea has traditionally been considered to be a self-limiting benign disease, requiring no therapy. However, there are recent reports that a protracted course can lead to disability and/or social isolation[32]. The signs and symptoms of chorea generally do not respond well to anti-inflammatory agents. Neuroleptics, benzodiazepines and antiepileptics are indicated, in combination with supportive measures such as rest in a quite room. Haloperidol and valproate have been reported to be effective in the treatment of chorea[33]. There is no convincing evidence that steroids are beneficial for the therapy of the chorea associated with rheumatic fever.

Prevention

Primary prevention

As elimination of the major risk factors for streptococcal infection is difficult to achieve, the mainstay of primary prevention for ARF remains primary prophylaxis, i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics. If commenced within 9 days of sore throat onset, a course of 10 days of penicillin V (500 mg bid PO in adults) or a single IM injection of 1.2 million units of benzathine penicillin G will prevent almost all cases of ARF that would otherwise have developed. In patients sensitive to penicillin, erythromycin 250 mg qid may be given for 7 to 10 days.

Table III: Duration of secondary prophylaxis of RF.

Category of patient	Duration of prophylaxis
Patient without proven carditis	For 5 years after the last attack or 18 years of age (whichever is longer)
Patient with carditis (mild mitral regurgitation or healed carditis)	For 10 years after the last attack, or 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
Valvular surgery	Lifelong

Secondary prevention

The mainstay of controlling ARF and RHD is secondary prevention. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if < 30 kg) delivered every 3 weeks or more frequently (e. g., every 2 weeks) to persons considered to be at particularly high risk. Oral penicillin V (250 mg) can be given twice-daily instead but is somewhat less effective than benzathine penicillin G. Penicillin allergic patients can receive erythromycin (250 mg) twice daily[34]. The recommended duration of secondary prophylaxis is shown in Table III.

Streptococcus vaccine

Several potential group A streptococcus vaccines are in the development process, including a multi-valent, M-serotype specific construct[35], an effective vaccine is unlikely to be available before the year 2015[36].

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ORIGINAL ARTICLE

JIACM 2010; 11(2) : 107-11

Subclinical Cardiac Involvement in Dengue Haemorrhagic Fever

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Abstract

Aim: *To study cardiac involvement in dengue haemorrhagic fever.*

Methodology: *A retrospective study was done including 28 patients of dengue haemorrhagic fever (DHF) admitted in the Nursing Home Unit at PGIMER, Dr R. M. L. Hospital, New Delhi, between July 2008 to October 2008 to detect any cardiac involvement in these patients. All patients included in the study fulfilled the WHO criteria[1] for diagnosis of dengue and were serology (IgM Elisa) positive. All patients investigated with CBC (including PCV and platelet counts), ECG, 2D-ECHO, cardiac enzymes (CPK, CPK-MB, TROPONIN-T, SGOT, LDH), USG abdomen, and X-ray chest.*

Result: *None of the patients had clinical features of overt myocarditis. 4 patients had sinus bradycardia and sinus tachycardia was present in 6 cases. There were no other ECG abnormalities. Out of 28 patients of DHF, 20 patients (71%) had significantly raised cardiac enzymes CPK-MB, LDH and SGOT. 12 patients tested positive for serum Troponin-T. 4 patients (14%) had grade 1 diastolic dysfunction in 2D-Echo, and 1 patient (3.5%) had mild pericardial effusion.*

Conclusion: *A significant number (71%) of patients of dengue developed asymptomatic involvement of heart as evidenced by raised cardiac enzymes (CPK-MB, S. trop.T, LDH and SGOT). Myocardial involvement was subclinical as 2D-Echo was normal in 23 patients (82%). Possible cause of raised cardiac enzymes in these patients is subclinical myocarditis.*

Introduction

Dengue fever is an acute febrile infectious disease, caused by any of the four serotypes (1, 2, 3 or 4) of a virus from the genus flavivirus, called dengue virus. The highest incidence of dengue is seen in Southeast Asia, India, and the American tropics. Dengue is transmitted by mosquitoes of the genus aedes, which are widely distributed in subtropical and tropical areas of the world. Dengue is classified as a major global health threat by the World Health Organisation (WHO). Initial dengue infection may be asymptomatic, may result in a nonspecific febrile illness, or may produce the symptom complex of classic dengue fever (DF)[1].

A small percentage of persons who have previously been infected by one dengue serotype develop bleeding and endothelial leak upon infection with another dengue serotype. This syndrome is termed dengue haemorrhagic fever (DHF). Some patients with dengue haemorrhagic fever develop shock (dengue shock syndrome [DSS]), which may cause death.

Dengue affects people of all ages. In Southeast Asia, where dengue is hyperendemic, dengue haemorrhagic fever usually affects children younger than 15 years[1].

Severe dengue infections may give rise to many complications such as liver failure, disseminated intravascular coagulation, encephalopathy, myocarditis, acute renal failure, and haemolytic uraemic syndrome[2]. Although these complications are generally rare, in recent years they have been reported with increasing frequency. Although shock in DHF/DSS has been attributed largely to decreased intravascular volume due to capillary leakage of plasma into the interstitial space, a few recent studies have reported that it may be due to cardiac involvement[5, 6, 10, 13]. Dengue virus rarely involves the heart in the form of myocarditis. There is limited data available for myocardial involvement in dengue. All the previous studies concentrated on impairment of left ventricular systolic function.

The purpose of this study was to assess whether there is any form of cardiac involvement (clinical or subclinical) in dengue and DHF, because most of our dengue patients had have raised cardiac markers.

Acute reversible myocarditis has been reported in patients with dengue infections. ST segment and T wave changes in the electrocardiogram together with low ejection fractions and global hypokinesia on radionuclide

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ventriculography have been found[6]. In another study, 16.7% of children had left ventricular dysfunction when assessed by two dimensional and colour doppler echocardiography[10]. The left ventricular failure may contribute to hypotension seen in DHF/dengue shock syndrome and may have implications in fluid management as fluid overload may worsen the condition[6, 10].

Material and method

28 patients of dengue/DHF were included in the study. All patients suffering from an acute febrile illness admitted to the nursing home unit of the department of medicine, PGIMER, Dr RML Hospital, New Delhi, who satisfied the WHO criteria[1] for the diagnosis of dengue fever, were selected for the study. These criteria included an acute febrile episode lasting two to seven days, positive tourniquet test, maculopapular rashes, petechiae or ecchymoses, mucosal bleeding, a platelet count of less than 100,000/mm and positive dengue IgM antibodies by ELISA method.

Complete blood count (including PCV, platelet), liver function tests, renal profile, a 12-lead electrocardiogram (ECG), cardiac enzymes (creatine phosphokinase [CPK] and its MB isoenzyme [CPK-MB]), serum Troponin-T, X-ray chest, USG abdomen, two-dimensional echocardiography (2D-Echo) during the acute phase of the febrile illness, and dengue IgM antibodies by ELISA method were the investigations carried out in all patients included in the study. Any patient who showed 2-D echocardiographic abnormalities unlikely to be due to chronic cardiac pathology, such as chronic valvular heart diseases, evidence of cardiomyopathies, ischaemic heart disease and hypertension, were assumed to have dengue virus-related acute myocarditis. Their ECG, CPK, and CPK-MB values, liver function tests, and clinical symptoms and signs related to the cardiovascular system were analysed. Patients had repeat 2-D echocardiographic examination three to four weeks later. The patients who had history of any type of heart disease were excluded from the study.

Results

Out of 28 patients, 18 were male and 10 were female, mean age was 30.14 years (range 17 to 48 years); fever was present in 26 patients (92%); tourniquet test was positive in all patients; rashes were present in 23 patients (82%). Mucosal bleeding was present in 4 patients (2 epistaxis, 1 gum bleeding, 1 melena). None of the patients had clinical features of overt myocarditis, such as significant sinus tachycardia, raised jugular venous pressure, triple rhythm, bilateral pulmonary crepitations and peripheral oedema. None complained of any chest discomfort or dyspnoea of any grade. Thrombocytopenia (platelets < 100,000) was present in all cases. Pleural effusion (rt. side) was seen in the X-ray of chest in 4 patients (14%), ascites was present in 4 patients (14%). Dengue antibodies (IgM-Elisa method) were positive in all patients. Eight cases were classified as Dengue Shock Syndrome with mean systolic pressure of 80 mm of Hg. These patients with shock were given intravenous fluids and dopamine was given to those who were refractory to intravenous fluid therapy. All patients with shock recovered by therapy and no mortality occurred in any patient.

Table I:

Patients	Age	Sex	Fever	Tourniquet test	Rashes	Ecchymoses	Mucosal bleeding
1	18	F	+++	Positive	Present	Absent	Absent
2	26	M	++	Positive	Present	Absent	Absent
3	25	M	+++	Positive	Present	Absent	Absent
4	19	M	++	Positive	Present	Absent	Absent
5	42	M	++	Positive	Absent	Absent	Absent
6	48	F	++	Positive	Absent	Absent	Absent
7	41	M	++++	Positive	Present	Absent	Absent
8	17	M	-	Positive	Present	Present	Present
9	48	F	++	Positive	Absent	Absent	Absent
10	40	M	+++	Positive	Present	Absent	Present
11	46	M	++	Positive	Present	Absent	Absent
12	23	M	+++	Positive	Present	Absent	Absent
13	28	F	++	Positive	Present	Absent	Absent
14	34	M	+++	Positive	Present	Absent	Absent
15	19	F	++	Positive	Absent	Absent	Present
16	37	M	-	Positive	Present	Absent	Absent
17	30	M	+++	Positive	Present	Present	Present
18	22	F	++	Positive	Anset	Absent	Absent
19	26	M	++	Positive	Present	Absent	Absent
20	25	F	+++	Positive	Present	Absent	Absent
21	25	M	++	Positive	Present	Absent	Absent
22	17	F	++	Positive	Present	Absent	Absent
23	30	M	+++	Positive	Present	Absent	Absent
24	40	M	++	Positive	Present	Absent	Absent
25	42	M	++	Positive	Present	Absent	Absent
26	32	M	++	Positive	Present	Absent	Absent
27	20	F	++	Positive	Present	Absent	Absent
28	26	F	++	Positive	Present	Absent	Absent

Cardiac enzymes estimation was done in all patients. Significant level of CPK-MB was raised in 22 patients (78.55%). Serum troponin T (Rapid card test) was weakly positive in 12 patients (42.8%). In electrocardiography, sinus bradycardia (HR < 60) was present in 4 patients (14.28%), and sinus tachycardia in 6 patients (21.4%). No QRS and ST changes were seen in any patient. 2D-Echo showed mean left ventricular ejection fraction 59% (range 52 – 66%); systolic dysfunction was absent in all patients; mild diastolic dysfunction was present in 4 patients (14.28%). Global hypokinesia was absent in all patients (Table III). Echocardiography was repeated after 4 weeks and was found to be normal in all patients.

Table II:

Patients	Dengue Serology	Platelet counts	SGOT/ SGPT	CPK/ CPK-MB	Serum Trop. T
Case 1	IgM+ve	30,000	459/135	1281/22	+ve
2	IgM+ve	40,000	340/128	88/34	+ve
3	IgM+ve	28,000	320/120	128/11	-ve
4	IgM+ve	39,450	371/110	321/24	-ve
5	IgM+ve	19,000	776/777	1309/43	+ve
6	IgM+ve	50,000	332/330	356/12	-ve
7	IgM+ve	11,000	453/238	563/31	-ve
8	IgM+ve	20,000	96/42	209/39	-ve
9	IgM+ve	20,000	279/220	529/28	+ve
10	IgM+ve	60,000	696/508	154/25	-ve
11	IgM+ve	55,000	152/96	2278/80	+ve
12	IgM+ve	67,000	278/176	530/51	+ve
13	IgM+ve	90,000	234/184	102/18	+ve
14	IgM+ve	25,000	270/148	643/66	+ve
15	IgM+ve	5,500	148/63	787/47	-ve
16	IgM+ve	80,000	68/57	649/88	+ve
17	IgM+ve	60,000	27/17	512/53	-ve
18	IgM+ve	10,000	269/162	54/14	-ve
19	IgM+ve	60,000	544/184	671/28	+ve
20	IgM+ve	23,000	260/160	69/13	-ve
21	IgM+ve	30,000	387/43	93/15	-ve
22	IgM+ve	25,000	231/39	200/28	-ve
23	IgM+ve	60,000	540/265	455/46	-ve
24	IgM+ve	34,000	32/12	544/28	-ve
25	IgM+ve	52,000	254/126	700/26	-ve
26	IgM+ve	46,000	26/18	520/40	+ve
27	IgM+ve	62,000	36/28	411/28	-ve
28	IgM+ve	41,000	128/95	594/68	+ve

Table III:

Case No	Electrocardiography				Echocardiography			
	HR	RR int.	QRS	ST	LVEF	Global hypokinesia	Distolic dysfunction	Systolic dysfunction
1	68	N	N	N	60%	Absent	Absent	Absent
2	55	N	N	N	56%	Absent	Present (gr1)	Absent
3	78	N	N	N	60%	Absent	Absent	Absent
4	86	N	N	N	58%	Absent	Absent	Absent
5	98	N	N	N	65%	Absent	Absent	Absent
6	66	N	N	N	56%	Absent	Present (gr1)	Absent
7	98	N	N	N	60%	Absent	Absent	Absent
8	100	N	N	N	60%	Absent	Absent	Absent
9	102	N	N	N	62%	Absent	Absent	Absent
10	110	N	N	N	66%	Absent	Absent	Absent
11	68	N	N	N	62%	Absent	Absent	Absent
12	96	N	N	N	60%	Absent	Absent	Absent
13	54	N	N	N	64%	Absent	Absent	Absent
14	48	N	N	N	56%	Absent	Present (gr1)	Absent
15	76	N	N	N	56%	Absent	Absent	Absent
16	88	N	N	N	54%	Absent	Absent	Absent
17	98	N	N	N	55%	Absent	Absent	Absent
18	92	N	N	N	58%	Absent	Absent	Absent
19	66	N	N	N	59%	Absent	Absent	Absent
20	62	N	N	N	62%	Absent	Absent	Absent
21	45	N	N	N	60%	Absent	Present (gr1)	Absent
22	78	N	N	N	56%	Absent	Absent	Absent
23	80	N	N	N	62%	Absent	Absent	Absent
24	94	N	N	N	62%	Absent	Absent	Absent
25	108	N	N	N	60%	Absent	Absent	Absent
26	112	N	N	N	52%	Absent	Absent	Absent
27	120	N	N	N	58%	Absent	Absent	Absent
28	45	N	N	N	62%	Absent	Absent	Absent

Discussion

Viral myocarditis is the result of a viral infection that produces myocardial necrosis, and this triggers an immune response for eliminating the viral agent (Kawai *et al*, 1999; Knowlton *et al*, 1999; Feldman *et al*, 2000). The definitive diagnosis of myocarditis has to be established by the demonstration of myocytolysis and the lymphocytic infiltrates in the endomyocardial biopsy (EMB) specimens (Aretz *et al*, 1987). However, EMB has confirmed the diagnosis of myocarditis in only about 10 – 25% of the patients in whom this disease was clinically suspected (Fowles *et al*, 1984; Parrillo *et al*, 1984; Mason *et al*, 1995), and repeated EMBs are not warranted in some clinical situations. During the course of myocarditis, the laboratory markers of myocardial cell damage, such as creatine kinase (CK) and creatine kinase MB isoform (CK-MB) levels are often within the normal range (Lauer *et al*, 1997; Smith *et al*, 1997). Cardiac isoforms of troponin T or I (cTnT, cTnI) are only expressed in cardiac muscle and their serum levels have been proved to be more

sensitive than the CK levels to detect myocardial injury in many clinical situations including unstable angina pectoris (Hamm *et al*, 1992; Bachmaier *et al*, 1995; Lauer *et al*, 1997; Smith *et al*, 1997). In clinically suspected myocarditis, the serum TnT level is elevated[3, 4] even in the absence of any histologic signs of myocarditis (Lauer *et al*, 1997; Smith *et al*, 1997). In autoimmune murine myocarditis, cardiac troponin is a more sensitive marker than creatine kinase MB isoform (CK-MB)[14], and an elevated troponin level clearly indicates myocarditis (Bachmaier *et al*, 1995; Smith *et al*, 1997). The present study shows that CPK-MB is significantly raised in 78.5% of cases. Although serum Trop-T is specific for myocardial injury, it is positive in our 12 cases as we have used the card test which is positive with higher level of serum troponin level. It is widely agreed that dengue haemorrhagic fever is an immunologically mediated disease, a mechanism similar to those involved in causing viral myocarditis, may play a role in the development of dengue virus related myocarditis[9]. Myocardial dysfunction can be seen in patients with DHF. Approximately 20% of those who developed DHF have a LV ejection fraction of less than 50%[11], and are likely to return to normal within a few weeks[6] (Wali *et al*, 1998). Electrocardiographic abnormalities[18, 19] have been reported in 44 – 75% of patients with viral haemorrhagic fever, and prolongation of the PR interval or sinus bradycardia commonly occurs (Smyth and Powell *et al*, 1954; Boon *et al*, 1967). Some have reported atrioventricular block[17] in variable degrees (Lim *et al*, 1970; Kongpattanayothin *et al*, 2000).

In this study, 4 cases (14%) had bradycardia in electrocardiography, and 4 cases (14%) had grade 1 diastolic dysfunction in 2D-echocardiography which is a manifestation of cardiac involvement. In other cases 2D-Echo was normal, but cardiac enzymes were significantly raised in most of these cases (serum CPK-MB level and S. trop. T). So there was subclinical cardiac involvement (myocarditis) present. The present study is supported by a study conducted in Srilanka (Satarasinghe RL *et al*, *Br J Cardiol* 2007) which showed asymptomatic cardiac involvement in dengue[20]. Serum troponin T was usually raised in most cases of myocarditis[3] and specific for myocardial injury. Similar findings were present in our cases. In our cases, CPK-MB was also raised by a significant level, that too being a marker of cardiac injury. Despite significantly raised levels of cardiac enzymes in our cases, clinical features and echocardiographic findings were not suggestive of myocarditis; so myocardial involvement in our cases was subclinical.

Conclusions

The results of this study revealed that myocardial involvement in dengue infections runs a benign course without long-term complications. Myocarditis in dengue may remains asymptomatic. Raised cardiac markers (CPK-MB, Trop .T) and 2D-Echocardiography are the main tools to diagnose the myocardial involvement. Endomyocardial biopsy is specific but positive in 20% of cases, and practically not feasible; follow-up echocardiography should be done after 4 to 6 week to detect any sequelae of myocarditis.

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ORIGINAL ARTICLE

JIACM 2010; 11(2) : 112-5

Significance of Cerebrospinal Fluid C-reactive Protein Level in Pyogenic and Non-pyogenic Meningitis in Adults

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Introduction

Acute pyogenic meningitis is the most common cause of suppurative infection in the central nervous system (CNS). The prognosis of pyogenic meningitis is critically dependent on a rapid and causal implementation of immediate treatment. However, clinical and biochemical parameters available are not reliable enough except when bacteria are found in the cerebrospinal fluid (CSF) under a microscope. Therefore, the initial treatment of acute pyogenic meningitis is most of the time presumptive. Use of biological markers, especially lymphokines and acute phase reactants has been proposed to facilitate initial diagnosis. Today, C-reactive protein (CRP) is one of the most widely used inflammatory markers in the emergency department to distinguish bacterial from non-bacterial infections.

Large number of studies conducted worldwide suggests that CRP level in the CSF is higher in pyogenic meningitis as compared to non-pyogenic meningitis and hence aids in the differential diagnosis and management of meningitis[1-6]. There are very few studies supporting the same from our country. Hence this study was designed to evaluate the same in our population.

Objective

Comparison of CSF CRP level to distinguish pyogenic from non-pyogenic meningitis in adults.

Materials and methods

CSF samples were obtained from patients admitted to the medical intensive care unit and the intensive care unit of Neurology at our centre. The study was conducted from March 2007 to September 2008. All patients above 18 years with clinical features suggestive of meningitis were included in the study. Patients less than 18 years, acute infections at sites other than central nervous system, patients with severe hepatic dysfunction, females on oral contraceptives and intrauterine devices, patients with severe dyslipidaemias and patients on steroids were not included in the study as these factors independently affect CRP levels[7-11].

A total 45 patients were included in the study. They were divided into three groups. The first group included patients with pyogenic meningitis; the second group included patients with non-pyogenic meningitis which was based on detailed history, clinical examination, and CSF analysis; and the third group included age and sex matched controls. CRP levels were measured by immunoturbidometric analysis (Figs. 1 and 2).

The statistical analysis was done using Statistical Package for Social Science (SPSS) software (Version 11). Analysis of variance (ANOVA) was used to test the difference between groups. In the above test, the "p" value less than 0.05 was accepted as statistically significant. The results were tabulated and graphically represented using Microsoft Word 2007.

Results

The mean age in pyogenic, non-pyogenic, and control group was 46.41 years, 39.26 years, and 42.66 years respectively. The male-to-female ratio in each group is described in Table I which compares the three groups on gender parameter.

Table I: Gender distribution in the three study groups

Sex	Pyogenic meningitis	Non-pyogenic meningitis	Control
Male	9	8	8
Female	6	7	7
Total	15	15	15

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Fig. 1 is an area diagram showing CRP levels in the three groups.

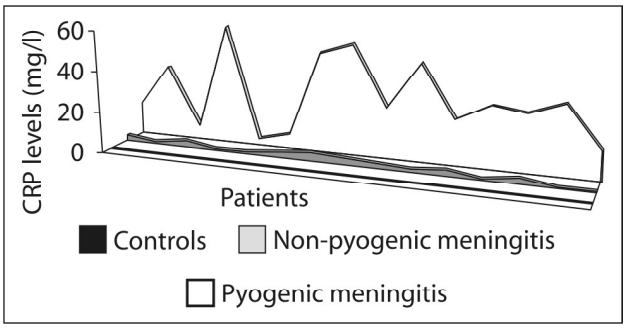

Fig. 1: *The CRP level was higher in pyogenic patients.*

Fig. 2 shows the mean CRP levels in the three groups.

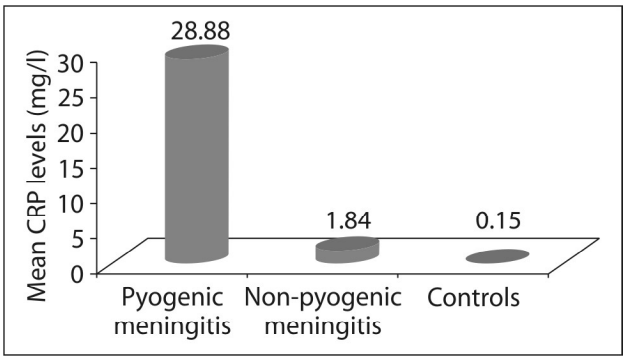

Fig. 2: *The value of mean CSF-CRP level was found to be significantly higher in the pyogenic meningitis group, compared to non-pyogenic meningitis and control groups.*

In the pyogenic meningitis group, organisms were seen microscopically in the CSF in all cases. The organisms were identified as *Streptococcus pneumoniae:* 8 (53.33%); *Neisseria meningitides:* 4 (26.66%); group B *Streptococci:* 2 (13.33%); and *Haemophilus influenzae:* 1 (6.66%). Out of 15 cases in the pyogenic group, bacterial growth in the CSF was observed in 10 cases (7 *S. pneumoniae* and 3 *N. meningitidis*). No growth was seen in 5 cases. All patients in this group presented with fever and had neck stiffness. 13 patients presented with altered sensorium. Generalised tonic clonic seizures were noted in 4 patients.

In the non-pyogenic group, 10 cases were diagnosed to have tubercular meningitis (66.66%) based on acid-fast bacilli staining and serology. Four cases were viral meningitis (26.66%), all of which were herpes simplex virus-2 based on serology, and 1 case was of fungal aetiology – cryptococcal meningitis (6.66%) based on dark ground microscopy and culture. All patients with tubercular meningitis presented with fever and had neck stiffness. 2 patients presented with altered sensorium and generalised tonic clonic seizures. All patients with viral meningitis presented with fever, neck stiffness and altered sensorium. None of these patients had seizures.

The value of mean CSF CRP level was found to be significantly higher in the pyogenic meningitis group (28.88 mg/l), compared to the non-pyogenic meningitis (1.84 mg/l) and control groups (0.15 mg/l) which was statistically significant ($p < 0.0001$) (Fig. 1 and 2). Among the pyogenic group, CSF CRP was higher in cases caused by Gram-negative organisms compared to Gram-positive organisms. The values of CSF CRP were slightly higher in the non-pyogenic meningitis group compared to the control group. However, it was not statistically significant.

Discussion

CRP is mainly synthesised in the liver. But studies show that CRP can also be synthesised in the neurons and lipopolysaccharide-S can induce CRP synthesis in extra-hepatic sites[1,2]. CRP levels are affected by factors such as hepatic dysfunction, dyslipidaemia, females on oral contraceptive pills, and patients on steroids, and hence were not included in the study.

In this study we found that the CSF CRP levels were significantly higher in pyogenic meningitis compared to non-pyogenic meningitis. Similar studies conducted by Przylalkowski *et al*[6], indicated that CRP levels in CSF were elevated significantly in pyogenic meningitis compared to non-pyogenic meningitis. The results of Indian studies by Vaishnavi *et al*[12] and by Tankhiwale *et al*[13] are in agreement with our study.

Gojan Rajs *et al*[14] reported from their study that CSF CRP levels are higher in Gram-negative pyogenic meningitis compared to Gram-positive pyogenic meningitis. Similar findings were seen in our study. However, majority of cases in our study were due to Gram-positive bacteria. This suggests that infection with Gram-negative bacteria enhances permeability of CRP through the blood brain barrier. It is possible that these findings reflect the ability of the endotoxin lipopolysaccharide-S, present in the

Gram-negative bacteria to affect the permeability of blood brain barrier. Nitric Oxide (NO) may be involved in this mechanism because its concentration in CSF is higher in Gram-negative meningitis as observed in other studies. This possibility is supported by the higher potency of Gram-negative bacteria to promote macrophage NO production, the enhanced production of NO in the CSF of pyogenic meningitis, and the role of NO in the permeability changes of the blood brain barrier in lipopolysaccharide-S induced experimental meningitis.

Another potential explanation for the present observation is that the lipopolysaccharide-S produced by the Gram-negative bacteria could induce local CRP production in the central nervous system. CRP can be produced in the neurons and lipopolysaccharide-S can induce CRP synthesis in extrahepatic sites. This may also explain the increase, albeit non significant, in serum CRP in Gram-negative cases[15, 16].

In three patients with pyogenic meningitis, CSF CRP was mildly elevated. This can be explained by the fact that minimal CSF inflammation may be apparent in patients undergoing lumbar puncture very early in the course of the disease and in patients with rapidly developing meningitis in whom bacterial multiplication can outpace the ability of the liver to mount a CRP response[17].

CSF CRP levels were significantly lower in non-pyogenic meningitis group, which included cases of tubercular meningitis, viral meningitis and fungal meningitis. Among the non-pyogenic group, CSF CRP levels were slightly higher in cases of tubercular meningitis compared to viral meningitis and control group; however, it was not statistically significant. Studies conducted by Pradowski *et al*[18] observed that CSF CRP levels were significantly lower in non-pyogenic meningitis compared to pyogenic meningitis. Similar studies conducted in India by Hemavani *et al*[5] and Vaishnavi *et al*[12] observed that CRP levels in CSF were significantly lower in patients with non-pyogenic meningitis compared to pyogenic meningitis. These studies conclude that CSF CRP estimation is a useful marker to differentiate pyogenic from non-pyogenic meningitis; however, it cannot differentiate between tuberculosis, fungal, and viral meningitis.

Conclusion

CSF CRP level was very high in pyogenic meningitis, may be mildly elevated in non-pyogenic meningitis, and hence is a useful diagnostic tool in pyogenic meningitis.

Summary

Acute pyogenic meningitis is the most common form of suppurative CNS infection which occurs throughout the world. The prognosis of pyogenic meningitis is critically dependent on a rapid causal diagnosis and implementation of immediate treatment. However, clinical and biochemical parameters available within the few hours that follow patients admission are not reliable enough, except when bacteria are to be found in the cerebrospinal fluid under the microscope. Therefore, the initial treatment of acute pyogenic meningitis is most often presumptive. A number of recent studies strongly suggest that measurements of CRP in CSF could reliably discriminate between pyogenic and non-pyogenic meningitis, hence the present study was undertaken to evaluate the same.

In our study, the value of mean CSF-CRP levels were found to be significantly higher in the pyogenic meningitis group, compared to non-pyogenic meningitis and control groups. This was statistically significant ($p < 0.0001$). Among the pyogenic group, CSF-CRP levels were higher in cases caused by Gram-negative organisms compared to Gram-positive organisms. The values of CSF-CRP were slightly higher in the non-pyogenic meningitis group compared to control group; however, it was not statistically significant. To conclude, CSF-CRP levels are very high in pyogenic meningitis, may be mildly elevated in non-pyogenic meningitis, and hence are a useful diagnostic tool in pyogenic meningitis.

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REVIEW ARTICLE

JIACM 2010; 11(2) : 116-20

Hypokalaemic Periodic Paralysis – Faces Behind the Mask: Profile in Rural Central India

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Abstract

Hypokalaemic periodic paralysis (HPP) is a rare syndrome of muscular weakness and paralysis associated with hypokalaemia. This serious type of periodic paralysis can result in arrhythmias, respiratory failure, and death. The severity of the attacks varies from mild pain and weakness to total paralysis. The attacks spontaneously abate and the patient recovers within 3 – 36 hours. Cognitive and sensory functions remain intact and deep tendon reflexes may be diminished or absent. We report a case series of 25 patients presenting with hypokalaemic periodic paralysis in a rural Indian community in central India. We also review its pathogenesis, clinical features, diagnosis, and treatment.

Key words: Hypokalaemia, paralysis, channelopathies.

Study

Over a three year period from January 2006 through December 2008, a total of 25 patients were admitted in Kasturba hospital, a tertiary care hospital located in Sevagram (a village in a rural area of Maharashtra, in Central India) with features of paralysis with aetiology as hypokalaemia. Of these 25 patients, 22 were males and the other 3 were females. Their ages ranged from 20 years to 66 years (mean: 42). Most of the patients (14 out of 25) had an acute presentation history of weakness within 3 days prior to hospital admission.

In 16 of the 25 patients, the onset of weakness occurred at night, between 10:00 pm and 6:00 am. Prior to onset of weakness, 3 patients described a heavy strenuous day at work, 7 reported symptoms of a gastrointestinal infection with vomiting, and 1 had been on an alcohol binge. In the rest, no specific underlying risk or any precipitating factor could be delineated.

Table I: Duration between onset and hospital presentation.

Duration of presentation	No of patients
< 3 days	14
4 – 7 days	8
8 – 30 days	1
> 30 days	2

The clinical presentation also varied in the form that 10 out of 25 patients had only the conventional lower limb paraplegia while the other 15 presented with weakness in both upper and lower limbs. None of the patients had any clinical features suggestive of hyperthyroidism such as tachycardia, palpitations, tremors, or a thyroid swelling, which is the commonest association with hypokalaemic periodic paralysis. Apart from the quadriparesis, only one patient had also documented respiratory paralysis for which mechanical ventilation was required. The respiratory paralysis and quadriparesis promptly responded to potassium replacement within 48 hours. None of these patients had sensory findings, cranial nerve abnormalities, or ocular signs. Two patients had cardiovascular complications in the form of a complete heart block in one and first degree heart block in another, both of which reverted back to sinus rhythm after potassium replacement.

All patients were hypokalaemic, with potassium levels ranging from 1.1 to 2.2 mmol/l (normal: 3.5 – 5.5 mmol/l). Investigations for aetiology revealed that out of 25 patients only one had abnormal thyroid profile suggestive of hyperthyroidism. All the other patients were euthyroid. However, urinary studies for potassium wasting revealed that urine pH was less than 6 in 7 patients with urine K^+ excretion of more than 15 meq/lit suggestive of renal tubular acidosis. In total, 23 patients had abnormal electrocardiograms – 21 showed U waves, and 2 showed ST depression with T-wave flattening. All patients were

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given intravenous potassium replacement and recovery in them ranged from 24 hours to 3 days. None of the patients had prolonged recovery time or residual paralysis (see Table II).

Table II: Patient characteristics.

Patient No.	Age in years	Sex	Presentation pattern	St. K^+	Serum creatinine level	Evidence of thyroid abnormality	Evidence of renal abnormality	Complications
1	22	M	Paraparesis	1.2	1.0	Absent	Absent	Absent
2	35	M	Quadriparesis	1.4	1.4	Absent	Absent	Absent
3	53	M	Quadriparesis	1.9	1.6	Absent	Absent	Absent
4	31	M	Paraparesis	1.5	2.0	Absent	Present	Respiratory
5	43	M	Quadriparesis	1.9	1.0	Absent	Absent	Absent
6	30	M	Paraparesis	1.3	1.0	Absent	Present	Absent
7	45	M	Paraparesis	1.0	1.0	Absent	Present	CVS
8	46	M	Paraparesis	1.9	1.1	Absent	Absent	Absent
9	35	M	Quadriparesis	1.6	1.7	Absent	Absent	Absent
10	44	M	Quadriparesis	1.4	1.8	Absent	Absent	Absent
11	62	M	Paraparesis	1.4	1.6	Absent	Absent	Absent
13	40	F	Quadriparesis	2.2	1.0	Absent	Absent	Absent
14	56	M	Paraparesis	1.5	1.1	Absent	Absent	Absent
15	66	M	Quadriparesis	1.5	1.5	Absent	Present	Absent
17	20	M	Paraparesis	2.0	1.0	Present	Absent	Absent
19	50	F	Quadriparesis	1.7	1.0	Absent	Absent	Absent
20	44	M	Quadriparesis	1.2	1.0	Absent	Absent	CVS
21	42	F	Quadriparesis	1.7	1.6	Absent	Present	Absent
22	54	M	Quadriparesis	1.6	1.8	Absent	Absent	Absent
23	25	M	Quadriparesis	1.1	1.2	Absent	Present	Absent
24	35	M	Paraparesis	1.7	1.2	Absent	Present	Absent
25	38	M	Paraparesis	1.9	2.0	Absent	Absent	Absent

Discussion

Acute systemic weakness is a common complaint in the emergency department and has a wide differential diagnosis that includes neurologic, metabolic, and infectious aetiologies. Channelopathies are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them[1]. These diseases may be either congenital (often resulting from a mutation or mutations in the encoding genes) or acquired (often resulting from an autoimmune attack on an ion channel)[2]. Around 24 types of different channelopathies of human skeletal muscle include hyper-, hypo- and normokalaemic (high, low, and normal potassium blood concentrations) periodic paralysis, myotonia congenita and paramyotonia congenita[3].

All primary periodic paralysis have some features in common; they are all treatable, and muscular weakness is reversible. The heterogeneous group of muscle diseases known as periodic paralyses (PP) is characterised by episodes of flaccid muscle weakness occurring at irregular intervals[4].

Hypokalaemic periodic paralysis

Hypokalaemic periodic paralysis is a rare channelopathy characterised by muscle weakness or paralysis with a

matching fall in potassium levels in the blood[5]. Hypokalaemia can be caused by disturbances in transcellular distribution of potassium or actual potassium depletion from renal or extrarenal losses[6]. Causes of periodic paralysis due to transcellular distribution of K^+ (non-depletion) include mainly familial periodic paralysis and thyrotoxicosis periodic paralysis and rare causes like barium poisoning[7] and glue sniffing[8].

Pathophysiology

When a condition causing K^+ depletion is not existent, total body potassium stores remain adequate, but serum potassium decreases due to potassium migration into muscle cells which is thought to be due to activation of sodium-potassium-stimulated ATPase at the cell surface causing potassium entry into the cell at the cost of extracellular fluid causing the muscle electrically inexcitable[9]. The exact method of potassium translocation is not known but is possibly secondary to an abnormality in muscle membrane[10].

Symptomatology results from alteration of membrane polarisation resulting in disturbances in function of excitable tissues such as muscle. Recent electrophysiologic studies have suggested that the fundamental defect in hyperkalaemic periodic paralysis may involve an increase in muscle membrane sodium permeability, but the problem with hypokalaemic periodic paralysis is possibly a calcium channel problem[11]. Genetic linkage data have suggested a defect in dihydropteridine binding, voltage-sensitive, skeletal muscle calcium channel[12].

Apart from a primary genetic cause, secondary periodic paralysis due to hypokalaemia can be caused by other aetiologies like thyrotoxic periodic paralysis[13], high carbohydrate diet[14, 15], renal tubular acidosis[16, 17], and poisoning[18].

Clinical presentation

Familial hypokalaemic periodic paralysis occurs as an autosomal dominant condition in two-thirds of cases and as sporadic cases in one-third. Onset occurs at adolescence. Men are more often affected because of decreased penetrance in women. The most prominent clinical features of hypokalaemia or potassium depletion are neuromuscular, although other systems, such as cardiovascular[19] and gastrointestinal, may also be affected[20]. Some patients complain of muscular weakness, especially of the lower extremities, while marked and generalised weakness of skeletal muscles is common with more severe potassium depletion. The attacks are often triggered by strenuous exercise followed by rest, high carbohydrate meals, meals with high sodium content, alcohol intoxication[21], sudden changes in temperature, and even excitement, noise or flashing lights[11].

Very severe hypokalaemia may lead to virtually total paralysis including respiratory, bulbar, and cranial musculature. Deaths from respiratory failure and arrhythmia have been reported[6, 22]. Attack frequency varies from daily to yearly, and each attack may last for a few hours or persist for several days. Recovery is usually sudden when it occurs. Some patients may fall into an abortive attack or develop chronic muscle weakness later in life. On physical examination, in addition to decreased motor power, the patient may demonstrate decreased or absent tendon reflexes. The sensations and level of consciousness are generally unaffected. Patients often report muscle pain and cognitive problems during attacks. Migraine is reported in up to 50% of all hypokalaemic periodic paralysis patients.

Diagnosis

Diagnosis of hypokalaemic paralysis should be considered in any patient presenting with a sudden onset, areflexic, pure motor weakness involving one or more limbs, without alteration in the level of consciousness or sphincter function, and laboratory evidence of hypokalaemia[23]. A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis of familial periodic paralysis. Abnormalities in the electrocardiogram (ECG) are common. The typical changes include flattening and inversion of T waves, appearance of U waves and ST segment sagging. ECG changes are, however, not well correlated with the severity of the disturbances in potassium metabolism[24].

Inter-attack muscle biopsies show the presence of single or multiple centrally placed vacuoles or tubular aggregates. In the midst of an attack of weakness, motor

conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In-between attacks, the EMG and nerve conduction studies are normal, with the exception that myopathic motor unit action potentials may be seen in patients with fixed weakness[6, 11]. The CMAP (Compound Muscle Amplitude Potential) test, also called the exercise EMG or X-EMG, is diagnostic in 70 – 80% of cases when done correctly[25]. Besides the patient history or a report of serum potassium being low-normal or low during an attack, the CMAP is the current standard for medical testing. Provocative testings used are oral glucose loading test, intravenous glucose challenge, and intra-arterial epinephrine test. These are not used frequently as they are potentially fatal and simpler methods for diagnosis are available.

Treatment

Treatment of hypokalaemic periodic paralysis focuses on relieving acute symptoms and preventing further attacks. Avoiding carbohydrate-rich meals and strenuous exercise, and taking acetazolamide (Diamox) or another carbonic anhydrase inhibitor, may help prevent attacks of weakness[26, 27]. The initial treatment of a patient with hypokalaemic FPP is oral potassium supplementation (0.2 – 0.4 mmol/kg), repeated at 15 – 30-minute intervals depending on the response[6]. Daily potassium dosage may reach upto100 – 150 meq of potassium bicarbonate. All patients should preferably be treated with oral potassium replacement.

The intravenous route for potassium replacement must be used when a patient is unable to take oral medications. IV potassium chloride 0.05 – 0.1 meq/kg body weight in 5% mannitol as a bolus is preferable to continuous infusion. Mannitol should be used as the solvent, as both sodium in normal saline and dextrose 5% worsen the attack. Only 10 meq at a time should be infused with intervals of 20 – 60 minutes, unless one is in a situation of cardiac arrhythmia or respiratory compromise. This is to avoid hyperkalaemia at the end of an attack with shift of potassium from intracellular compartment into the blood. Continuous ECG monitoring and sequential serum potassium measurements are mandatory.

Prophylaxis against recurrent periodic attacks include 100 – 200 mg/day of spironolactone[28], and 250 – 750 mg/day acetazolamide. Dichlorphenamide is another drug which is shown to be effective in the prevention of episodic weakness in hypokalaemic periodic paralysis[27]. Some patients benefit from extra magnesium[29], or fish oil, while these same nutrients will make other patients worse. Patients and care givers should take extreme caution with all new drugs and treatment plans. The prognosis for periodic paralysis varies, but the life span is expected to be normal.

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REVIEW ARTICLE

JIACM 2010; 11(2) : 121-6

Immune Reconstitution Inflammatory Syndrome after Initiation of Antiretroviral Therapy for HIV

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Introduction

Since the diagnosis of the Human Immunodeficiency virus in the early 1980s, the disease has affected hundreds of thousands of individuals across the globe. It is estimated that by the end of 2007, there were 33 million people infected with the virus[1], and it is estimated that over 4 million people are accessing antiretroviral (ART) therapy in low- and middle-income countries by the close of 2008[2]. The advent of ART has had a considerable impact on the survival of the people[3] and has resulted in fall of viral load and subsequent rise in CD4+ T-cells and immune restoration[4]. However, some patients experience clinical deterioration as a consequence of the rapid and dysregulated restoration of the antigen-specific immune response[5,6]. Such a response has been termed as Immune Reconstitution Inflammatory Syndrome (IRIS) or Immune Restoration Disease (IRD) or Immune Reconstitution Syndrome (IRS).

The fact that immune reconstitution occurs was known with some diseases such as *Mycobacterium tuberculosis*[7] and leprae[8] infection and were termed paradoxical reaction. However, the recognition that such a spectrum of conditions can also present with HIV treatment, became known in the late nineties. A similar scenario of immune reconstitution has been reported in non HIV-infected individuals undergoing various medical interventions such as organ transplant recipients[9].

In 2006, Robertson *et al*[10] defined the immune reconstitution inflammatory syndrome as a spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery.

Table I: Infectious and noninfectious causes of IRIS in HIV-infected patients (Adapted from Murdoch *et al*[11]).

Infectious aetiologies

- Mycobacteria
  - *Mycobacterium tuberculosis*
  - *Mycobacterium avium* complex
  - Other mycobacteria
- *Cytomegalovirus*
- Herpes viruses
  - Herpes zoster virus
  - Herpes simplex virus
  - Herpes virus-associated Kaposi's sarcoma
- *Cryptococcus neoformans*
- *Pneumocystis jirovecii* pneumonia (PCP)
- *Histoplasma capsulatum*
- Toxoplasmosis
- Hepatitis B virus
- Hepatitis C virus
- Progressive multifocal leukoencephalitis
- Parvovirus B19
- *Strongyloides stercoralis* infection and other parasitic infections
- Molluscum contagiosum and genital warts
- Sinusitis
- Folliculitis

Noninfectious aetiologies

- Rheumatologic/autoimmune
  - Rheumatoid arthritis, systemic lupus erythematosus (SLE)
  - Graves' disease
  - Autoimmune thyroid disease
- Sarcoidosis and granulomatous reactions
- Tattoo ink
- AIDS-related lymphoma
- Guillain-Barré syndrome (GBS)
- Interstitial lymphoid pneumonitis

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Immunopathogenesis in HIV infection and pathogenesis of IRIS

The current theories concerning the pathogenesis of the syndrome involve a combination of:

- underlying antigenic burden,
- the degree of immune restoration following HAART, and
- host genetic susceptibility.

Antigenic burden

These pathogenic mechanisms may interact and likely depend on the underlying burden of the infectious or noninfectious agent. Although IRIS could be elicited by an infectious or noninfectious agent, the presence of an antigenic stimulus for development of the syndrome appears necessary. Clinically dormant or silent infections sometimes get unmasked during IRIS and are characterised by heightened inflammatory response or clinical presentation that could suggest that there has been restoration of the antigen-specific immunity. Such IRIS, though not limited to these organisms, are observed with MAC, *cryptococcus* and *mycobacterium tuberculosis*.

In noninfectious causes of IRIS, autoimmunity to innate antigens plays a likely role in the syndrome. Bell *et al*[12] in 2002, have described exacerbation of rheumatoid arthritis and other autoimmune diseases.

Immune restoration

It has been hypothesised that the degree of immune restoration that occurs may have a relation to the development of IRIS. This facor is discussed in depth subsequently in the article.

Epidemiology and risk factors for IRIS

IRIS has been found to be most prevalent in people with a severely compromised immune system at baseline. Risk factors common to the widely varying manifestations of IRIS are difficult to identify and are often challenging to establish even within single cohorts. Several efforts have been done by researchers to determine the risk factors for development of IRIS. Some of the clinical factors are enumerated in Table II.

Table II: Clinical factors associated with the development of IRIS† (Murdoch *et al*[11]).

Risk factors:

- Male sex
- Younger age
- Lower CD4 cell count at ART initiation
- Higher HIV RNA at ART initiation
- Lower CD4 cell percentage at ART initiation
- Lower CD4: CD8 ratio at ART initiation
- More rapid initial fall in HIV RNA on ART
- Antiretroviral naïve at time of OI diagnosis
- Shorter interval between OI therapy initiation and ART initiation

† Derived from cohorts where IRIS due to multiple pathogens were reported (i.e., cohorts which examined only TB-IRIS were excluded).

A high viral load before initiation of therapy or a rapid drop on HAART seems to be an important predictive factor for IRIS. Shelbourne *et al*[13] in 2005 documented that 31.7% of the cohort developed IRIS, when they were studying the incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. They reported that antiretroviral drug-naive patients who start HAART in close proximity to the diagnosis of an opportunistic infection and have a rapid decline in HIV-1 RNA level should be monitored for development of this disorder.

However, French[14] and colleagues in 2000 had reported in their retrospective study that 25% of the total patients exhibited one or more disease episodes after HAART, that was related to a pre-existent or subclinical infection by an opportunistic pathogen. They also reported that these episodes were most common in patients with a baseline CD4 T-cell count of < 50/μl and occurred most often during the first 2 months of therapy and when CD4 T-cell counts were increasing. This difference in reported prevalence could probably be due to the fact that Shelboune *et al* included only those patients who had received HAART and were coinfected with *Mycobacterium tuberculosis*, *Mycobacterium avium complex*, or *Cryptococcus neoformans*, while French and others included all patients who were administered ART at a centre. In 2007, Yukari *et al*[15] also confirmed these findings that the most immunosuppressed patients treated with the most potent regimens, particularly PI-based regimens,

resulting in significant HIV viral load declines are at greatest risk for the development of IRIS after HAART initiation. However, like French *et al*[13], they did not find any correlation of risk of developing IRIS and absolute CD4 T-cell increase.

Though definitive role of immunological mechanism is believed in IRIS along with other factors, some evidence has been generated in support that there could be qualitative changes in lymphocyte function or lymphocyte phenotypic expression. An increase in memory CD4 cell types is observed[16] possibly as a result of redistribution from peripheral lymphoid tissue[17]. This CD4 phenotype is primed to recognise previous antigenic stimuli, and thus may be responsible for manifestations of IRIS seen soon after ART initiation. After this redistribution, naïve T-cells increase and are thought to be responsible for the later quantitative increase in CD4 cell counts[18]. Based on these observations, Murdoch[11] has suggested that IRIS may be due to a combination of both quantitative restoration of immunity as well as qualitative function and phenotypic expression observed soon after the initiation of ART.

There have been reports of increased levels of Interleukin 6 (IL-6) in patients with IRIS[19], and consequently, this may explain the excessive Th1 response to mycobacterial antigens[20] in subjects with clinical IRIS.

What is the Indian take on IRIS ?

Immune reconstitution inflammatory syndrome: This is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. Antiretroviral therapy partially restores immune defects caused by chronic HIV infection, including the restoration of protective pathogen-specific immune responses. The protective response sometimes causes (atypical) inflammatory manifestations to concurrent infective or non-infective conditions, e.g., TB, MAC, or CMV. Clinically, IRIS manifests itself as the occurrence or worsening of clinical and/or laboratory parameters, despite a favourable CD4 count (and viral load). The temporal association between the commencement of HAART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue to the diagnosis of IRIS.

IRIS can manifest itself in a variety of ways. In India, the agreed practical definition of IRIS would be the "occurrence or manifestations of new OIs or existing OIs within six weeks to six months after initiating ART, with an increase in CD4 count"[21,2].

Points to see for diagnosis of IRIS (Indian guidelines 2007)[21].

Temporal association between the initiation of ART and the development of clinical phenomena (mostly within 3 months): Typically, IRIS occurs within 2 – 12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months).

- Unexpected localised disease, e.g., lymph nodes (appearance or enlargement and/or suppuration), or involving liver or spleen
- Exaggerated inflammatory reaction, e.g., severe fever, with exclusion of other causes of painful lesions
- Atypical inflammatory response in affected tissues, e.g., granulomas, suppuration, necrosis
- Perivascular lymphocytic inflammatory cell infiltrate
- Progression of organ dysfunction or enlargement of pre-existing lesions
- Development or enlargement of cerebral space-occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
- Progressive pneumonitis or the development of organising pneumonia after treatment for pulmonary MTB or PCP
- Onset or worsening of uveitis/vitritis after the resolution of CMV retinitis
- Fever and cytopenia after treatment for disseminated MAC

Treatment of IRIS

There are no standard guidelines for the treatment of IRIS. There is very limited information on the effectiveness of various interventions for managing it, and little evidence from randomised clinical trials. Most cases resolve without any additional treatment. Milder forms of IRIS resolve with continuing anti-infective therapy and HAART. In the majority of cases, HAART can be safely continued and need not be interrupted. In

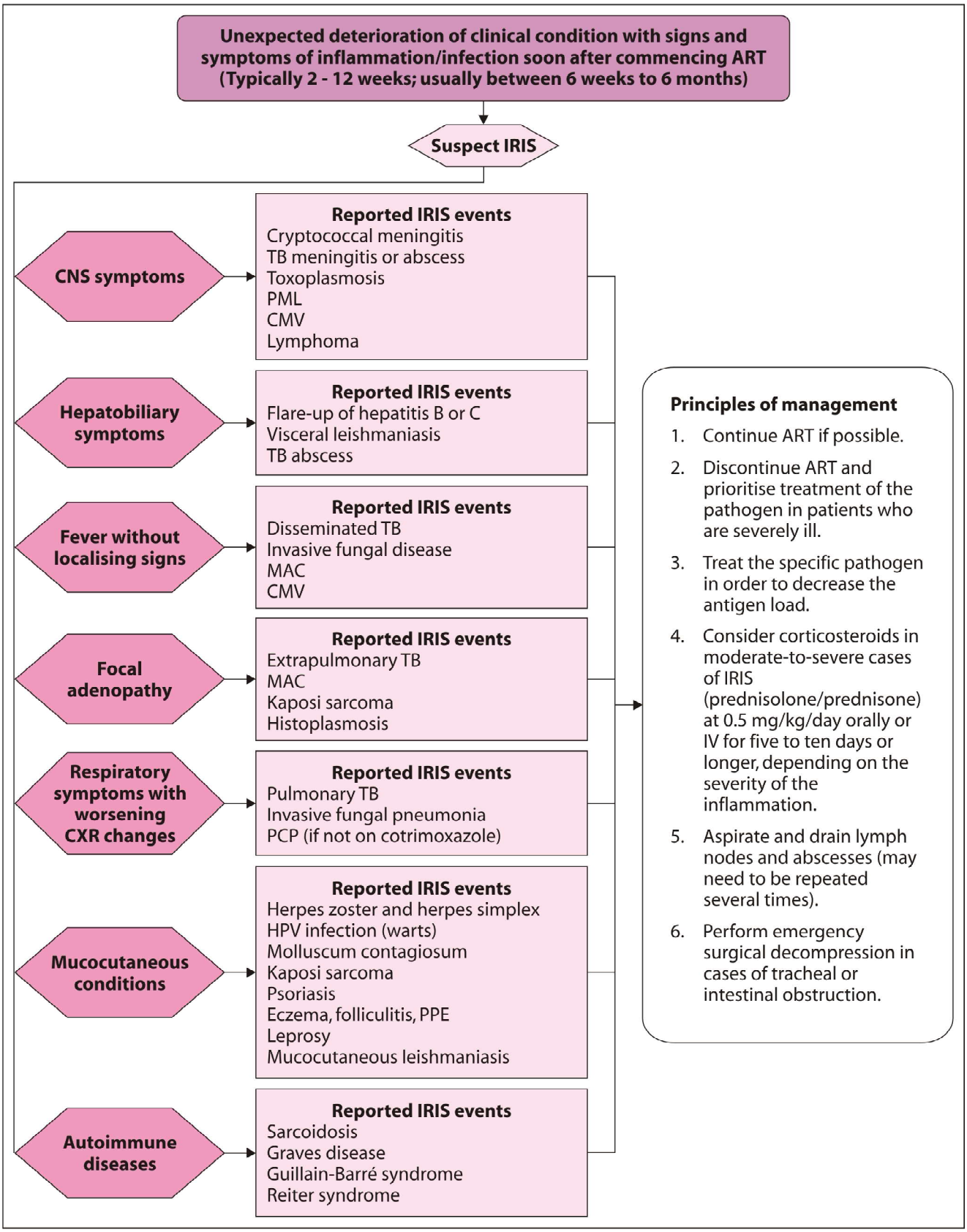

Fig. 1: *Managing Immune Reconstitution Inflammatory Syndrome (IRIS) – Indian guidelines*[21].

general, most clinicians prefer to continue ART if the CD4 count is below 100/mm^3 or if the patient presents with IRIS months after the initiation of HAART. However, the discontinuation of ART should be considered if the inflammatory responses are considered life-threatening (e.g., intracranial IRIS leading to encephalitis, cerebritis, perilesional cerebral oedema, and pulmonary IRIS with ARDS (acute respiratory distress syndrome), or are unresponsive to steroids. Discontinuation of the treatment should also be considered if the pathogens involved are not amenable to specific antimicrobials (e.g., Parvovirus B19, polyomavirus JC causing PML (progressive multifocal leukoencephalopathy), or if ART toxicity is the main differential diagnosis (e.g., hepatitis). Non-steroidal anti-inflammatory drugs (NSAIDs) are helpful in controlling inflammation and fever associated with IRIS. However, in severe IRIS, a short course of oral prednisolone is required to alleviate the symptoms. The dosage and duration of treatment required is variable and should be judged clinically. Severe disease requires at least 1 - 2 mg of prednisolone per kg body weight. Thalidomide has also been tried effectively in some patients.

Consequences

Patients starting HAART with lower CD4 cells/µl (and particularly those who have a high viral load) require close clinical monitoring during the first weeks with anticipation of any IRIS in case they have rapid fall in viral load and have any associated risk. Some people recommend a thorough screening for the common infectious agents like mycobacterial infections, crytococcal, and cytomegaloviral infection.

The Indian guidelines have suggested a flow chart (Fig. 1) for managing the IRIS/suspected IRIS.

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JIACM 2010; 11(2) : 127

Phlyctenular Conjunctivitis

*Sumeet Singla**

A 40-year-old undernourished alcoholic presented with a swelling on the right side of the neck, malaise, weight loss, and night sweats since 3 weeks. A non-tender, non-inflamed, fluctuant swelling was palpable in the right posterior triangle of the neck (Fig. 1). Lungs were clear and no other nodes could be palpated. An ultrasound study of the neck showed matted lymph nodes with calcification and necrotic fluid inside. Mantoux test showed induration of 25 mm by 24 mm, and FNAC showed caseous material with acid-fast bacilli. HIV was non-reactive. Weight-adjusted 5 drug ATT (HRZES) was prescribed. One week after starting ATT, he complained of intense irritation, redness, and watering from the left eye. Examination showed a whitish, raised nodule near the medial limbus with intense conjunctival inflammation (Fig. 2). A diagnosis of extrapulmonary tuberculosis with phlyctenular conjunctivitis was made and steroid and antihistaminic eye drops were added. The phlycten resolved after 2 weeks, without any residual scarring.

Phlyctenular keratoconjunctivitis (PKC) is a type IV hypersensitivity response in the cornea and/or conjunctiva to a variety of distinct conditions, tuberculosis (evident or occult) being the commonest in India. Tuberculosis as an aetiological association is being supplanted by staphylococcal infection and worm infestation. In a study from Delhi[1], tuberculosis was implicated in 77% (86/112) of all cases of PKC. Worm

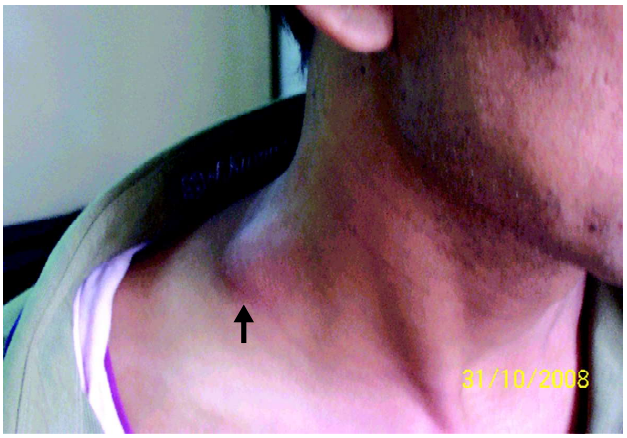

Fig. 1: *Lump of cervical lymphadenopathy on right side of neck (arrow).*

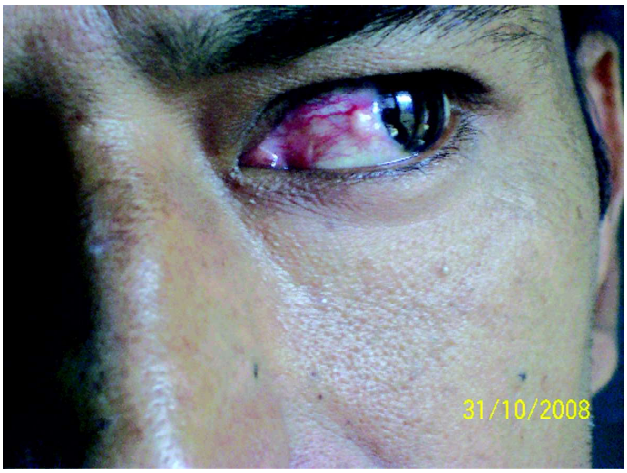

Fig. 2: *Left eye showing conjunctival phlycten near medial limbus.*

infestation was found in 14 patients (12.4%), whereas 7 (6.2%) had staphylococcal blepharitis. Thirteen patients had evidence of multiple aetiologies, of which one causative factor was always tuberculosis. In this study, PKC lesions were observed to be more severe and recurrent in patients with tuberculosis. The most common underlying tubercular focus was found to be the lungs (56/86), followed by lymph nodes.

Conjunctival phlyctens are usually transient and asymptomatic, but occasionally – in larger phlyctens – frank pustular conjunctivitis may develop with subsequent penetration into sclera, leading to permanent scar formation. Corneal phlyctens present with lacrimation, photophobia, and blepharospasm, and tend to leave opacities, leading to permanent vision impairment or occasionally blindness. A simple eye examination in all patients with tuberculosis will result in timely institution of local treatment for PKC and ameliorate the unwanted complications of visual disability.

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CASE REPORT

JIACM 2010; 11(2): 128-30

Novel Pulmonary Presentation of *Mycobacterium interjectum*

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Abstract

Nontuberculous mycobacteria (NTM) have been shown to cause disseminated disease in immunocompromised individuals as well as local infection in the immunocompetent. In 2006, the incidence of NTM disease varied from 1.0 to 1.8 cases per 100,000 in industrialised countries. The number of NTM species and diagnoses have increased dramatically as a result of improved isolation techniques and sequencing of the 16S rRNA as a standard for identifying new species. The NTM known as Mycobacterium interjectum has been well documented as a source of infection in children and immunocompromised adults; however, there are no descriptions of disease in healthy individuals. To date, no human-to-human transmission has been described, and infections are believed to be acquired from environmental exposure. The following is a description of significant pulmonary disease in an immunocompetent gentleman with M. interjectum as the identified pathogen.

Key words: Nontuberculous mycobacteria, Chest wall abscess, Mycobacterium interjectum.

Introduction

Nontuberculous mycobacteria (NTM) have been shown to cause disseminated disease in immunocompromised individuals as well as local infection in the immunocompetent. In 2006, the incidence of NTM disease varied from 1.0 to 1.8 cases per 100,000 in industrialised countries. The number of NTM species and diagnoses have increased dramatically as a result of improved isolation techniques and sequencing of the 16S rRNA as a standard for identifying new species. The NTM known as *Mycobacterium interjectum* has been well documented as a source of infection in children and immunocompromised adults; however, there are no descriptions of disease in healthy individuals. To date, no human-to-human transmission has been described, and infections are believed to be acquired from environmental exposure.

Case report

A 56-year-old white male presented with pain in the right axilla of two months duration. He was initially diagnosed via CT scan at an other hospital with an infection of the lung parenchyma, but this was not seen on a repeat scan at yet another hospital. Increasing pain, waking the patient from sleep, prompted his presentation. He described a nonproductive cough of six months duration, subjective fever, and dyspnoea on exertion. The patient was taking no medications and has no history of chronic obstructive pulmonary disease (COPD). Past medical history is significant for pneumonia as a child, tobacco abuse of fifteen pack-years, and *Mycobacterium avium complex* (MAC) of the left lung that was treated and lost to follow-up eleven years prior.

The patient was afebrile with stable vitals and an oxygen saturation of 90% on room air. Examination revealed coarse breath sounds bilaterally. The right chest wall and axilla were diffusely tender and demonstrated crepitus on palpation. No erythema, ulceration, or lymphadenopathy was noted.

Laboratory data included:- Hb: 11.7 g/dl, Hct: 34.5%, WBC: 11,000 cells/µl, platelets: 719,000 cells/µl, MCV 84.2 µm^3, normal basic metabolic panel, and normal liver enzymes. Blood cultures, HIV, and tuberculin skin tests were negative. Iron studies revealed:- iron level: 18 µg/dl, ferritin: 99.1 ng/ml, total iron binding capacity: 225 µg/dl, iron saturation: 7%, and WESR: 90 mm/hr. These values indicated a chronic inflammatory process, thus thrombocytosis was classified as reactive.

CT scan demonstrated bilateral cavitary lesions of the lung apices (Fig. 1), as well as inflammation and an infectious process of the right lung with extension of infection through the anterior lateral chest wall with a small abscess and air collection posterior to the pectoralis.

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Aspiration of the fluid collection recovered 4 ml of thick, bloody, purulent material that was sent for cytology and microbiological analysis (Fig. 1). Three sputum samples taken on different days, bronchioalveolar lavage (BAL), and the aspirated fluid were each found to contain acid-fast bacteria.

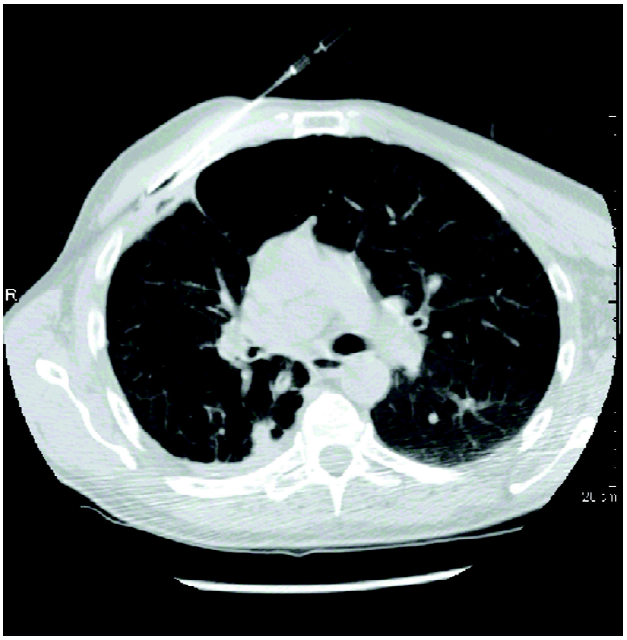

Fig. 1: *Extensive cavitary lesions of both upper lobes with soft-tissue density outlining right upper lobe cavities and CT-directed aspiration of right anterior chest wall air-fluid collection.*

The patient was discharged with a presumptive diagnosis of recurrent MAC, and prescribed ethambutol 1,200 mg daily, rifampin 300 mg daily, and clarithromycin 500 mg twice daily with instructions to follow-up with pulmonary medicine.

After discharge, cultures of the aspirate for nocardia and actinomycetes, cytology, and blood cultures, were all negative. Mycobacterium samples are analysed, and if a diagnosis of MAC or *M. tuberculosis* is not made, sequencing of 16S rRNA is performed. Sputum cultures, bronchioalveolar lavage, and aspirate were all found to contain *Mycobacterium interjectum* as identified by DNA sequencing.

Discussion

The number of nontuberculous mycobacteria (NTM) species and diagnoses have increased dramatically as a result of improved isolation techniques and sequencing of the 16S rRNA as a standard for identification of NTM species[1]. *Mycobacterium interjectum* was first identified in 1993 in a child with chronic lymphadenitis[2]. Fifteen cases have been reported, nine of which are associated with lymphadenitis in children aged one to three[3, 4]. Of the six cases in adults, the only case considered clinically significant is a 52-year-old female with severe COPD and multiple positive cultures[5]. Of note, there are no previous documented infections in immunocompetent healthy adults.

The bacterium presented in a novel fashion with crepitus and pain from lung and soft-tissue damage in an apparently healthy 56-year-old male. The American Thoracic Society has set stringent criteria to diagnose NTM infection[1]; this patient exceeds these requirements meeting each possible criterion.

As no features of cutaneous infection were present, we believe that the bacterium eroded the lung tissue to the extent of forming an abscess deep to the pectoralis muscle allowing air to escape into soft tissues. After reviewing imaging and physical exam findings, it was determined that the axillary pain was the result of pectoralis inflammation.

We theorize that childhood pneumonia, which required hospitalisation, left the lungs scarred, allowing colonisation with the mycobacterium. Tobacco could be an additional risk factor though there are minimal radiological and clinical signs of COPD, and this would not explain the diagnosis of MAC eleven years prior. Genetic factors such as interferon-γ or interleukin 12 deficiencies were also considered; however, these would predispose to disseminated disease[1]. We also speculate the previous diagnosis of MAC was actually *M. interjectum*, and as the patient failed to follow-up, the bacterium was never cleared.

Conclusion

To our knowledge this is the first description of *M. interjectum* as a virulent pathogen in a non-immunocompromised healthy adult. While the source of infection as well as why virulence is noted in this individual can only be hypothesised, it is clear that *M. interjectum*

can act as a human pathogen producing significant disease. As more laboratories adopt 16S rRNA gene sequencing for NTM identification, further descriptions of this and other NTM species as pathogens are likely in the future.

Acknowledgements

We would like to thank David Webb, MD, and Clarence Joe, MD, for their help in preparing this case report.

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CASE REPORT

JIACM 2010; 11(2) : 131-2

Lead aVR in Tricyclic Antidepressant Overdose: Need for a More Respectable Look

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Case report

A 23-year-old male was found to be unconscious in his house early morning at 6.00 am and brought to the emergency room. He had not suffered from any illness till date. On examination, he was comatose with a poor respiratory effort. His pulse was rapid and feeble. His blood pressure was not recordable. His GCS (Glasgow Coma Scale) was E1 M4 V1. Pupils were moderately dilated (4 mm), sluggish, and reacting to light. No lateralisation was demonstrated, reflexes were symmetrical, and neck was supple. There were no outward signs of physical violence. His capillary blood glucose was 125 mg/dl. Arterial blood gas analysis showed a pH of 7.14, pCO_2 22 mmHg, pO_2 58 mmHg, bicarbonate of 12 mmol/l. His other blood chemistries were within normal limits.

His airway was protected with an endotracheal tube and he was mechanically ventilated. His hypotension was unresponsive to the IV fluid challenge (1 litre normal saline), hence a high dose of norepinephrine was initiated.

The ECG of this patient given below reveals sinus tachycardia (134/min). The QTc was prolonged (617 ms), and the QRS complexes widened (136 ms); there was a positive R wave (4 mm) in lead aVR.

Since there were no cardiac manifestations, the possibility of tricyclic antidepressant overdosage was considered. Gastric lavage was performed and activated charcoal was administered.

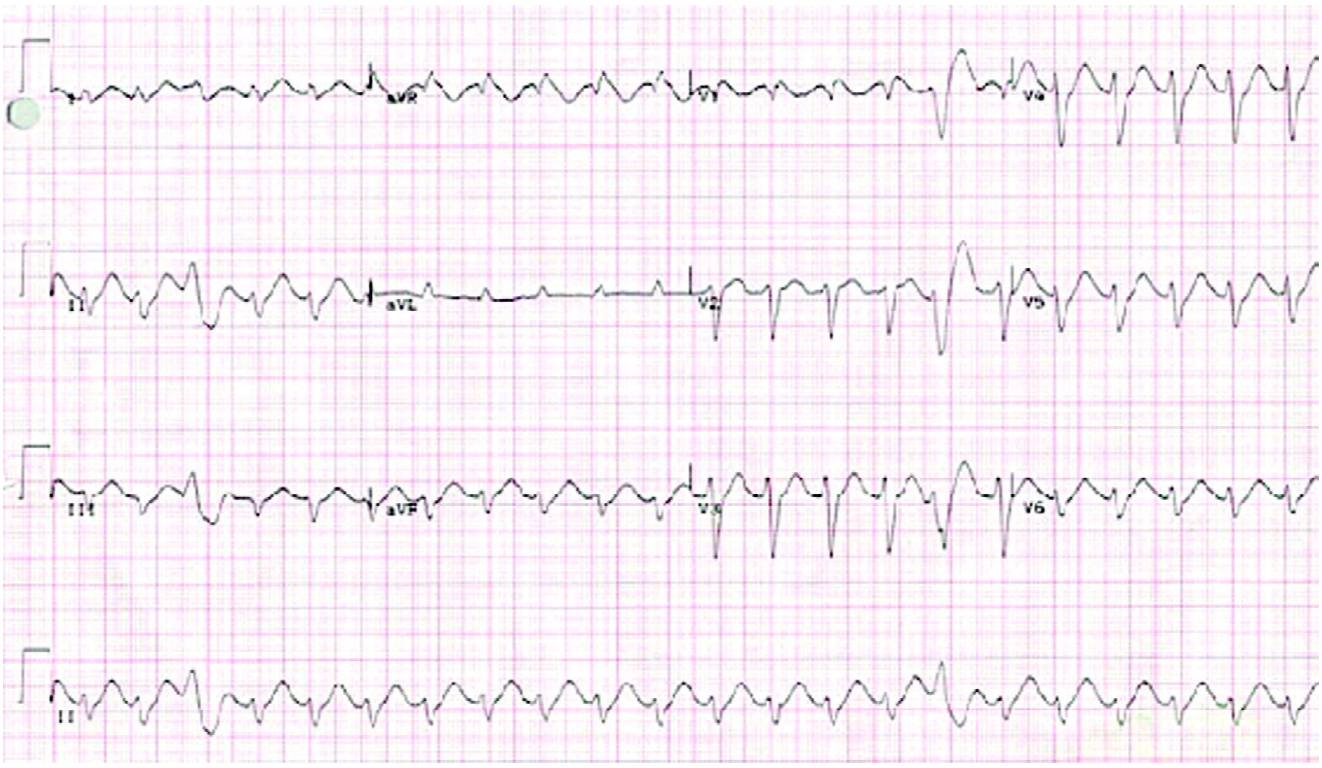

Fig. 1: *ECG showing sinus tachycardia, prolonged QTc, widened QRS complexes, and positive R wave in aVR.*

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100 ml of 7.5% sodium bicarbonate was administered over 30 minutes, and followed by a continuous infusion which was titrated against the urinary pH and arterial blood gases. Subsequently, toxicological screening revealed amitriptyline level of 3.2 mcg/ml. He was subsequently discharged on day 5 after psychiatric counselling.

Discussion

Tricyclic antidepressants (TCAs) remain as the widely prescribed drugs to treat major depression, despite availability of less toxic alternatives[1]. Of all the antidepressants, TCAs are the most toxic drugs often used for suicide attempts[2]. As the clinical signs are nonspecific[3], the diagnosis of TCA intoxication is found to be a difficult task. Plasma TCA levels are difficult to determine, and are not readily available. Fortunately, for treating physician, ECG has emerged as an effective, diagnostic bedside tool that can provide the important information, in assessing the patients of TCA overdose[4].

The ECG changes commonly associated with TCA overdose are QRS duration > 100 ms, QTc interval > 430 ms, right axis deviation (RAD) of 120 – 270 degrees in the terminal 40 ms frontal plane QRS vector, R/S ratio > 0.7 in lead aVR, and R wave in lead aVR > 3 mm[5]. Among these R in lead aVR is the better marker of TCA overdose. The ECG changes seen in TCA overdose are mainly due to the sodium channel blocking.

The widening of QRS and QTc prolongation are also noticed in carbamazepine, antihistaminic, and class IA anti-arrhythmic drug toxicity.

Conclusion

This ECG highlights the significance of lead aVR, which is often ignored. In this patient, ECG clues had led to an earlier diagnosis and thus specific therapy. Therefore, in any young, comatose patient with ECG changes, TCA intoxication should be suspected.

Acknowledgement

We acknowledge the help of Dr. B. Bakthavathsalam, MD, Director of the Chellam Hospitals for logistical support.

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CASE REPORT

JIACM 2010; 11(2) : 133-5

Thyrotoxic Hypokalaemic Periodic Paralysis

Shweta Sahai, Atul Sahai***

Abstract

Hypokalaemic periodic paralysis is a well recognised clinical entity with varied aetiology. The commonest cause described amongst the Caucasian population is the primary type of hypokalaemic periodic paralysis, which is familial. A greater incidence of secondary hypokalaemic periodic paralysis has been reported from the eastern population. Here, we describe the case of a young man who presented to us with acute quadriplegia as a result of hypokalaemia. Subtle symptoms and signs led us to the suspicion of thyrotoxicosis, which was proved on investigations. Review of literature revealed that secondary causes of hypokalaemic periodic paralysis like thyrotoxicosis, have a higher incidence among men of Asian origin. Hence, the possibility of hypokalaemia being secondary to a specific disease should always be entertained in our setting because treatment of the primary disease is definitive and prevents further attacks of hypokalaemic paralysis.

Key words: Hypokalaemia, thyrotoxicosis.

Introduction

Hypokalaemic periodic paralysis (HPP) is a group of disorders with varying aetiology. The presentation in this disorder is the sudden onset of weakness in all four limbs, either simultaneously or sequentially. The usual precipitating causes are diarrhoea, vomiting, a high carbohydrate diet or vigorous exercise, especially during the hot summer months. HPP can be classified as:

1. Primary: Familial hypokalaemic periodic paralysis.
2. Secondary HPP due to disorders like:
   a. Thyrotoxicosis
   b. Conn's syndrome
   c. Renal tubular acidosis
   d. Gitelman syndrome

The primary familial type of HPP is the commoner type amongst the Caucasian population. Secondary forms of HPP are now being increasingly recognised as causes of HPP from Asian countries. The recognition of this fact is important in order to ascertain the specific cause of HPP so that definitive treatment may be given for the prevention of further attacks. Here we report the case of a young man who presented with acute flaccid areflexic quadriplegia due to hypokalaemia. Subtle clinical signs and symptoms led to investigations and a hyperthyroid condition was detected. The relative rarity of this condition in India prompted us to examine the available literature and report the case.

Case report

A 30-year-old man was referred to us with the history of sudden-onset weakness of both lower limbs which ascended rapidly within 5 hours to involve both upper limbs. There were neither sensory symptoms nor any bladder/bowel involvement. He gave no history of fever or URTI preceding the illness. There was no history of loose stools, vomiting, vigorous exercise, or excessive carbohydrate intake prior to onset of weakness. There was no history of similar past episodes. On examination, his pulse was 120 per minute, BP 130/90, and he was well hydrated. CNS examination showed him to be conscious, well oriented, and without any cranial nerve palsy. Motor power was grade '0' in all four limbs. There was no involvement of the respiratory muscles. All deep tendon reflexes were absent. Bilateral plantars were flexor. Sensory examination was normal.

Routine haemogram, renal functions, and liver functions were normal. Random blood sugar was 148 mg%. Serum potassium was found to be 1.1 meq/l. ECG showed sinus tachycardia and prominent 'U' waves.

He was treated with 90 meq of potassium over 24 hours, after which he showed complete neurological recovery. The ECG continued to show sinus tachycardia. Repeat serum potassium was 5.2 meq/l, after which the

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intravenous potassium was discontinued.

There were a few interesting features in the case which raised the possibility of a secondary cause of hypokalaemia:

1. There was no obvious precipitating cause of hypokalaemia like gastroenteritis, excessive sweating (the weather was cool), or high carbohydrate intake.
2. There was persistent sinus tachycardia on ECG in the absence of fever or dehydration.
3. After neurological recovery, the DTR (deep tendon reflexes) were exaggerated.
4. The age of the patient was 30 years, which made familial HPP unlikely.

Free T4 and TSH estimations were performed on the suspicion of thyrotoxicosis based on the above findings. FT4 was 37.09 (normal values: 12 – 32 pmol/l) and TSH was less than 0.05 MIU/l. An ultrasound of the thyroid gland revealed an adenoma of 8 by 10 mm. He was given neomercazole 10 mg tid which was gradually tapered to 10 mg od over two weeks. He was also prescribed slow release propranolol 40 mg od. He continues to be stable on this treatment and a normal diet. There have been no repeat episodes of paralysis three months later.

Discussion

Hypokalaemic periodic paralysis refers to a rare condition characterised by episodic weakness of the muscles due to hypokalaemia. It commonly occurs during the summer months when potassium loss is excessive due to sweating or gastroenteritis. A high intake of carbohydrates, especially in the form of aerated cold drinks has been recently found to be a precipitating cause.

The tendency for hypokalaemia can be due a number of causes. The commonest cause described in the caucasian population is the 'familial hypokalaemic periodic paralysis'[1]. This entity is due to a defect in the calcium channels of the muscles (channelopathy). It occurs as an autosomal dominant condition in two-third cases and is sporadic in the remaining one-third. Secondary type of HPP refers to a group of disorders where the hypokalaemia is secondary to some other underlying disorder like thyrotoxicosis, Conn syndrome, renal tubular acidosis or Gitelman syndrome. The secondary type appears to be commoner amongst the Asian population, and thyrotoxic HPP being the commonest cause described for HPP in the far eastern countries like China and Japan[2, 3]. Approximately 2% of thyrotoxic patients in these countries suffer from HPP.

The cause of HPP in thyrotoxicosis appears to be excessive adrenergic stimulation, which pushes the potassium intracellularly.

The treatment of familial HPP is by acetazolamide and avoidance of high carbohydrate intake, which is usually effective. The treatment of secondary HPP is, obviously, correction of the primary disorder. Acetazolamide has been found to actually worsen the paralysis in secondary HPP. Another important difference to be kept in mind is the temporary nature of hypokalaemia in thyrotoxicosis. Overzealous correction of hypokalaemia without monitoring may land the patient in hyperkalaemia, in contrast to primary HPP where hyperkalaemia is unlikely to occur with intravenous potassium.

The exact incidence of secondary HPP in India is not known, but there have been quite a few case reports[4-6]. An excellent attempt was made by Rao *et al* to find out the aetiology of HPP in a retrospective analysis of 31 patients. They found that out of 31 cases:

- 13 had renal tubular acidosis (42%)
- 13 had Conn syndrome
- 02 had sporadic periodic paralysis
- 02 had thyrotoxic periodic paralysis and
- 01 had Gitelman syndrome.

Interestingly, both the patients having TPP were natives of West Bengal, though this study was conducted in South India[7]. These findings were quite different from those of another Indian series of 22 cases reported by Arya[8]. 12 out of 22 (54%) had secondary HPP due to gastroenteritis, thyrotoxicosis, and diuretic use.

In a large series of 97 cases from Taiwan[2], 40% patients had thyrotoxic periodic paralysis and 21% had sporadic periodic paralysis. Overall 68% had secondary periodic paralysis.

Conclusion

Thyrotoxicosis is a rare but potentially treatable cause of hypokalaemic periodic paralysis. Definitive treatment of thyrotoxicosis effectively stops furthur attacks of paralysis. Review of literature reveals that the incidence of TPP is quite high amongst the far-eastern population. The incidence in India appears not as high, but sufficient enough to maintain a high index of suspicion, especially in young males.

Age of onset above 25, persistent tachycardia, exaggerated DTR and a lack of traditional precipitating causes should alert the clinician about the possibility of this entity. Acetazolamide, the treatment of choice in familial HPP, is contraindicated in TPP. Also, there is a real danger of hyperkalaemia in TPP, so the potassium levels should be very closely monitored after initiating intravenous potassium.

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CASE REPORT

JIACM 2010; 11(2) : 136-8

Shoe Leather Softener Poisoning

*Mridul Chaturvedi**

Abstract

Shoe leather softener is a combination of two aromatic solvents; 70% toluene and 30% benzene. We report an increased incidence of shoe leather softener poisoning. Clinical manifestation are due to hepatotoxicity of toluene. It has a high mortality and there is yet no specific antidote available, so the management is conservative.

Keywords: Benzene, toluene, hepatorenal toxicity of toluene.

Shoe leather softener is a combination of two aromatic solvents: 30% benzene and 70% toluene. Basically it is used in shoe industries for softening of leather. Recently we have reported an increased incidence of suicidal ingestion of shoe leather softener in shoe industries. It is a highly fatal combination of aromatic solvents with a very high mortality.

Benzene (C_6H_6) occurs naturally. It is primarily derived from petroleum products[1]. It is a colourless, clear liquid at a temperature of 25°C, having a sweet odour, is soluble in alcohol, and is used primarily as an intermediate in the manufacture of a number of chemicals like phenolic resins and nylons[2].

The most common form of benzene exposure is occupational. Individuals working in industries involved with benzene products – like petrochemical industries, coke manufacturing, rubber tyre industries – are all at risk of benzene exposure[3].

Acute oral exposure is uncommon. Poisoning usually results from homicidal intentions, or attempted suicide.

Toluene (methyl benzene) is an aromatic hydrocarbon (C_7H_8) commonly used as an industrial solvent for the manufacturing of paints, chemicals, pharmaceuticals, and rubber[4]. At room temperature toluene is a colourless sweet-smelling liquid. Toluene toxicity can occur from accidental or deliberate inhalation of fumes, and ingestion or absorption through the skin. Workers with a history of asthma induced by solvent exposure should also be warned about and protected from short-term exposure to high concentrations[5, 6].

Case report

A 28-year-old male, labourer of a shoe factory was brought to the Emergency Deptt. of S.N. Medical College, Agra with a history of alleged intake of shoe softener about 100 to 150 ml in the 1 hour lunch break at the factory. This was followed by severe burning sensation in abdomen with nausea. The patient had no H/O vomiting or frothing, or intercurrent illness during that period. At the time of admission, his sensorium was slightly altered, his GCS score was E4 V4 M6 = 14/15.

Patient was slightly anxious, and had an expression of guilt for what he had done. His pulse was 80 per min. regular, and BP was 120/80 Hg in the right arm in supine position. He was afebrile, hydration was normal, and there was no cyanosis, oedema, pallor, icterus, or lymphadenopathy. Rest of the systemic examination was within normal limits. Gastric lavage was done, and patient was put on conservative treatment. During the course of his illness, urine output decreased slightly on the 2nd day but became normal on the 3rd day and remained normal thereafter. The patient became slightly icteric on the 2nd day (serum bil 2.7 D – 0.5 and I – 2.2). His serum hepatic markers started rising from the 2nd day (SGPT/SGOT increased up to the level of 4,995/5,448 respectively), from the 3rd day these began to decline and came within normal limits by the 7th day. On routine urine cytological and biochemical examination, there was also a proteinuria (+2) on 2nd day of admission but this proteinuria disappeared on the 7th – 8th day of admission. On the second day of illness there was a slight rise of S. creatinine (1.3 mg/dl) which came to normal on the 7th day of illness

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(serum creatinine 0.9 mg/dl). PT level on the 3rd day was 27 sec (INR 2.0) and came to 14 sec (INR1.01) on the 9th day. Patient was discharged on the 12th day of admission in a satisfactory condition with follow-up advice about his renal and hepatic biochemical markers. At the time of discharge, he was well-oriented, there was no nausea or vomiting or burning sensation in the abdomen and all his biochemical investigation were within normal limit.

Table 1: Biochemical investigations in a patient of shoe softener poisoning.

Date	28/1/09	30/1/09	31/1/09	2/2/09	4/2/09	5/2/09
Hb	14.2	14.0	14.4	14.3	14.0	14.1
TLC	19,900	10,600	9,088	9,460	8,800	8,400
DLC	P90,L8E1M1	P88L10E2M0	P82L16E1M1	P80L18E2M1	P82L16E1M1	P80L16E2M2
P/C	90,000	10,000	12,000	10,8000	11,600	11,800
GBP	Normocytic, normochromic			Normocytic, normochromic		
SGOT	48.1	5448	1682	625	213.5	108.6
SGPT	17.88	4995	5480	1260	431.5	186.2
PT/INR			27 sec/2.0			14 sec/1.01
Urine Sugar	Trace	Nil	Nil	Nil	Nil	Nil
Albumin	Nil	+2	+3	+2	Trace	Nil
RBS	126	138	130	128	124	116
S. Na/K	136/4.6	138/4.8	140/4.6	144/4.9	145/4.2	145/4.4
S. Ca	9.6	9.5	9.8	9.7	9.8	9.9
S. Creatinine		1.3			0.9	
S. Bil T/D/I				2.7/0.5/2.2		

Discussion

Basically, a shoe leather softener is a combination of two aromatic hydrocarbon solvents, i.e., benzene and toluene. So the clinical manifestation of shoe softener poisoning is supposed to be the manifestation of benzene and toluene toxicity. Our case presented mainly with a slight alteration in consciousness and hepatorenal toxicity of shoe softener poisoning, which in our case appeared on the 2nd and 3rd day of illness, and after 7 to 8 days of conservative treatment it subsided. As such, no hepatorenal toxicity for benzene is known in literature, but hepatorenal toxicity of toluene is very well described. Hepatotoxicity of toluene manifests itself with ascites, jaundice, hepatomegaly, and liver failure[7]. Renal toxicity from toluene exposure includes renal tubular acidosis, hypokalaemia, hypophosphataemia, hyperchloraemia, azotaemia, pyuria, haematuria, and proteinuria.

Large oral ingestion of benzene has resulted in nausea, vomiting, ataxia, visual disturbances, CNS depression, tachycardia, and pneumonitis[8]. A non-fatal ingestion resulted in severe gastritis follwed by pyloric stenosis and peripheral swelling and oedema[9].

Acute ingestion of benzene – over 10 ml – may prove lethal[8]. Diagnosis of benzene poisoning can be made by detection of phenol in urine. Overall, no specific guideline is available for shoe softener poisoning as there is no proven antidotal therapy available for benzene and toluene poisoning. Administration of N-acetyl cysteine may be of benefit in limiting the haematological toxicity of acute poisoning[10]. In case of ingestion, vomiting should not be induced because benzene can produce chemical pneumonitis. It should be ensured that the patient's airway is properly protected before initiating orogastric tube lavage. Gastric lavage is indicated if large amount of poison has been ingested or if the patient is seen within an hour of ingestion. Activated charcoal may be used because it

decreases benzene absorbtion in experimental animals and benefits are likely to be similar in humans.

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CASE REPORT

JIACM 2010; 11(2) : 139-40

Cryptococcal Meningitis in Patients of Acquired Immunodeficiency Syndrome

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Human immunodeficiency virus (HIV) infection has emerged as the fifth leading cause of death, affecting approximately 40.3 million people worldwide[1]. Cryptococcosis is one of the acquired immunodeficiency syndrome (AIDS) defining illnesses[2]. Cryptococcosis is the commonest central nervous system (CNS) fungal pathogen in immunocompromised patients[3,4]. It has become the most common lethal fungal infection in patients with acquired immunodeficiency syndrome (AIDS) worldwide[5-7]. Recent data indicate that incidence of *C. neoformans* infection is high in developing countries like India[3,8].

Three cases of cryptococcal meningitis in acquired immunodeficiency syndrome (AIDS) patients are being reported here from the Government Medical College, Amritsar, Punjab.

HIV status of all the three cases was confirmed at ICTC, department of microbiology, GMC, Amritsar.

Case report

Case 1

A 35-year-old HIV-positive patient was admitted in the emergency ward of Guru Nanak Dev hospital on 20.03.2008 with the chief complaints of gradually increasing headache for the last one week and fever for the last 6 days. Fever was continuous, high-grade, along with chills and rigors. He also had 2 - 3 episodes of vomiting. For the last 2 days, the patient was showing altered sensorium. He was being treated in a private hospital with IV antibiotics. On examination, neck rigidity was noticed. CD4 count of the patient was 37/cmm. Lumbar puncture was done and CSF was received in the department of microbiology, which, after processing was examined. Wet mount, Gram's staining and India ink preparation was done which revealed 4 - 6 µm budding yeast cells with capsule. CSF was cultured by standard procedures[9]. Creamy white mucoid colonies were seen on Sabouraud's dextrose agar medium. Identification of *Cryptococcus neoformans* was established by its growth at 37°C, urease production, and inositol assimilation test. Antigen detection was also done. Antigen titres in CSF were 1,024 and in serum were < 128. The patient responded well to antifungal treatment (amphotericin B).

Case 2

A 40-year-old male HIV-positive patient, farmer by occupation, was admitted to the emergency ward of our hospital on 9.07.2008 with the chief complaints of headache, fever, weakness of right side of the body along with progressive aphasia and severe oedema of all the four limbs. On examination, neck rigidity was noted. CD4 count of the patient was 2/cmm and he was on ART for the last 6 months. CSF was received in our department after lumbar puncture. After proper processing, the sample was examined. Wet mount, Gram's staining, and India ink preparation revealed budding yeast cells with capsule showing various aberrant forms (elongated cells). CSF was cultured by standard procedures[9]. Creamy white mucoid colonies were seen on Sabouraud's dextrose agar medium. Identification of *Cryptococcus neoformans* was established by its growth at 37°C, urease production, and inositol assimilation test. Antigen detection was done by latex agglutination. Antigen titres in CSF were 1,024. The patient responded well to the antifungal treatment (amphotericin and fluconazole) initially, but died of cardiac failure after 15 days of admission.

Case 3

A 35-year-old HIV-positive male patient was admitted to the medicine ward of GNDH on 10.10.2008 with the chief

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complaints of fever, headache for the last 20 days, and jaundice for the last 10 days along with altered sensoriun for the last 2 – 3 days. On examination, neck rigidity was noticed. CD4 count of the patient was not known. After lumbar puncture, CSF was received. Wet mount, Gram's staining, and India ink preparation revealed budding yeast cells with capsule. CSF was cultured by standard procedures[9]. Creamy white mucoid colonies were seen on Sabouraud's dextrose agar medium. Identification of *Cryptococcus neoformans* was established by its growth at 37°C, urease production, and inositol assimilation test. Antigen detection was done by latex agglutination. Antigen titres in serum were 256. CSF for antigen titres could not be obtained as the patient developed papilloedema on the 3rd day of admission. He was given antifungal therapy but he died on the 6th day of admission.

Discussion

After Cytomegalovirus (CMV), *Pneumocystis jiroveci* and *Mycobacterium avium intracellulare*, *Cryptococcus neoformans* is the fourth commonest cause of life-threatening infection in AIDS patients[10]. Two cases of cryptococcal meningitis were reported in acquired immunodeficiency syndrome patients from our own centre in the year 2001[11]. Untreated, cryptococcal meningitis is fatal. With the high incidence of cryptococcal meningitis in AIDS, it is important to examine all CSF specimens from HIV-infected persons with meningitis for cryptococci. Thus, timely diagnosis and initiating appropriate treatment at the earliest can significantly reduce the morbidity and mortality of the disease and improve the outcome.

Acknowledgement

We are thankful Dr. A. Chakraborty, In-charge, Mycology Division, Department of Medical Microbiology, Post-Graduate Institute of Medical Education and Research, Chandigarh for performing antigen detection in serum and CSF for Cryptococcus in these cases.

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CASE REPORT

JIACM 2010; 11(2) : 141-3

Dengue Meningoencephalitis

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Introduction

Dengue presents as an acute febrile episode with severe headache, bodyache and retro-orbital pain. The spectrum of the disease may vary from a simple febrile illness to the more fatal dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)[1]. Involvement of the central nervous system (CNS) is usually in the form of encephalopathy[2]. Direct involvement of the CNS has been rarely reported. We present one such case of dengue infection manifesting as meningoencephalitis.

Case report

A 24-year-old male presented to us with complaints of fever, retro-orbital headache, and body ache of one week duration, vomiting and altered sensorium since one day. Fever was intermittent, high grade, associated with chills and rigors, partly relieved by medications. The patient had one episode of vomiting, non-projectile, non-blood stained and non-bile stained. There was no history of any rashes or bleeding tendencies. The patient was a resident of a dengue endemic area. Past history, family history, and personal history were non-contributory.

On examination, the patient was restless and agitated. He was febrile (101°F) and had tachycardia (130/min). CNS examination revealed neck stiffness, positive Kernig's and Brudzinski's signs. There were no focal neurological deficits. Abdominal examination revealed mild hepatomegaly. Other systemic examination was unremarkable. A provisional diagnosis of meningoencephalitis was made and the patient was started on empiric antibiotics and supportive care.

Investigations revealed thrombocytopenia, otherwise a normal complete blood count (haemoglobin – 13 g/dl; total count – 10,900 cells/dl; neutrophils – 78; lymphocytes – 16; eosinophils – 4; monocytes – 2; platelets – 40,000/dl). Peripheral smear for malaria parasite was negative. Urine routine showed no abnormalities. Renal and liver functions were within normal limits. Chest X-ray showed bilateral minimal pleural effusion. Ultrasonography of abdomen and pelvis revealed hepatosplenomegaly with mild ascites.

The patient received platelet transfusion following which the counts improved. He developed two episodes of generalised tonic clonic seizures (GTCS) on the second day of admission. CT brain plain was normal. Cerebrospinal fluid (CSF) analysis showed mild lymphocytosis with normal sugar and proteins (CSF analysis – appearance – clear, pressure – normal, cells – 10 (all lymphocytes), proteins – 32 mg/dl, sugar – 55 mg/dl). CSF PCR for tuberculosis and herpes simplex virus was negative. CSF was negative for cryptococcus in India-ink preparation. Blood, urine, and CSF cultures showed no growth. Serum and CSF dengue IgM were positive (Bio Standard Diagnostics, India). The test is a solid phase immunochromatographic assay for rapid and qualitative detection of IgM antibodies to dengue virus in human serum, plasma, or whole blood. Its sensitivity and specificity compared to haemagglutination inhibition test is 99.4% and 93% respectively[3].

A revised diagnosis of dengue meningoencephalitis with thrombocytopenia was made and the patient was treated with anticonvulsant, and other supportive measures. Platelet transfusions and intensive monitoring with adequate fluid balance was maintained. Patient improved over the next three days and was subsequently shifted to the wards. On the eighth day of admission, the patient was stable and therefore discharged. At follow-up after one month, patient was doing well with no neurological sequelae.

Discussion

The most severe sequelae of dengue infection described are dengue haemorrhagic fever and dengue shock

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syndrome. Neurological manifestations as atypical manifestations in dengue infection were first reported in 1976[1]. Many neurological manifestations such as headache, seizure, altered sensorium, behavioural disturbances in patients with dengue infection have been described. They were long thought to be due to an encephalopathy-like state as there was no evidence to demonstrate the direct invasion of the CNS[4, 5]. The mechanism of the encephalopathy was said to be due to cerebral oedema, cerebral haemorrhage, hyponatraemia, hepatic failure, cerebral anoxia, microcapillary haemorrhage, and release of toxic products[6].

Recently, studies have shown that dengue virus is capable of direct invasion of the CNS. Animal studies have shown that the virus is known to release cytokines that could breach the blood-brain barrier, thus being capable of CNS invasion[7]. Lum and his collegues reported six cases of dengue encephalitis in Malaysia[8]. Diagnosis was based on CSF microscopy. While dengue virus serotype-3 was found in blood and CSF in four cases, serotype-2 was isolated from CSF in one other case by Polymerase Chain Reaction (PCR) technique. In the other case, virology was negative, but IgM antibodies against dengue were demonstrable in blood and CSF.

The common symptoms of dengue encephalitis in a retrospective study by Pancharoen and Thisyakorn were altered consciousness (83.3%), seizures (45.2%), mental confusion (23.8%), nuchal rigidity (21.4%), limb spasticity (9.5%), positive clonus (4.8%), hemiplegia (2.4%), and positive Kernig's sign (2.4%)[9].

Dengue encephalitis can be confirmed by demonstrating either the virus or the IgM antibodies for the same in CSF. As the infection is self-resolving, specific treatment is usually not required. Treatment includes conservative approach with fluid support and intensive monitoring[10].

Patients with dengue encephalitis run a greater risk to develop DHF/DSS. While encephalitis per se runs a benign course, the associated mortality in these patients is attributed to DHF/DSS[11]. In the six confirmed dengue encephalitis cases in Malaysia, four patients had complete neurological recovery by the seventh day of admission. One died due to multi-organ dysfunction while the other had prolonged drowsiness with residual palsy[8]. Solomon *et al* found no mortality among 21 patients with dengue encephalitis. Median coma recovery time was 3.5 days. While 15 patients had full recovery, 6 had sequelae (spastic paraparesis, post-transverse myelitis, residual spasticity, post-encephalitis, abnormal affect and personality disorder)[12].

Though dengue is raging in epidemic proportions in India, not many reports of dengue encephalitis have been reported from this region. A few cases suggestive of dengue encephalitis have been reported by Ruth and co-workers[13], and by Chauhan *et al*[14]. Recently, a case of dengue encephalitis confirmed by positive CSF serology with MRI findings of encephalitis was reported in Delhi[15].

In the present case, the patient presented with symptoms suggestive of a neurological involvement. A battery of investigations for the common causative factor for the same came to be negative. Since the patient was a resident of a dengue endemic area and his symptoms and routine investigations suggested a clinical picture of dengue fever, the patient's CSF was tested for IgM antibodies against dengue virus. A positive serology confirmed CNS infection by dengue virus.

In conclusion, neurological manifestations during dengue infection are not uncommon. The symptoms are not only due to changes such as cerebral oedema, hyponatraemia but can also be due to direct invasion of the CNS by the virus. Dengue should be considered in the differential diagnosis of acute viral encephalitis especially in the tropics where arboviral infections have reached epidemic proportions. Early intervention and prompt supportive care can reduce the morbidity and mortality among these cases.

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CASE REPORT

JIACM 2010; 11(2) : 144-5

Chédiak-Higashi Syndrome: A Rare Clinical Entity Revisited

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Introduction

Chédiak-Higashi syndrome (CHS) is a rare childhood autosomal recessive disorder of the immune system that affects multiple systems of the body. Patients exhibit hypopigmentation of skin, eyes, and hair, prolonged bleeding time, recurrent infections, easy bruisability, abnormal natural killer cell function and peripheral neuropathy. Mutations have been found in CHS1 gene or LYST and are localised to bands $1q_{42-43}$ which lead to abnormal intracellular protein transport.

The disease is often fatal in childhood as a result of infection or an accelerated lymphoma-like phase; only a few patients live to adulthood. Progressive neurological dysfunction may be the dominant feature in few of these patients.

Case report

A four-year-old child presented to the paediatrics OPD with fever, cough, and ulcers in the mouth. His father gave history of recurrent infections since birth – mostly upper respiratory tract infections or sino-pulmonary involvement. Family history was not contributory. No other sibling or family member had frequent infections or light coloured hair/patches on skin.

On examination, he had light coloured hair, hypopigmented patches on skin, aphthous ulcers in mouth, and congested tonsils. The systemic examination was unremarkable. Peripheral blood picture showed an absolute neutropenia (400/µl), coarse giant granules in neutrophils along with dot like inclusions in lymphocytes.

The child was diagnosed as Chédiak-Higashi syndrome on the basis of clinical features and peripheral blood smear findings. He was given symptomatic treatment (antipyretics and antibiotics) and discharged from the hospital after counselling of his parents.

Short review

Chédiak-Higashi syndrome (CHS) was described by Beguez Cesar in 1943, Steinbrinck in 1948, Chédiak in 1952, and Higashi in 1954. It is a rare autosomal recessive immunodeficiency disorder that affects multiple systems of the body. It is characterised by abnormal intracellular protein transport. The CHS gene affects the synthesis and/or maintenance of storage and secretory granules in various types of cells. Lysosomes of leucocytes, fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, melanosomes of melanocytes are generally larger in size and irregular in morphology. The CHS protein

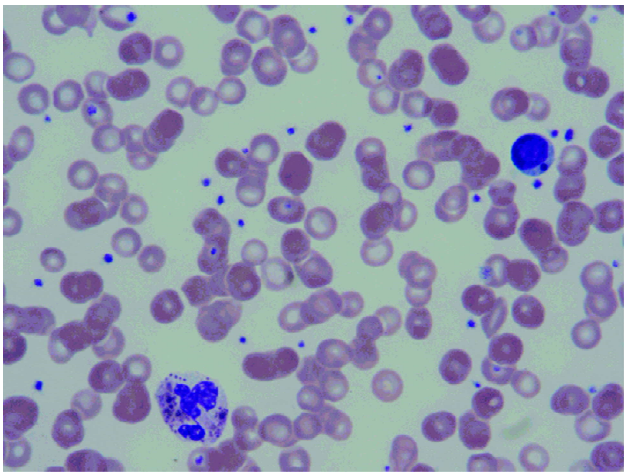

Fig. 1: *Peripheral smear of Chédiak-Higashi syndrome with giant granules in granulocytes (several granules) and lymphocytes (single abnormal granule).*

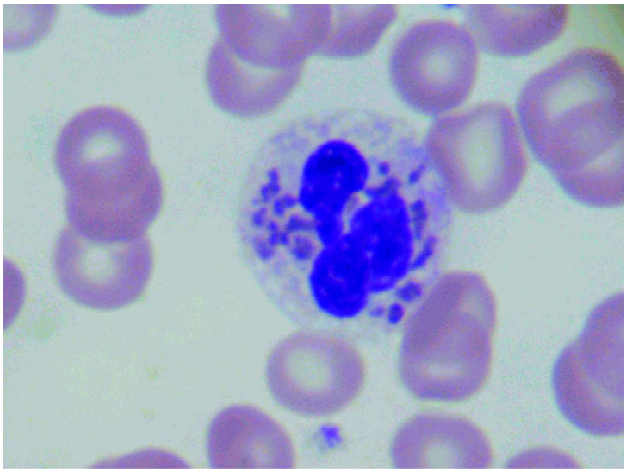

Fig. 2: *Peripheral blood smear showing giant granules in a neutrophil in Chédiak-Higashi syndrome.*

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is expressed in the cytoplasm of cells of a variety of tissues and represent an abnormality of organellar protein trafficking.

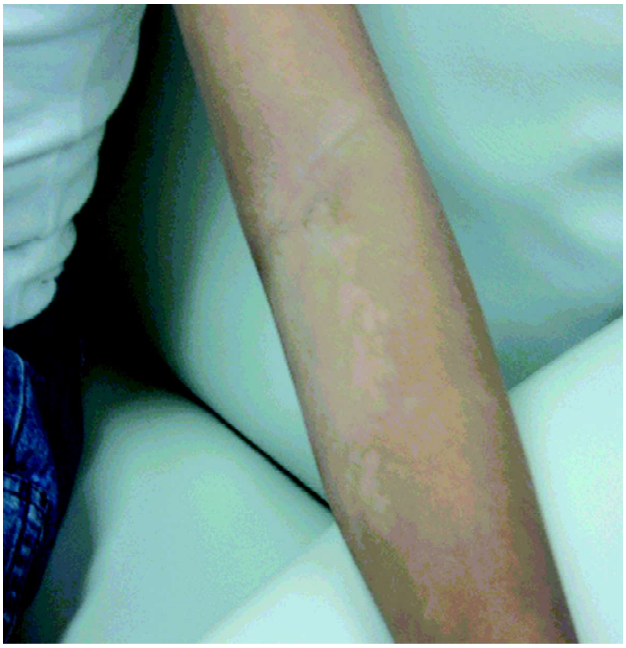

Fig. 3: *Hypopigmented patch on the patient's forearm and arm.*

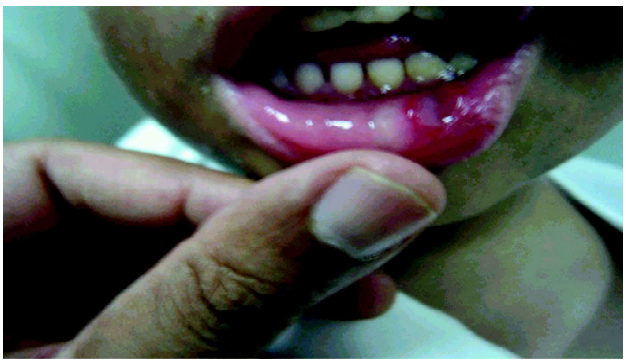

Fig. 4: *Ulcer on the mucosa of lower lip.*

Infants born with CHS have non-pigmented skin (similar to albinos) but in patchy distribution, blonde hair, and blue eyes. Symptoms usually appear soon after birth and include adenopathy, aphthae, gingivitis, hyperhidrosis, jaundice, severe and extensive pyoderma, recurrent sino-pulmonary infections, and fever unrelated to any recognisable infection. Progressive neurological deterioration is common in patients who survive early childhood. Generally such patients enter an accelerated phase of the disease causing enlargement of the liver, spleen, lymph nodes, with concurrent severe leucopenia

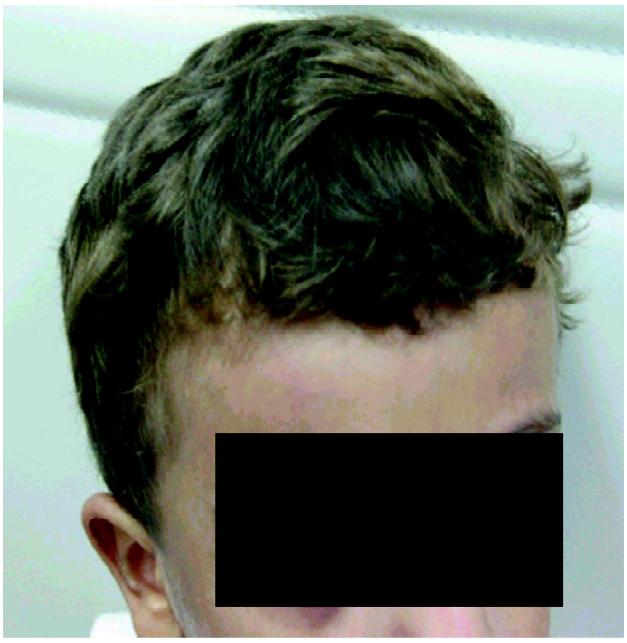

Fig. 5: *Hypopigmented hair in CHS.*

and thrombocytopenia resulting in death from infection or bleeding.

Diagnosis of CHS is made on peripheral blood smear by the presence of neutropenia; and recognition of characteristic giant granules in neutrophils, eosinophils, and single granule in lymphocyte. Bone marrow smears reveal giant inclusion bodies in leukocyte precursor cells which are peroxidase positive. Our patient had absolute neutropenia, coarse giant granules in neutrophils with single inclusion in lymphocytes.

Allogenic bone marrow transplantation from HLA-matched donor is the therapy of choice. It alleviates the immune problems and the accelerated phase, but does not inhibit the development of neurological disorders which become worse with age. Without BMT, children die before 10 years of age from infection or – less commonly – due to haemorrhage. Longer survival is possible but the lymph nodes, liver, spleen becomes enlarged and a malignant lymphoma develops. Few patients have survived 20 years of age.

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CASE REPORT

JIACM 2010; 11(2) : 147-52

Retinal Vasculitis with Rapidly Progressive Glomerulonephritis in Systemic Lupus Erythematosus

*Sourya Acharya**, SN Mahajan*, Samarth Shukla***, Pradeep Sune****, Kavita Chaudhry*****, Siddharth Subhedar******

Abstract

Retinal vasculitis is characterised by inflammation of the vessels of the retina[1]. The detection and characterisation of retinal vasculitis may help in the diagnosis and management of certain disorders associated with ocular inflammation. These include systemic autoimmune disorders, some infectious diseases, and certain ocular disorders. This case, a 22-year-old female, presented with fever since 20 days, blurring of vision in both eyes since 14 days, swelling over face and lower limbs since 10 days, and decreased urinary output since 7 days.

Key words: Retinal vasculitis, systemic autoimmune disorders.

Introduction

The classic symptom of retinal vasculitis is a painless decrease in vision. Other symptoms may include a blind spot from ischaemia-induced scotomas or floaters from vitritis. With macular involvement, patients may present with metamorphopsia (change in shape of an object) or abnormalities in colour vision. Retinal vasculitis can also be asymptomatic.

Retinal vasculitis ranges in severity from mild to severe. Damage to the blood vessels of the retina can cause minimal, partial, or even complete blindness. Retinal vascular lesions are the most common ophthalmologic manifestation of systemic lupus erythematosus (SLE), occurring in 3% to 29% of cases, generally late in the disease. More rare is the severe vaso-occlusive disease, often termed "retinal vasculitis", which includes central retinal artery occlusion, multifocal arteriolar occlusions, extensive capillary nonperfusion and central venous occlusion[2,3]. Patients with SLE and raised serum concentration of anticardiolipin antibodies have a higher risk of developing occlusive ocular vascular disease[3,4]. Ocular involvement in SLE is an indicator of active systemic disease, most importantly nephropathy and cerebral lupus[5].

Case report

A 22-year-old female presented with fever since 20 days, blurring of vision in both eyes since 14 days, swelling over lower limbs and face since 10 days, and oliguria since 7 days (Figs. 3 - 6). There was no history of haematuria, pain in abdomen, distention of abdomen, chest pain, dysnoea, haemoptysis, arthralgia and sore throat prior to the fever. There was no history of seizures. She was newly married. Her menstrual history and past history was insignificant.

On clinical examination, her blood pressure was normal, tachycardia was present, pallor was present, there was no glossitis or koilonychia. JVP was normal. Bilateral oedema of feet (pitting type) and puffiness of face was present. There was no rash, oral ulcers, arthritis. Systemic examination was normal. Ophthalmologic examination showed bilateral diminution of vision with visual acuity limited to finger counting upto 3 meter distance.

On investigation, haemoglobin was 11 gm%, TLC was 2,800/mm^3, platelet count was 2,80,000/µl. Urine analysis revealed proteinuria (+++), few RBCs (4 - 5) per high power field, 24-hour urinary protein was 2.7 gm/dl, serum urea 62 mg%, and serum creatinine of 3.4 mg%. HIV I and II by ELISA was negative. Serum ASO titre was negative. Serum ANA 4.08 (> 1 is positive) and dsDNA 58.42 (> 20 is positive) were strongly positive.

Fundus examination revealed multiple retinal haemorrhages, cotton wool spots bilaterally (Figs. 1, 2).

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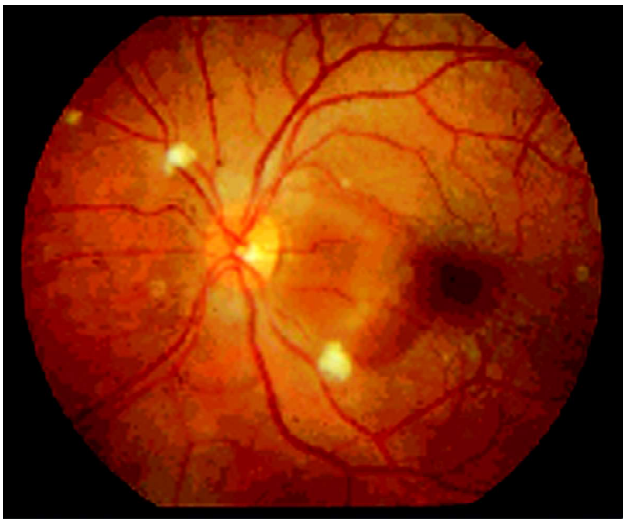


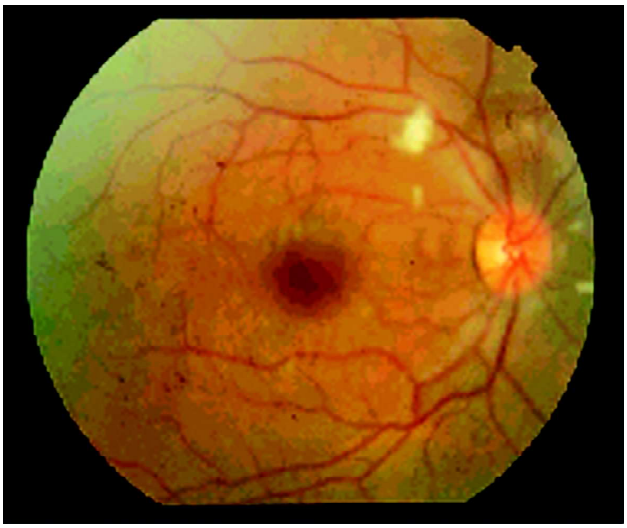


Fig. 1 and 2: *Fundus showing multiple cotton-wool spots and haemorrhages highly suggestive of retinal vasculitis.*

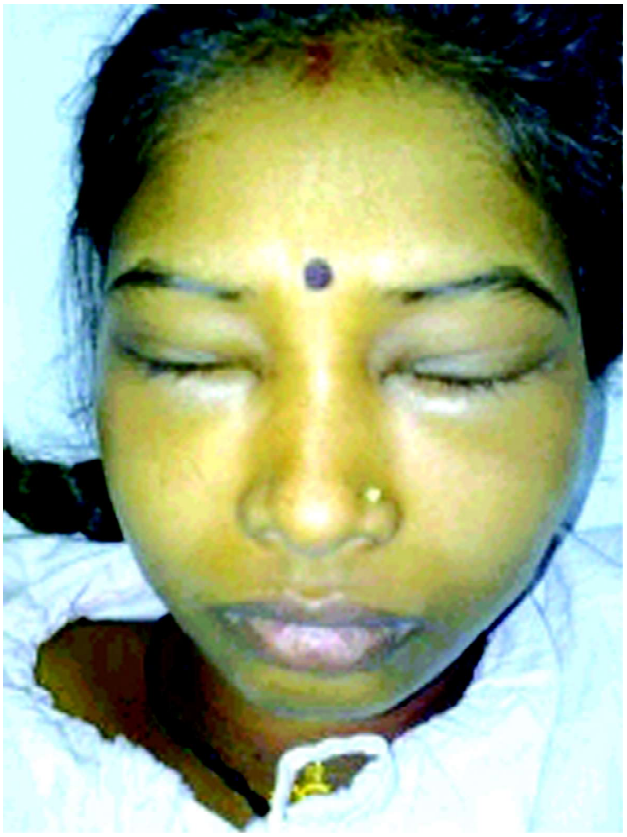


Fig. 3:

Kidney biopsy was done in view of rapidly deteriorating renal function with increased serum creatinine levels. It revealed features of membranous glomerulonephritis with formation of subepithelial crescents suggestive of RPGN (Figs. 7 – 11). Our case was fulfilling the criteria for

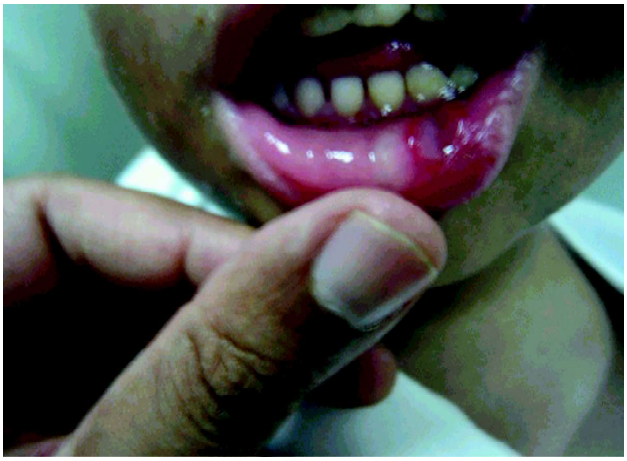
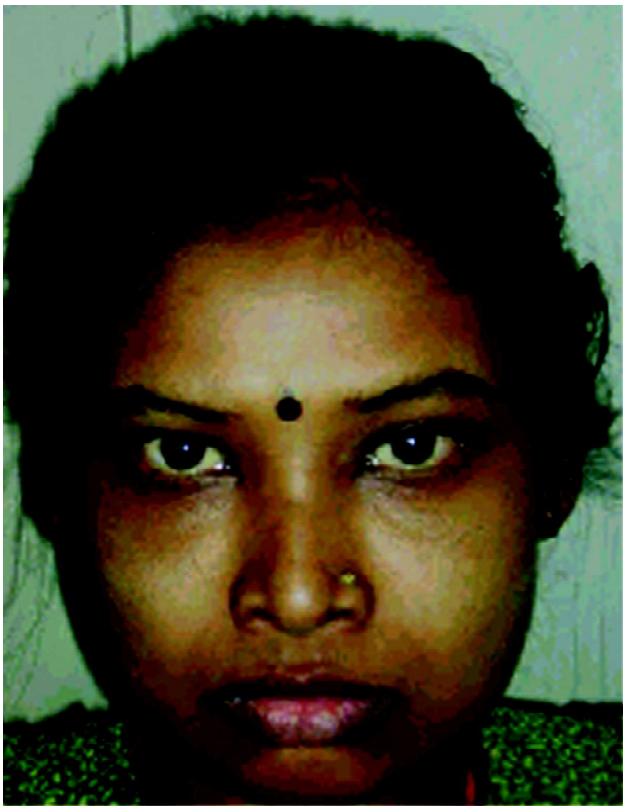


Fig. 4:

diagnosis of SLE by the American Rheumatologic Association. She was started on intravenous methyl-prednisolone 1 gm daily for 3 days followed by oral prednisolone 1 mg/kg/day with diuretics and ACE-inhibitor therapy. After 15 days, her oedema subsided, proteinuria reduced (24-hour urinary protein was 1.7 gms), urine output increased and vision improved to 6/24. Serum creatinine after 2 weeks decreased to 0.67 mg%. The patient was discharged with 40 mg prednisolone and was told to come for follow-up after 2 weeks.

Discussion

Retinal vascular manifestation is the most common form of ophthalmic involvement in patients with systemic lupus erythematosus (SLE). Most frequently, these consist of



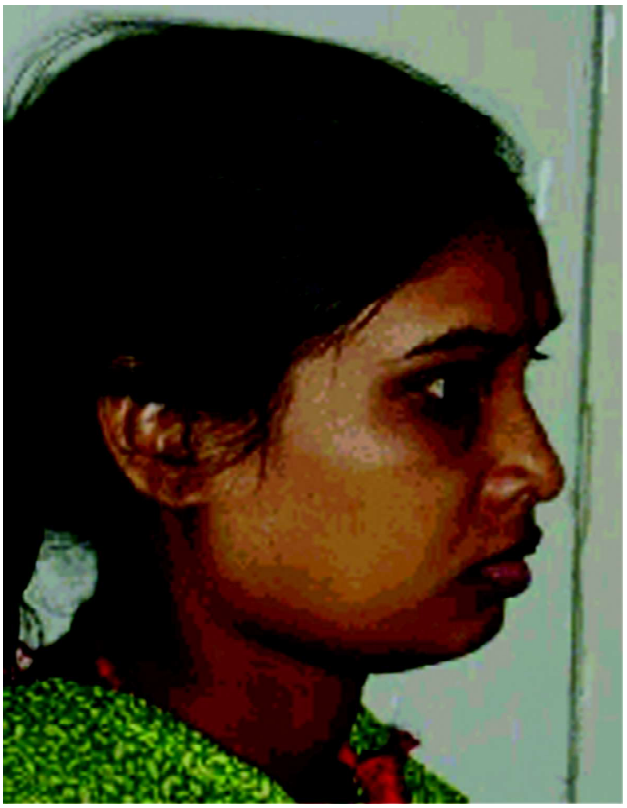


Fig. 6:

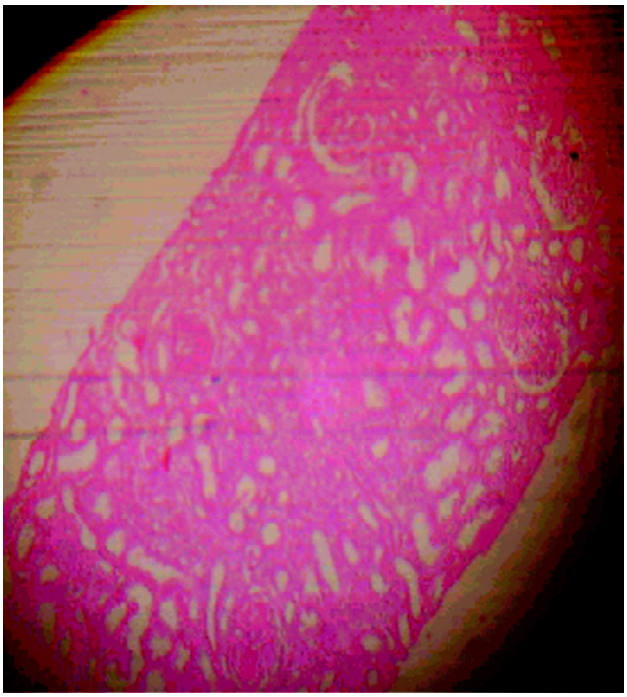


Fig. 7: *Renal biopsy (scan).*

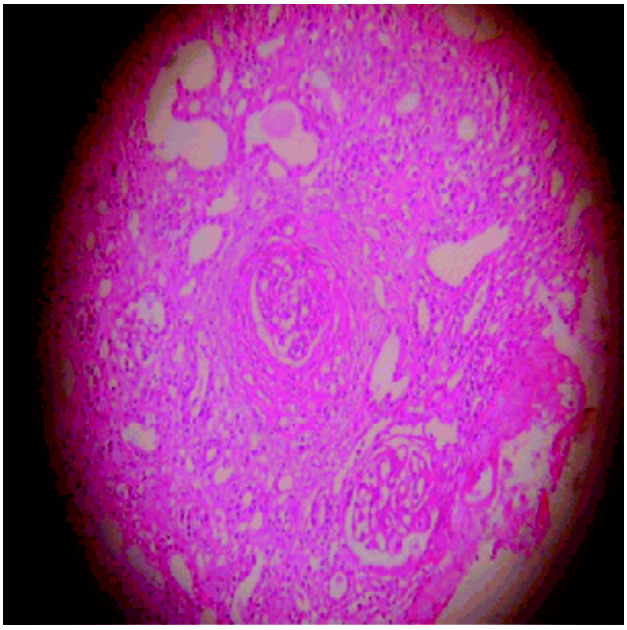


Fig. 8: *Scan view – pathological glomeruli.*

cotton-wool spots with or without intraretinal haemorrhages[2, 5, 6].

Retinal vasculitis is an inflammatory disease of the blood vessels of the retina that may be associated with primary ocular conditions or with inflammatory or infectious diseases in other parts of the body (systemic diseases).

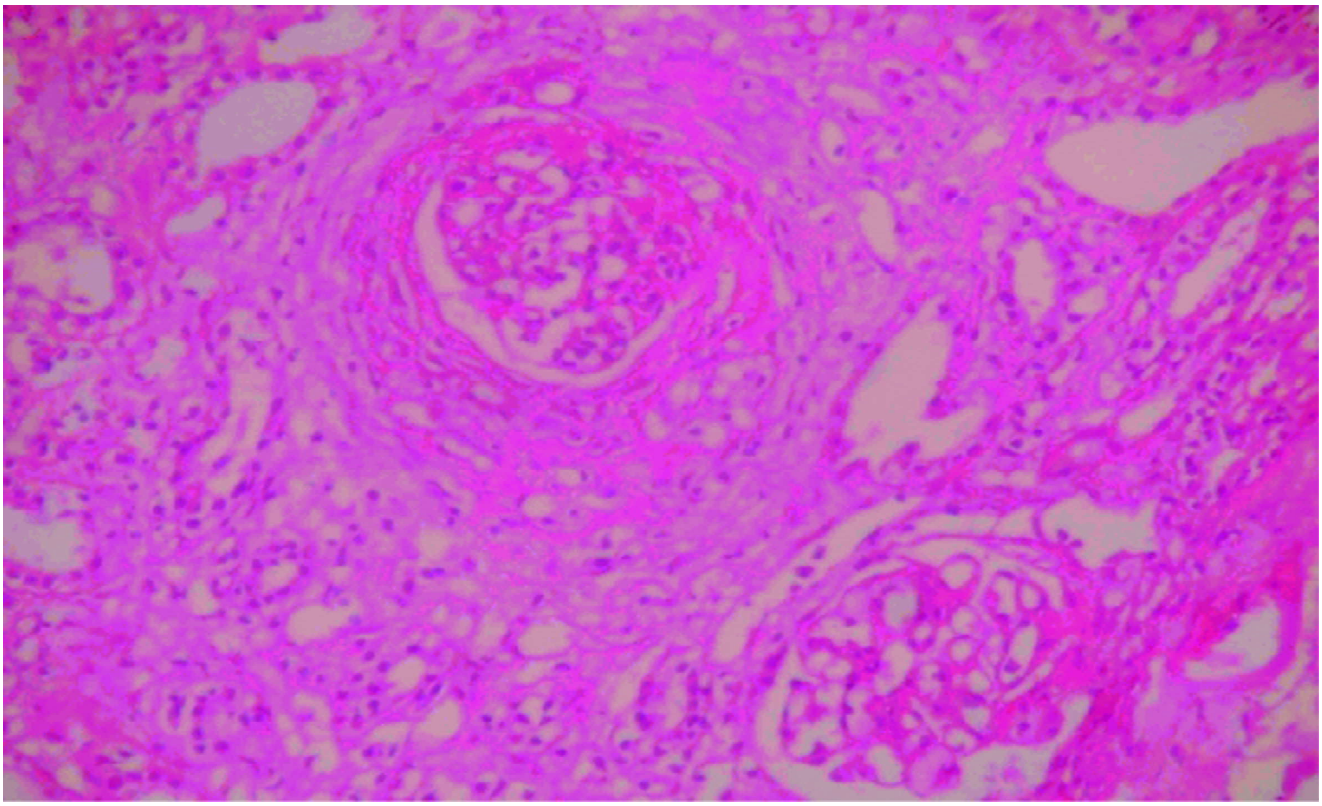


Fig. 9: *HPE showing crescentic and membranous glomerulonephritis (10x view).*

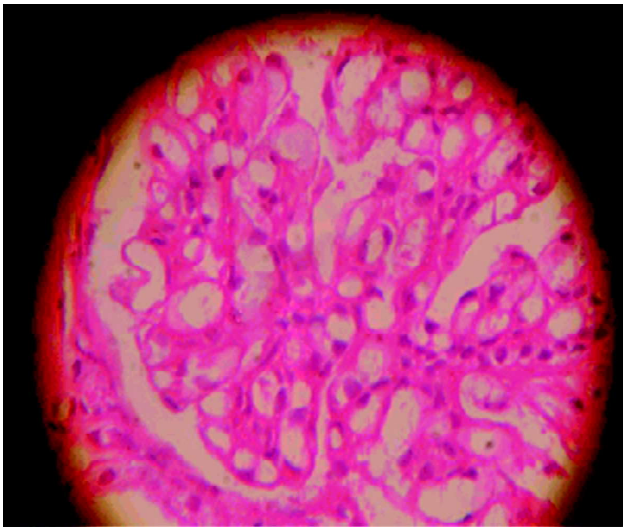


Fig. 10: *HPE showing crescentic glomerulus (40x view).*

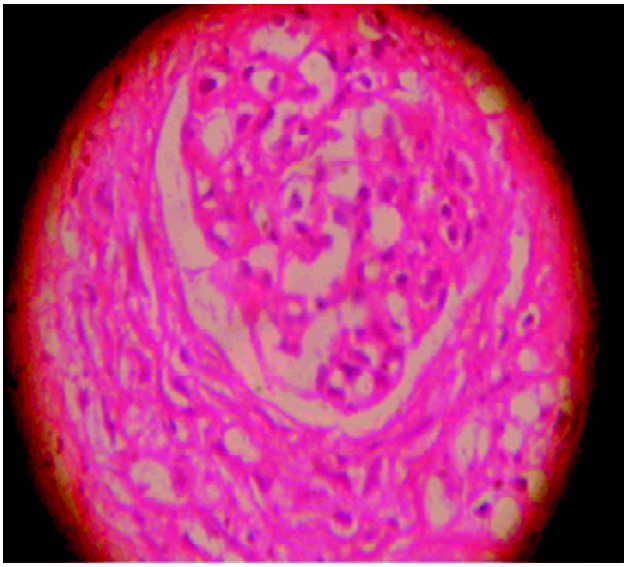


Fig. 11: *HPE showing membranous glomerulus (40x view).*

The most common systemic diseases associated with retinal vasculitis are Behçet's disease, sarcoidosis, and multiple sclerosis. Associations have also been noted with Wegener's granulomatosis, systemic lupus erythematosus, polyarteritis nodosa, and other rheumatologic conditions. Infectious agents which may produce a retinal vasculitis include bacteria (for example syphilis or tuberculosis), viruses (for example herpes family viruses), and parasites (including *Toxocara canis*). Primary ocular causes of retinal vasculitis include Eales disease, pars planitis, birdshot retinochoroidopathy, and Fuchs uveitis syndrome.

In SLE, almost any part of the eye can be involved by a thrombotic or inflammatory process. Optic neuritis, ischaemic optic neuropathy are also commonly seen. Scleritis and retinal vasculitis require systemic steroids and/or immunosuppressive therapy.

It is unfortunate that ophthalmologic manifestations are not included in the diagnostic criteria of SLE. It is not uncommon to see patients who have not been diagnosed with SLE, who have developed an ocular manifestation in advance of diagnosis of SLE (like in this case, visual symptoms preceded symptoms of nephropathy). Development of retinal vasculitis in a patient of SLE is the harbinger of increased systemic disease activity – especially nephropathy and CNS lupus[5]. SLE patients with retinal involvement have significantly decreased survival compared with SLE without retinal involvement[7]. The classic finding of lupus retinal vasculitis is cotton wool spots[4,5]. Majority of patients have non-proliferative disease. Severe visual loss is not markedly seen in this group, whose retinopathy improves with corticosteroid/immunosuppressive therapy[2]. In our patient, nephropathy was also present. SLE represents the most frequent cause of renal involvement. The choriocapillaris-Bruch membrane retinal pigment epithelium complex is morphologically similar to glomerular basement membrane (GBM); they are stucturally homologous, selectively permeable with positive charge. Both have high content of heparan sulphate, the only difference being the collagenous zone of Bruch membrane which is thicker than the GBM[8].

The histopathlgical report (Fig. 3) of kidney biopsy in our patient revealed features of membranous nephritis with crescentic nephritis, i.e., RPGN (uniform thickening of GBM along peripheral capillary loops with subepithelial crescent formations). RPGN is a clinico-pathological syndrome characterised by acute crescentic GN with rapidly progressive renal failure secondary to any systemic disease, infection or it can be idiopathic. Clinical presentation, serological tests and renal biopsy confirms the diagnosis and underlying disease. Immunofluorescence microscopy divides RPGN into 3 categories (types I, II, III) according to the patterns of the immune complex deposits. SLE typically causes type II RPGN (granular deposits on GBM)[9]. RPGN in SLE is characterised by deposition of IgG in GBM. The renal presentation is highly variable. The serum dsDNA levels consistently correlate with disease severity, histopathology, clinical course, and response to therapy[9]. Of the types of lupus nephritis, the worse prognosis is associated with class IV (diffuse proliferative GN)[10,11].

Membranous lupus nephritis is the only form in which proteinuria may be the only dominant manifestation without significant urinary sediments, red cell casts (like in this case).

Conclusion

SLE is a multisystem immune disorder. Ocular manifestation can occur, though it has not been included in the diagnostic criteria. Ocular involvement indicates high systemic disease activity. Severe retinal disease may lead to blindness if not detected and treated early in the course of the disease. So every patient of SLE – irrespective of visual symptoms – should undergo ophthalmogical examination. Renal involvement can occur at any time during the course of the disease. It can be silent. Though renal biopsy is not necessary in SLE patients whose renal function is rapidly deteriorating when they have active urinary sediment, it becomes necessary in atypical presentations not defining a pure nephritic or nephrotic syndrome and/or rising serum creatinine to levels more than 3 mg%, so that early diagnosis will lead to prompt initiation of management. Biopsy is also indicated when rapidly deteriorating renal disease does not respond to prompt initiation of glucocorticoid therapy. Lastly, patients with mild clinical disease should have a biopsy to determine if they have active, severe, inflammatory lesions, which might respond to therapy.

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CASE REPORT

JIACM 2010; 11(2) : 153-4

Wegener's Granulomatosis Masquerading as Trigeminal Neuralgia

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Abstract

Here, we are reporting a case of Wegener's granulomatosis with trigeminal neuralgia for its rarity and unusual presentation. Although trigeminal neuropathy has been reported in patients of systemic lupus erythematosus, Sjögren's syndrome, scleroderma, and mixed connective tissue disorder, yet to the best of our knowledge, trigeminal neuralgia as an initial presenting neurological feature of Wegener's granulomatosis is a rarity.

Key words: Wegener's granulomatosis, trigeminal neuralgia, vasculitis, initial.

Introduction

Vasculitis is a clinicopathologic entity characterised by a compromise of the vascular lumen as a consequence of inflammatory damage to the vessels resulting in ischaemic injury to the affected tissue. Vasculitis may be primary or secondary. It may be confined to single organ or involve multiple organs simultaneously[1].

Wegener's granulomatosis is a primary form of vasculitis characterised by vasculitic affliction of the upper and lower respiratory tracts alongwith the kidneys. Nervous system involvement, though uncommon, is characterised by cranial neuritis, exophthalmos, vestibulopathy, deafness, intracranial sinovenous thrombosis, intracerebral/subarachnoid haemorrhage, seizures, cerebritis, diabetes insipidus, myopathy, peripheral neuropathy, and rarely intracranial granulomas. A limited form of Wegener's granulomatosis is conspicuous by the absence of renal involvement[2-7]. Although trigeminal neuropathy in various systemic vasculitides has been reported, yet trigeminal neuralgia as an initial presenting neurological feature of Wegener's granulomatosis is a rarity[6,7].

Case

A 52-year-old black male presented with paroxysmal, neuralgiform pain on the left side of his forehead and upper half of face for the last nine months. This was followed within a six weeks period by redness of the left eye, excessive lacrimation, and intermittent bleeding from left nostril. Two months later, he developed erythematous rash on the left side of his face and nose. About four months prior to onset of the left hemifacial pain, the patient had developed gangrene of his left big toe which was subsequently amputated after routine investigations including collagen profile which were found to be unremarkable. There was no history of fever, arthritis, rash on any other part of body, hypertension, diabetes mellitus, tuberculosis, application of any chemical agent to face, haemoptysis, haematuria, or any drug intake prior to onset of illness. The patient had quit smoking one year earlier. General physical examination revealed erythematous, papular rash on left upper portion of the face and nose. Systemic examination was noncontributory except for neurological evaluation which revealed diminished tactile and thermal sensations in ophthalmic and maxillary nerve distribution on the left side. Left conjunctival and corneal reflexes, too, were absent. Ophthalmological evaluation was conspicuous by anterior uveitis as evidenced by the presence of anterior chamber flare, posterior synechiae formation and pigment deposition on the lens on slit-lamp examination. Otorhinolaryngological examination showed nonpigmented nasal mucosa on left side with loss of lower lateral cartilage of ala alongwith mucosa and overlying skin. Routine investigations including haemogram (except mild anaemia and elevated ESR), urinalysis, kidney function tests, chest skiagram, high resolution computed tomographic scan of chest, paranasal sinus radiography, and abdominal ultrasonography were normal.

Antineutrophil cytoplasmic antibody (c-ANCA) was positive, but ANA and anti-dsDNA, antiphospholipid antibody, serum VDRL, hepatitis serology, lipid profile, and CSF analysis were unremarkable. Serum cryoglobulins were absent whereas serum electrophoresis showed IgA hypergammaglobulinaemia. MRI scanning of brain including osteomeatal complex revealed bilateral maxillary polyps with right basal ganglionic lacunar infarct. Histopathological examination of affected nasal mucosa and adjoining skin showed infiltration by inflammatory cells (polymorphs,

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eosinophils) admixed with proteinaceous material and acanthotic squamous epithelium. Medium-sized vessels showed evidence of fibrinoid necrosis with inflammatory cell infiltration and features of vasculitis (Fig. 1). The histopathological features were suggestive of Wegener's granulomatosis.

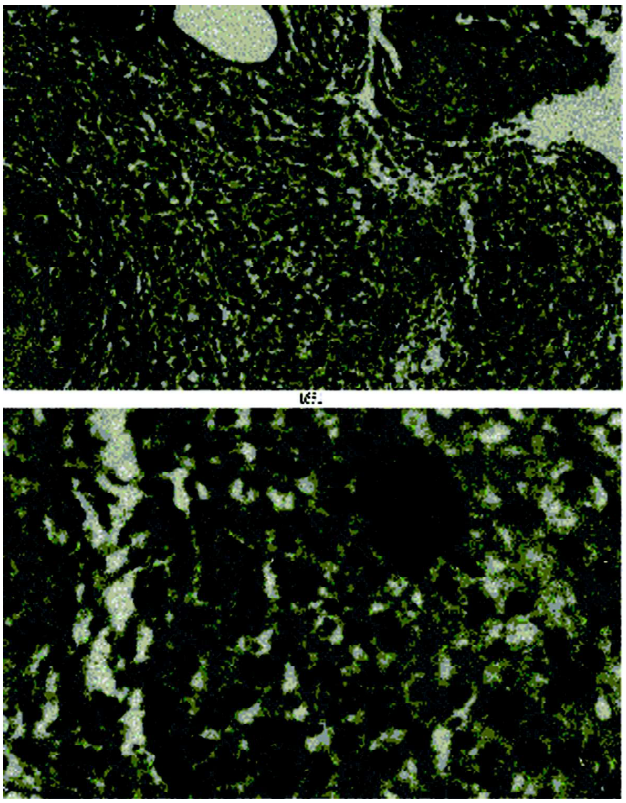

Fig. 1: *HPE of nasal mucosa and adjoining skin showing features suggestive of Wegener's granulamatosis.*

Discussion

Wegner's granulomatosis, an uncommon form of vasculitis, is rare in blacks and has equal gender distribution.

Involvement of upper respiratory tract including paranasal sinuses is seen in 95% of cases. Paranasal sinus involvement is characterised by sinus pain, purulent/ bloody nasal discharge, nasal mucosal ulceration, and septal perforation. Pulmonary manifestations of the disease like cough, dyspnoea, haemoptysis, pleuritis, pulmonary infiltrates and nodules are found in about 90% of patients. Ophthalmic involvement seen in about one-half of cases is characterised by conjunctivitis, dacrocystitis, episcleritis, scleritis, proptosis, eye pain, sclerouveitis, and ciliary vessel vasculitis. Dermatological lesions found in 15 to 45% cases comprise of papular rash, vesicles, palpable purpura, subcutaneous nodules with histopathological evidence of vasculitis[7]. Antineutrophil cytoplasmic antibody (c-ANCA) is positive in about 90 - 95% cases[8]. Nervous system involvement seen in about one-fifth of the cases, is manifested apart from other features, by cranial neuritis, peripheral neuropathy, and cerebral vasculitis. Our patient had features of secondary left trigeminal neuralgia as was corroborated by male sex, objective involvement of ophthalmic and maxillary divisions of the trigeminal nerve with neuroradiological, laboratory, and histopathological features of a limited form of Wegener's granulomatosis. Left basal ganglionic infarct can be attributed to the concurrent cerebral vasculitis as the patient had no other identifiable risk factor for lacunar stroke. Trigeminal neuropathy can be accounted for by vasculitis-induced focal demyelination of the nerve at the trigeminal root entry zone or cisternal portion of the nerve or gasserian ganglion where motor and proprioceptive fibres bypass the sensory root. This focal demyelination results in ephaptic impulse transmission which may be responsible for neuralgiform pain.

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CASE REPORT

JIACM 2010; 11(2) : 157-60

Hypercalcaemic Crisis: A First Presentation of Secondary Metastases to Skull with Cancer of Unknown Primary

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Abstract

Hypercalcaemic crisis is a life-threatening condition that is currently rather rare[1]. Hypercalcaemic crisis is a condition involving the decompensation of hypercalcaemia, which could have existed for a longer period or could be acute at the first instance of this electrolyte disturbance[2,3]. We report a case of hypercalcaemic crisis which was a first presentation in a patient of metastatic carcinoma in skull bone with unknown primary cancer.

Introduction

Hypercalcaemic crisis or severe hypercalcaemia represents a life-threatening emergency. The most common cause is hypercalcaemia of malignancy[4], although compensated hypercalcaemia is caused by malignancies in 70% of cases, by primary hyperparathyroidism (pHPT) in 20% of cases, and by other (rarer) conditions in the remaining 10%[5]. Granulomatous diseases, previously undetected primary hyperparathyroidism, medication-induced hypercalcaemia, and a few rarer causes may result in this endocrine emergency as well. Hypercalcaemia may decompensate from a more or less chronic status into a critical and life-threatening condition, hypercalcaemic crisis[7]. The leading symptoms that characterise the crisis are oliguria and anuria as well as somnolence and coma[7]. After a hypercalcaemic crisis is recognised, an emergency diagnostic programme has to be followed either to prove or to exclude primary hyperparathyroidism. The diagnostic programme should be performed within hours; during this time, serum calcium should be lowered. Treatment of choice is haemodialysis against a calcium-free dialysate[10,11,12]. Bisphosphonates could be useful as adjuvant drugs[3].

Case report

A 36-year-old female patient was admitted to the emergency department of Dr. RML Hospital, New Delhi, in a state of altered sensorium since the last two days. According to her husband, she was apparently well two days back, when she developed insidious onset altered sensorium following nausea and two episodes of vomiting. There was no h/o of fever/headache/head trauma/poisonous substance intake. No history suggestive of diabetes/hypertension/heat stroke/ sedative intake. There was h/o low back pain for two months on and off for which the patient was taking analgesics. No h/o vaginal discharge or bleeding per vaginum. On examination, her general condition was critical, Glasgow Coma Scale was 7/15 ($E_2V_1M_4$). Pulse was 84/min, BP-150/90 mmHg mild pallor was present, no icterus/clubbing/cyanosis/oedema/fever. Lymph nodes were palpable in the left axilla (medial and anterior group: multiple, hard). Thyroid was normal; hydration was normal, no rashes, and no evidence of bleeding from any site. There was a swelling present in scalp on left fronto-

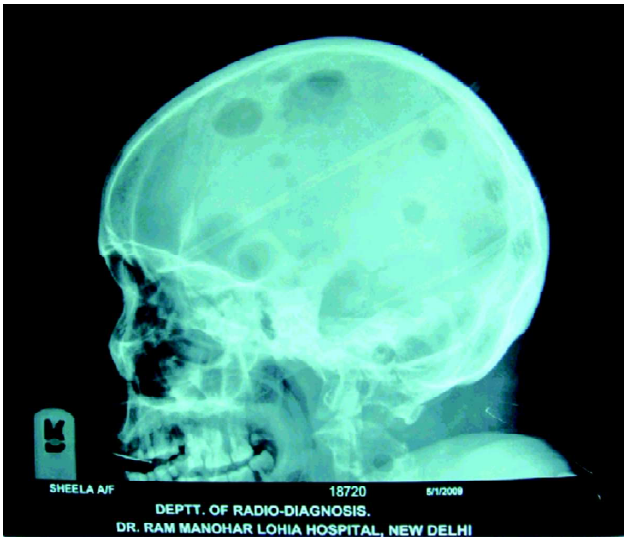

Fig. 1: *X-ray of skull showing multiple lytic lesions.*

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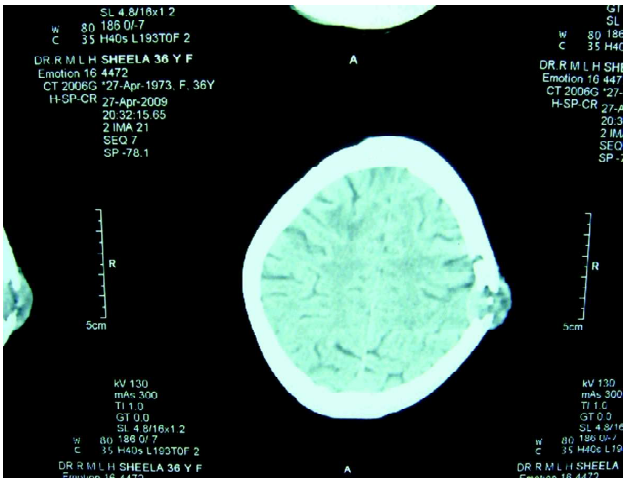

Fig. 2: *CT scan of head showing secondary metastasis in skull bone.*

temporal region (5.0 x 4.0 cm in size, firm in consistency). Breast examination revealed a hard lump of 5.0 x 3.0 cm in outer and upper quadrant of left breast, no signs of inflammation on skin over it. Respiratory and cardiovascular systems were within normal limits P/A examination – mild hepatomegaly was present. Central nervous system examination – patient was unconscious, signs of meningeal irritation were absent, no focal neurological deficit, plantar reflexes were B/L flexor, and pupils were B/L normal in size and reaction. Gynaecological examination was normal. Investigations – Hb: 9.5 gm%, TLC: 21,800/cumm, DLC: P-85, L-10, M-3, E-2, ESR: 10 mm in 1st hour, platelets: 2,40,000/cumm, PS: RBCs normocytic, normochromic, no haemoparasite, no toxic granules, blood sugar (F): 108 mg/dl, (PP): 138 mgs, urine – alb: nil, sugar: nil, RBC: 1 – 2/HPF, pus cells 0 – 2/hpf, S. cr: 5.4 mg/dl, B. urea: 165 mg/dl, S. Na^{+}/K^{+}140/4.5 meq/lit, S. ca^{++} 15.3 mg/dl, S. phosphate: 6.8, S. protein: 7.0 gm/dl. Alb: 2.2, Glob: 4.8, (albumin corrected s. calcium was16.74), S. bil: 0.5 mg/dl (T) 0.2 (D) 0.3 (I), SGOT/SGPT: 26/20 IU/L. S. iron: 54 mcg/dl, TIBC: 209, saturation: 25.8%. Serum parathormone level: 3.3 pg/ml (N-14.0 – 72.0 pg/ml), S. ammonia: 12 (normal). Thyroid function was normal. Serum protein electrophoresis was normal, 'M' band was not present. Bence Jone's protein in urine was not present, urine culture: sterile, blood culture: sterile, HIV: nonreactive, HbsAg: nonreactive, antiHCV (IgG): nonreactive. CSF- protein: 40 mg/dl, sugar: 70 mg/dl, TLC: no cells. Bone marrow – there was a small poorly cohesive cluster of large cells interspersed among marrow cells with high N: C ratio with a small amount of cytoplasm, nuclei are prominent, findings suggestive of metastasis to bone marrow (? epithelial malignancy). FNAC (scalp swelling) – group of highly pleomorphic large cells with orangeophilic cytoplasm showing a squamoid differentiation. The cytological features suggestive of metastatic carcinoma, showing squamous differentiation. Pap smear was normal. FNAC from left breast lump – smear showed groups and singly scattered highly pleomorphic large cells with high N:C ratio and prominent macronucleoli, showing squamous differentiation, the cytological features are suggestive of metastatic malignant tumour with squamous differentiation.

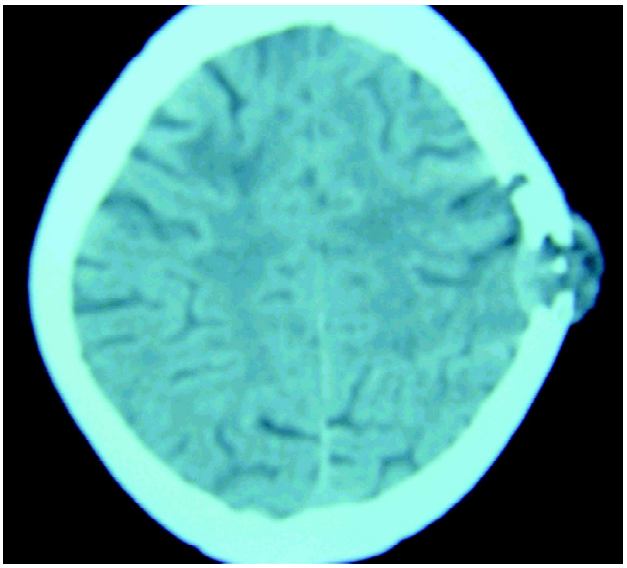

Fig. 3: *CT scan of head showing secondary metastasis in skull bone with normal brain parenchyma.*

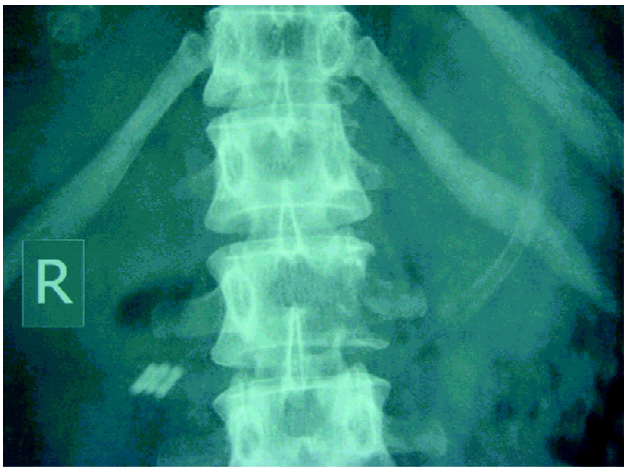

Fig. 4: *X-ray of lumbar spine showing lytic lesion in L_2 vertebra.*

X-ray chest – bronchovascular markings were prominent, and heart size was normal; X-ray skull showed multiple punched-out lytic lesions, X-ray spine – ill-defined lytic lesion in body of L_2 vertebra. USG abdomen – mild hepatomegaly, no retroperitoneal lymphadenopathy, pelvic organs were normal. CT scan head – multiple bony gaps seen in skull bone, hypodense areas present in these gaps, brain parenchyma appears normal. Findings suggestive of secondary metastases in skull bones. CECT thorax and abdomen could not be done due to deranged renal function test (S. cr: 5.4 mg/dl, B. urea: 165 mg/dl) and critical condition of patient. In view of the clinical examination and investigation findings, a diagnosis of hypercalcaemic crisis due to secondary metastasis with unknown primary was made, and treatment started with intravenous normal saline. Loop diuretics were given after maintaining hydration. Serum calcium and other electrolytes were measured frequently. Serum calcium level decreased from 15.3 mg/dl to 13.5 mg/dl after 48 hours of treatment. Zoledronic acid was given to further decrease the calcium level which decreased to 11.5 mg/dl after 3 days. The patient improved and her GCS became 10/15 ($E_3V_3M_4$). Later on, the patient expired due to sudden cardiac arrest.

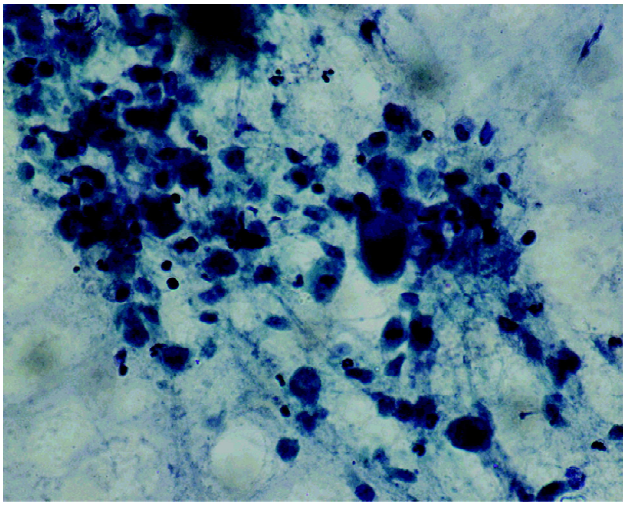

Fig. 5: *FNAC of scalp swelling showing a group of highly pleomorphic large cells with orangeophilic cytoplasm showing a squamoid differentiation suggestive of metastatic carcinoma.*

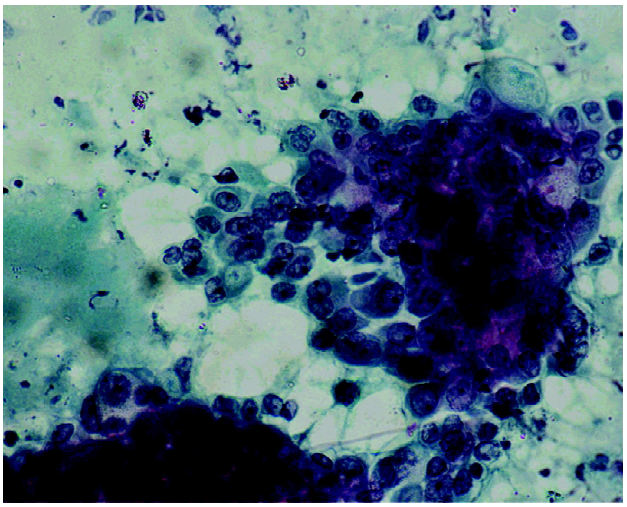

Fig. 6: *FNAC of breast lump shows groups and singly scattered highly pleomorphic large cells with high N:C ratio and prominent macronucleoli, showing squamous differentiation, the cytological features are suggestive of metastatic malignant tumour with squamous differentiation.*

Discussion

We describe a case of fatal, decompensated hypercalcaemia (hypercalcaemic crisis) caused by a secondary metastatic carcinoma in skull and other bones, whose primary cancer was unknown. The cancer of unknown primary accounts for 3 – 5% of all human cancers[3]. The standard diagnostic procedure[3] for the majority of patients includes histopathologic review of biopsy specimens with the use of immunohistochemistry, chest radiography, computed tomography of the abdomen and pelvis, and in certain cases mammography, fail to identify the primary. The four common histologic diagnoses are: adenocarcinoma (70%), poorly differentiated carcinoma (20%), squamous cell carcinoma (10%), and poorly differentiated neoplasm (5%)[3]. The prognosis for most patients with unknown primary tumours is poor, with survival often less than 6 months from diagnosis[3]. In females, the breasts and lungs are the most common primary disease sites; approximately 80% of cancers that spread to bone arise in these locations[12]. In males, cancers of the prostate and lungs make up 80% of the carcinomas that metastasise to bone, the remaining 20% of primary disease sites in patients of both sexes are the kidney, gut, and thyroid, as well as sites of unknown origin[12]. Most patients with metastatic bone disease survive for 6 – 48 months[14]. In general, patients with breast and prostate carcinoma live longer than do persons with lung carcinoma[14]. Patients with renal cell or thyroid carcinoma have a variable life expectancy. Hypercalcaemia is the result of excessive

skeletal calcium release, increased intestinal calcium absorption, or inadequate excretion of calcium. The two most common conditions that account for 90% of patients with hypercalcaemia are primary hyperparathyroidism and cancer[14]. Malignancies such as multiple myeloma, lymphoma, and metastatic breast cancer can invade bone and cause direct bone reabsorption leading to hypercalcaemia. Other malignancies can release parathyroid hormone-like substances that cause hypercalcaemia. Rarer causes of hypercalcaemia include use of thiazide diuretics, lithium therapy, excessive vitamin D intake, immobilisation, hyperthyroidism, and complicated renal failure[14]. Hypercalcaemic crisis is a rare manifestation and is characterised by calcium levels usually above 15 mg/dl and severe symptoms of hypercalcaemia, particularly central nervous system (CNS) dysfunction[7]. Abdominal pain, pancreatitis, peptic ulcer disease, nausea, and vomiting are also seen more commonly in these patients[6,7]. The mechanism whereby a crisis develops is not clear, but dehydration, intercurrent illness, and possibly infarction of parathyroid adenoma in some patients all play roles. Patients with calcium levels greater than 14 mg per dl or symptomatic patients with calcium levels greater than 12 mg per dl should be immediately and aggressively treated[3]. The safest and most effective treatment of hypercalcaemic crisis is saline rehydration followed by furosemide (Lasix) diuresis, calcitonin, and bisphosphonates[10,11,12]. Most cases of hypercalcaemic crisis are reported in primary hyperparathyroidism[9]. Several studies have found excessive mortality in hypercalcaemic crisis in patients with hyperparathyroidism, with most of the excess caused by cardiovascular disease. The largest study included 4,461 patients and measured an increased mortality risk of 1.71 for men and 1.85 for women[9]. Studies of hypercalcaemic crisis in malignancy are few. Edelson GW *et al*[4] described a similar hypercalcaemic crisis in malignancy. Kar *et al*[2] described that acute severe hypercalcaemia may be the first presentation of malignancy, as in our case. Our case is a typical case of hypercalcaemic crisis, which was the first presentation of this oncological emergency. Distant metastases are usually a late complication of any malignancy, but in our case this is an initial presentation of malignancy which is rare. Hypercalcaemic crisis is a rare first presentation of a malignancy. A similar rare case has been presented here. As hypercalcaemic crisis has very high mortality (50%), immediate diagnosis and aggressive treatment is mandatory.

Conclusion

Acute severe hypercalcaemia (hypercalcaemic crisis) may be the first presentation of malignancy. It should be diagnosed immediately and treated accordingly to save the life of the patient from this oncological emergency.

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