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VIEWPOINT

JIACM 2015; 16(3-4): 182-3

Human mind and quantum healing

*BM Hegde**

"The impossibility of conceiving that this grand and wondrous universe, with our conscious selves, arose through chance, seems to me the chief argument for the existence of God."

– Charles Darwin 1809 - 1882.

Human body is an extension of the human consciousness. The latter is what should be considered human mind. Unlike what we have learnt and are taught, mind is not inside the brain. Human brain, despite the billions of neurones, or nerve cells and their connections called synapses, cannot account for the mind. The mind is not even in the body but mind is all over extending even beyond us into the universal consciousness of which we are individual parts.

Consciousness is fundamental and all else is derived from consciousness. It was Wilder Penfield, a Nobel Prize winning Canadian neurosurgeon, who is the father of the concept which put mind inside the brain by his experiments during neurosurgical operations on a waking patient. He was very proud of his discovery up until his wisdom grew and he realised his mistakes to write thus in 1958: "None of the actions that we attribute to the mind has been initiated by electrode stimulation or epileptic discharges…. there is no area of the grey matter as far as my experience goes, which local epileptic discharge brings to pass what could be called mind action…. what the mind does is different. It is not to be accounted for by any neuronal mechanism that I can discover…. To expect the highest brain mechanism or any set of reflexes; however, complicated, to carry out what the mind does, and thus perform all the functions of the mind, is quite absurd."The mind is the canvas on which our thoughts are projected and is a part of our consciousness. Our body is a holographic projection of our consciousness. Therefore, we should have complete control over our bodies if we try[1].

The universal consciousness is that vital energy that runs this world which we can call as 'All that is'– which believers call 'God' and scientists call 'consciousness'. Quantum physics, which turned conventional solid state physics upside down, has an important principle which is that our thoughts determine reality. Early in the 1900s they proved this beyond a shadow of a doubt with an experiment called the double slit experiment. The observer's awareness determines the behaviour of energy at the quantum level. This universe is only our perception. There is no perception without a perceiver. Similarly all living things have their perceptions. While we have our individual universe they have theirs. So to be precise, we live in a multiverse and not a universe. This is well brought out in that beautiful book by Rupert Sheldrake – *Dogs That Know When Their Owners Are Coming Home*[2]. Consciousness is not contained within the world or matter. Consciousness contains all matter and the world. The universe is therefore, a unified living process. It resembles a hologram. All our advances in material sciences have been external development. We need to look inside for enlightenment which the Eastern sages and rishis have been preaching and practising for eons for peace, tranquillity and happiness for themselves and society in general. Spirituality, therefore, is just sharing and caring for others and in the bargain getting and giving happiness to our fellow humans.

In a special collection of articles published beginning 1 July 2005, *Science* magazine celebrates the Journal's 125th anniversary with a look forward — at the most compelling puzzles and questions facing scientists today. A special, free news feature in *Science* explores 125 big questions that face scientific inquiry over the next quarter-century. Most of these questions, of course, could be answered in Eastern philosophy and in teleology[3]. Nobel Laureate Peter Medawar, pioneer in tissue transplants, in his book *Limits of Science* asks some of those questions and answers them in his own inimitable style. He feels that science is only an enterprise like religion which has been designed to answer certain mundane questions but not be able to answer esoteric questions like who am I? Where have I come from? And, Wither am I going?, etc. He compares positive sciences to a railway engine built to run on a track but not be able to fly like an aeroplane[4].

Nobel Laureate physiologist, Charles Sherrington, in his acceptance speech in 1899 at a young age of 42 when he was appointed as a professor of physiology at Liverpool University said: "Positive sciences cannot answer the question 'why'? They can, at best, answer 'how' or 'how much'? But, not 'why'? Just as a host of brilliant quantum physicists had to go beyond pure materialism to understand the reality of this universe through quantum mechanics,

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we in medicine will have to go beyond our reductionist materialistic medical science. The added advantage is that understanding the mind will enable us to use the mind to heal the body which is but an illusion of the mind. Particle-wave dichotomy where the one changes to the other nearly 1,044 times in a second understanding the mind gives birth to quantum healing. Just as a molecule has the blue print of its genes, the mind has a blue print of the body stored safely and it can remodel the body based on the mind understanding the disease process. David Wiebers, an Emeritus professor of Neurology at the Mayo Clinic, is his classic, The Theory of Reality, has distilled the wisdom of the progress made in this realm in the last half a century. I strongly recommend that book to readers to understand the intricacies of consciousness[1].

In conclusion, one could easily say that we (our mind) are the masters of this creation as we alone can determine what manifests from the fields that we control. "There is highly suggestive evidence of the existence of this energetic blueprint (or human energy field) in the new research on DNA which proves that it transmits, receives, and thus reads energy directly from the field," writes Brandon West. He continues: "If we can change our beliefs about ourselves, and thus if we can change the energy that defines our energy field, then we can change the energetic blueprint which our body aligns with as it re-materialises (after an illness) back into form 1,044 times per second." After a heart attack, if outside intervention does not happen, the heart remodels itself so beautifully.

Western medical reductionist research which has almost 95% of its results as only noise but an occasional signal even there is missed by the main stream medical world. Five studies are very important to prove my point above that quantum healing occurs through our minds. The Oxford study of real placebo even in pain relief, the Harvard study of senior cardiologists going for their annual conference leaving seriously ill patients in their ICUs resulting in better outcomes compared to when they were doing all kinds of interventions in such patients when they were present, death and disability rates falling when doctors went on strike in Israel, and finally Japan with the lowest doctor patient ratio among the 14 industrialised countries having the best health standards, lowest death and disability rates and highest longevity compared to the USA with too many doctors and specialists, must have warned us that we are barking up the wrong tree. RCT study of coronary revascularisation using laser beam did show that with or without surgery (patient was told that the operation went off very well) had similar results. We did not take these serious studies into consideration to find out that the mind eventually heals and not the drugs and surgery that we use except as an emergency quick-fix[5-9].

In reality it is easy to think of ourselves as an energy field organising itself into a body or as pure consciousness through our bodies. Our mind is non-local and not in our brain or body – as detailed above meaning thereby that mind does not need the brain or body to exist. Where IS the mind? Never Mind!

"Everyone who is seriously involved in the pursuit of science becomes convinced that a spirit is manifest in the laws of the universe – a spirit vastly superior to that of man, and one in the face of which we with our modest powers must feel humble. In this way the pursuit of science leads to a religious feeling of a special sort, which is indeed quite different from the religiosity of someone more naive."

– Albert Einstein.

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"Modern medicine is a negation of health. It isn't organised to serve human health, but only itself, as an institution. It makes more people sick than it heals."

– Ivan Illich.

ORIGINAL ARTICLE

JIACM 2015; 16(3-4): 184-6

Evaluation of subclinical thyroid disorders in an asymptomatic adult population of Muzaffarnagar region

YB Agrawal, Nita Garg*, CR Raghushaker***, Sudeep Kumar****

Abstract

Objective: The aim of our study was to determine the percentage of males and females suffering from subclinical thyroid disorders in the various age groups in the rural and suburban population of Muzaffarnagar.

Methodology: A hospital based cross-sectional study was conducted on patients attending the out-patient departments of medicine and gynaecology. Residents of nearby villages were also included in this study. 550 cases, both males (211) and females (339) lying in the age group 20 - 70 yrs were selected randomly. They were divided into 2 groups according to age and sex. 20 to 40 yrs and above 40 yrs. Serum T3, Serum T4, and Serum TSH was assayed using chemilumiscent immunoassay method.

Result: Out of the 211 males, 82 males in the age group 20 - 40 yrs and 129 males above 40 yrs were included in this study. 10 males (12.20%) in the age group 20 - 40 yrs were having subclinical hypothyroidism and 2 males (2.44%) was suffering from subclinical hyperthyroidism. Of the 129 males, 23 males (17.83 %) above 40 yrs were having subclinical hypothyroidism and 4 males (2.33%, TSH) above 40 yrs were having subclinical hyperthyroidism. Out of the 339 females, 152 females in the age group 20 - 40 yrs, 30 females (19.74%) were suffering from subclinical hypothyroidism and 5 females (3.29%) were suffering from subclinical hyperthyroidism. Of 187 females above 40 yrs, 30 females (16.04%) were having subclinical hypothyroidism and 12 females (6.42%) were suffering from subclinical hyperthyroidism. Conclusion: Assessment in high risk groups is recommended, as there is an increasing prevalence of subclinical thyroid disease which may with time progress to overt thyroid disorder, so we encourage assessment of thyroid function in high risk groups specially the elderly. Early diagnosis and treatment may prevent complications like atrial fibrillation, osteoporosis, atherosclerosis, etc.

Key words: Subclinical hypothyroidism, subclinical hyperthyroidism, TSH.

Introduction

Subclinical thyroid dysfunction is defined as an abnormal serum thyroid stimulating hormone level (reference range: 0.45 to 4.50 µlU/ml) and free thyroxine and tri-iodothyronine levels within their reference ranges. Subclinical or mild thyroid disease is a common disorder, particularly in the middle-aged and elderly individuals[1]. Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction. Some patients will progress to overt disease, and in some patients, the serum TSH concentration will remain stable over time or will spontaneously return to the normal reference range[2].

Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum T_3 and T_4 concentration is within its normal reference range[3]. Subclinical hypothyroidism is associated with progression to overt hypothyroidism, and there is fair evidence that serum TSH levels greater than 10 µlU/l are associated with elevations in total and LDL cholesterol levels[4-6]. Women with subclinical hypothyroidism had a higher incidence of diastolic hypertension, hypertriglyceridaemia, elevated TC/HDL cholesterol and LDL/HDL cholesterol ratios[7].

Subclinical hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range, when serum T_3 and T_4 concentrations are within their normal reference ranges[3]. Subclinical hyperthyroidism may result from endogenous overproduction of thyroid hormone, or intended or inadvertent over-administration of thyroid hormone. Subclinical hyperthyroidism is much less common than subclinical hypothyroidism and it is more common in women than men, in blacks than whites, and in the elderly. Few people with a serum TSH between 0.1 and 0.45 µlU/l progress to overt hyperthyroidism[8]. It appears to be associated with atrial fibrillation, reduced bone mineral density, cardiac dysfunction, and progression to overt hyperthyroidism[5,9,10].

Materials and method

A hospital based cross-sectional study was conducted on patients attending the out-patient departments of medicine and gynaecology of MMC, Muzaffarnagar (UP) during a period of 6 months from April 2012 to September 2012. 550 cases

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(211males and 339 females) in the age group 20 - 70 yrs were selected randomly. Exclusion criteria were age less than 20 yrs or more than 70 yrs. All blood samples were collected in fasting state and serum T3, T4, and TSH were estimated using chemilumiscent immunoassay method (CLIA).

Results

A total number of 550 subjects (211 males, 339 females) in the age group 20 - 70 yrs were selected randomly and assayed for serum T3, T4 and TSH.

Out of the 211 males, 82 males in the age group (20 - 40 yrs) and 129 males above 40 yrs were included in this study. 10 males (12.20%) in the age group 20 - 40 yrs were having subclinical hypothyroidism and 2 male (2.44%) was suffering from subclinical hyperthyroidism. Of the 129 males, 23 males (17.83%) above 40 yrs were having subclinical hypothyroidism and 4 males (2.33%, TSH) above 40 yrs were having subclinical hyperthyroidism.

Out of the 339 females, 152 females in the age group 20 - 40 yrs, 30 females (19.74%) were suffering from subclinical hypothyroidism and 5 females (3.29%) were suffering from subclinical hyperthyroidism. Of 187 females above 40 yrs, 30 females (16.04%) were having subclinical hypothyroidism and 12 females (6.42%) were suffering from subclinical hyperthyroidism. These observations are tabulated in Table I and depicted graphically in Fig. 1. The Tables II and III represent variables among different age groups expressed in mean with standard deviation.

Table III: Variables of healthy controls of different age groups.

Variable	Male		Female	
	20 - 40 yrs	40 yrs and above	20 - 40 yrs	40 yrs and above
Age	31.55 ± 5.0	50.9 ± 5.9	30.17 ± 5.65	50.32 ± 6.66
T_3 (ng/ml)	1.35 ± 0.3	1.29 ± 0 .33	1.21 ± 0.37	1.06 ± 0.24
T_4 (µg/dl)	7.65 ± 1.65	7.63 ± 1.73	7.72 ± 1.7	8.9 ± 1.82
TSH (µlU/ml)	2.2 ± 1.06	2.58 ± 1.01	2.53 ± 1.16	2.34 ± 1.04

Discussion

Subclinical thyroid dysfunction is a common clinical problem with many controversial issues regarding screening, evaluation, and management. The prevalence of subclinical hypothyroidism is 4% to 10% in the general population. Up to 15 - 20% in women who are over 60 yrs of age[11]. Hypothyroidism is more common in women than in men, probably because hormonal imbalance acts as a trigger for thyroid problems.

Mild thyroid failure represents an early stage thyroid disease that will commonly progress to overt hypothyroidism. Mild thyroid failure is often asymptomatic; however nearly 30% of patients with this condition may have symptoms that are suggestive of thyroid hormone deficiency. Of patients with subclinical hypothyroidism, approximately 2 - 5% per year will progress to overt hypothyroidism[8, 12].

Subclinical hyperthyroidism is much less common than

Table I: Percentage of subclinical hypothyroidism and subclinical hyperthyroidism in the given population.

Sex	Males (211)				Females (339)			
Age	(20 to 40 yrs)		(40 yrs and above)		(20 to 40 yrs)		(40 yrs and above)	
	N = 82	%	N = 129	%	N = 152	%	N = 187	%
Normal	70	85.36	102	79.07	117	76.97	135	72.19
Subclinical hypothyroidism	10	12.20	23	17.83	30	19.74	40	21.29
Subclinical hyperthyroidism	2	2.44	4	3.10	5	3.29	12	6.42

Table II: T_3, T_4 and TSH in different age groups of subclinical hypothyroidism and subclinical hyperthyroidism.

	Subclinical hypothyroidism				Subclinical hyperthyroidism			
	Male		Female		Male		Female	
Variable	20 - 40 yrs	40 yrs and above	20 - 40 yrs	40 yrs and above	20 - 40 yrs	40 yrs and above	20 - 40 yrs	40 yrs and above
Age	34.2 ± 4.56	53.96 ± 5.76	32.66 ± 3.72	50.42 ± 5.61	32..0 ± 2.82	54.75 ± 8.8	33.88 ± 6.76	47.41 ± 5.5
T_3 (ng/mL)	1.12 ± 0.41	1.05 ± 0.23	1.26 ± 0.36	1.04 ± 0.21	1.32 ± 0.12	1.76 ± 0.27	1.13 ± 0.26	1.22 ± 0.33
T_4 (µg/dL)	6.0 ± 2.29	8.08 ± 1.29	7.71 ± 1.85	8.47 ± 1.74	5.73 ± 0.17	9.14 ± 2.11	7.30 ± 1.58	8.44 ± 1.71
TSH (µlU/mL)	6.3 ± 0.96	6.79 ± 1.08	7.03 ± 1.26	7.0 ± 1.31	0.15 ± 0.05	0.185 ± 0.02	0.17 ± 0.03	0.10 ± 0.05

T_3: Tri-iodothyronine, T_4: free thyroxine, TSH: thyroid stimulating hormone.

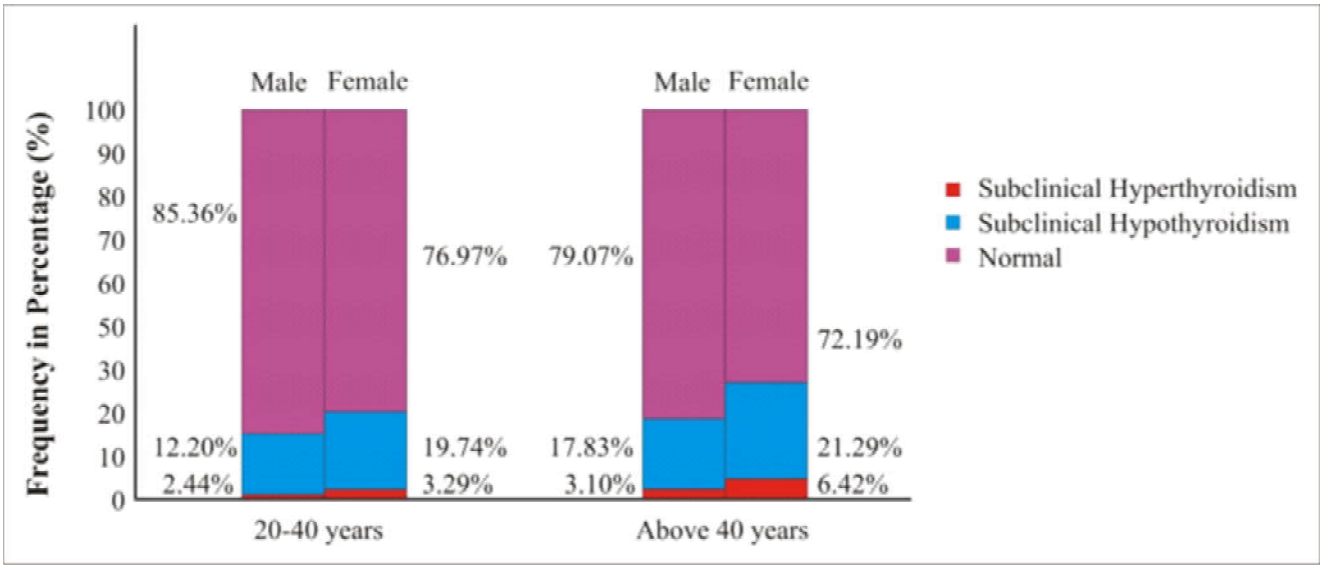

Fig.1: *Frequency of subclinical thyroid disorders among different age groups in the given population*

subclinical hypothyroidism. When the lower limit of TSH is less than 0.4 µIU/l, 3.2% of the population is defined as having subclinical hyperthyroidism[13]. Subclinical hyperthyroid disease is more common in women than in men, in blacks than whites, and in the elderly[8]. The presence of goitre, personal history of previous thyroid disease, family history of thyroid disease, etc., all make prevalence of subclinical hyperthyroidism decrease to 0.7%[13]. Overt hyperthyroidism is defined as a serum TSH level lower than 0.1 µIU/l with serum T_4, T_3 concentrations above the normal reference range. Few persons with a serum TSH between 0.1 and 0.45 µIU/l progress to overt hyperthyroidism[8].

Conclusion

Consequences of subclinical thyroid diseases are minimal, so we do not recommend routine treatment of patients with TSH levels (0.1 to 10 µIU/l). The 2002 consensus group's expert panel also discouraged population based screening, but "encouraged" assessment in high risk groups, as there is an increasing prevalence of subclinical thyroid disease which may with time progress to overt thyroid disorder, so we encourage assessment of thyroid function in high risk groups specially the elderly. Early diagnosis and treatment may prevent complications like atrial fibrillation, osteoporosis, atherosclerosis, etc.

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ORIGINAL ARTICLE

JIACM 2015; 16(3-4): 187-97

Prevalence of type 2 diabetes mellitus and its risk factors in the age group 40 years and above in the Kashmir valley of the Indian subcontinent

Ishrat Hussain Dar, Showkat Hussain Dar*, Ruhail Ahmed Bhat**, Muqtasid Ahmed Kamili***, Samia Rashid Mir*****

Abstract

Aims: To assess the prevalence of type 2 diabetes mellitus and its risk factors in the adult age group from 40 years and above in the Kashmir valley of Jammu & Kashmir State.

Methods: 3,972 people aged 40 years and above from the twin districts of Anantnag and Srinagar were randomly selected from both the rural and urban areas after explaining the purpose and aims of the study. They were subjected to a detailed general and physical examination which included a questionnaire, anthropometry, and a fasting blood sample for estimation of blood sugar and lipids. The who and ada criteria were used to classify diabetes.

Results: The total prevalence of type 2 diabetes in the sample examined was found to be 6.31% with a higher prevalence in the urban than in the rural areas. The urban prevalence was 7.15 % and the rural prevalence was 5.50 %. Total prevalence of diabetes was more in the age group of 50 - 59 years in both urban and rural areas (9.35 % vs 8.58 %) thus reflecting a narrowing gap between the two groups. Urban females had a higher prevalence of diabetes as compared with the urban males (8.15% vs 6.52%) whereas rural males had a slightly more prevalence than rural females (5.69% vs 5.28%). Prevalence of diabetes was more in people of social class i than in people of social class v (10.08% vs 5.04%) and more in literate people than illiterate people (7.01% vs 5.24%). A higher prevalence of diabetes was noted in people with a strong family history of diabetes (19.44% vs 6.07%), sedentary lifestyle (9.47% vs 4.44%), obesity (12.03% vs 3.92%). Equal prevalence was noted in both smokers and non smokers (6.06% vs 6.43%). Prevalence of diabetes was more in people with dyslipidaemia – particularly hypertriglyceridaemia.

Conclusions: This study that follows previous other studies shows that diabetes in Kashmir is assuming alarming epidemic proportions just like other states in the rest of the country. Prevalence of diabetes has increased in both sexes and no significant difference is seen in the rural and urban areas. Obesity, sedentary lifestyle, social class I and family history of diabetes contribute more to its prevalence and need to be tackled.

Introduction

Diabetes is the most common non communicable disease and type 2 diabetes constitutes almost 90% of the total diabetic population with a steady increase over the last two decades worldwide that has assumed epidemic proportions. Once thought of as a disease of the elderly, diabetes has shifted down a generation to affect people of working age particularly in the developing countries. This has serious repercussions particularly for the working class and has resulted in increased morbidity and mortality resulting in economic imbalances. Current data shows that there are more than 285 million adults with diabetes and the figure is set to rise to 438 million by 2030. Two-thirds of the world's population with diabetes live in developing countries caused largely due to the rapid socio-economic transitions of modernisation and urbanisation. More than 60% of the diabetics live in Asia[1]. India and China together account for more than one third of the Asian diabetic population. Around 51 million and 43 million of the diabetic population live in India and China respectively. A recent survey carried out in China has estimated that the diabetic population has already crossed 91 million and has probably overtaken India[2]. The International Diabetes Federation in its 5th edition of the World Diabetes Atlas may show an escalation in the prevalence of diabetes worldwide particularly for South East Asia . The smaller countries of the Indian subcontinent like Pakistan, Bangladesh and Sri Lanka are also witnessing a rapid increase in type 2 diabetes. Prevalence of diabetes in India is slated to touch 70 million by 2025 and 87 million by 2030 AD[3]. The first authentic data on the prevalence of diabetes mellitus in India came from the multicentre study conducted by the Indian Council of Medical Research in 1971 which reported the prevalence of diabetes type 2 in the urban and rural populations (aged > 14 years) to be 2.3% and 1.5% respectively. Since then the prevalence of type 2 diabetes in India has steadily risen from 1.2% in 1971 to 20.1% in 2007[4,5]. The diabetes

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epidemic in India has thus assumed pandemic proportions with even the rural population showing an unpleasant rise in its prevalence to 12.5%[6]. Indian population is not homogenous and differs in ethnicity, place of origin, religion and diet. The state of Jammu and Kashmir has followed the rest of the country in registering an increase in the prevalence of type 2 diabetes with studies over the years depicting the pattern of rising prevalence 1.89% to 4%[7,8]. The valley of Kashmir which lies in the northern region of the Indian subcontinent with a predominantly Muslim population of uniform ethnicity has been undergoing similar changes of modernity, sedentary lifestyle and obesity has also shown an increase in the reported prevalence of diabetes and not much data has been available in this regard. In this context the present study was undertaken to determine the prevalence of type 2 diabetes in people aged 40 years and above as this productive segment is the most vulnerable to suffer from diabetes and its aftermath. The relationship of diabetes to various variables like age, sex, obesity, socio-economic status, smoking, dyslipdaemia, family history of diabetes and rural/urban background was also studied.

Materials and methods

The present study was conducted in the two districts of the Kashmir valley, i.e., Anantnag and Srinagar in both the rural and urban areas. Details of the population were obtained from the Directorate of Economics and Statistics Department reference manuals. In the Anantnag district which lies to the southern side of the Kashmir Valley the rural survey was carried out in the 3 cluster villages of Brakpora, Bul Bul Nowgam and Nunwani by random sampling. These villages lie at a distance of 4 - 6 km from the main town. The total population of this study area was 8,460 and the target population was 3,500. The urban survey was carried out in the 3 cluster mohallas of Anantnag town out of 64 mohallas. The 3 mohallas selected were Cheeni Chowk, Rishi Bazar and Qazi Mohalla. The total population of these 3 mohallas was 11,000 out of which 3,979 was the target population. The rural survey in Srinagar district was carried out in the 3 villages of Khonmoh (A and B) and Zewan about 15 km from the capital city of Srinagar. The total population of these villages was 11,452 out of which 3,200 was the target population. The urban survey of Srinagar city was carried out in the Chattabal area in 3 out of 13 mohallas namely Bagh Sunderbala, Mughal Mohalla and Guzerbal. The total population of these mohallas was 13,393 out of which 3,214 was the target population. All people from 40 years and above from the target population in the defined areas were invited to participate in the study. Out of the 4,000 people (1,000 from each defined area) designed to enter the study 3,972 voluntarily participated and 28 people declined or remained absent. The purpose of the survey and study was explained beforehand to the target population and inclusion was purely voluntary. Subjects were requested to remain fasting at least 12 hours before the study and not to take any non vegetarian diet at least for 3 days prior to the study to ensure correctness of the blood lipid levels. A detailed history including family history of diabetes and history regarding various lifestyle risk factors like education, occupation, type of job, physical activity, amount and type of diet intake, smoking and alcohol was taken. Obesity was determined by using the waist hip ratio and Quetlet index (weight in kilograms/ height in metre^2). The waist was measured at the narrowest point between the rib cage and the iliac crests and the hip at the maximum point around the buttock. Subjects were weighed without shoes or extra clothes on a properly calibrated portable weighing machine. Height was measured in centimeters by making the subjects to stand barefoot with the medial malleoli close together, the ankles and the occiput in close approximation to a properly marked wall. A fixed metal measuring tape was used for the purpose. A fasting blood sample for estimation of sugar and lipids was taken from each participant.

Specimen collection and preservation

5 ml of a venous blood sample was drawn in disposable syringe from fasting volunteers and the following procedures were adopted.

For blood sugar

2 ml of blood was taken in a clean dry tube (serum separator tube) containing potassium oxalate and fluoride. Potassium fluoride acts as an enzyme poison and prevents glycolysis. Hence samples could be left at room temperature for 3 - 4 hours without any appreciable change in glucose concentration. The samples were then analysed for blood sugar using glucose oxidase-peroxidase (GOD-POD) method on a fully automatic autoanalyser (Hitachi 912). The kit used was DPEC-GOD/POD from Roche Laboratories Ltd. (Diagnostic Division).

For lipid frofile

3 ml of venous blood taken in a clean dry serum separator tube was taken and left for some time to obtain serum and prevent haemolysis. It was then centrifuged at 5,000 rpm for 10 minutes to separate serum from the cells. Serum was transported in a cold chamber (Vaccine Carrier with Ice Packs manufactured by Apex Continental Limited New Delhi) and then kept overnight in a refrigerator at 2 - 8° C. Samples were then analysed in the Biochemistry

Department Laboratory of SMHS Hospital (Associated Hospital of Govt Medical College Srinagar) on a fully automatic biochemistry (Hitachi 912) analyser.

Diagnostic criteria

1. Illiteracy was defined when no formal education was reported or the subject could neither read nor write[9].
2. All smokers (present and past who smoked tobacco/ cigarettes) were grouped together to avoid bias in the smoking users category. Non smokers were grouped as those who had never smoked or had left smoking 10 years before or more[9].
3. Criteria for the diagnosis of high fat intake was when the individual consumed more than 35 gm of visible fat / day or 1 kg of visible fat/month classified by the AHA Diet Heart Statement as more than the desirable amount of total visible fat allowed/day[10].
4. Physical activity was measured by work related and leisure time activity and the criteria (Paffenberger *et al*) to classify a person as sedentary were[11]:
   a) Who walks < 9 miles/week.
   b) Climbs < 20 flights of stairs/week.
   c) Performs no moderately vigorous sports exercise or job related activity. Persons not doing any leisure time physical activity were classified as sedentary.
5. Obesity was defined as BMI of 25 kg/m^2 or more whereas abdominal obesity was defined as waist hip ratio (WHR) of > 0.90 in males and > 0.80 in females[12].
6. Diabetes was defined as under:
   a) Known type 2 diabetes was defined as physician diagnosed diabetes mellitus as ascertained from the medical records by the doctor irrespective of drug treatment in the age group of 40 years and above after excluding type 1 diabetes.
   b) Type 2 diabetes was defined as fasting plasma glucose of 126 mg/dl or more as per the WHO and ADA criteria[13,14].
7. Dyslipidemia: the recommendations of the Expert Panel on National Cholesterol Education Programme were followed[15]:

	TC	TG	HDL	LDL
Desirable (mg/dl)	< 200	< 160	> 60	< 100
Borderline (mg/dl)	< 200 - 239	41 - 60	131 - 159	
Undesirable (mg/dl)	> 240	< 40	> 160	

8. Socio-economic status

It was assessed by Kappusswamy classification (modified 2003) into 5 classes. The classification[16] was based on educational status, occupation and income per capita per month. Highest socio-economic Class was Ist with a total score of 26 - 29 or above and lowest socio-economic class was Vth with a total score of < 5.

Statistical analysis

The data obtained from the study was analysed by the Chi square test and p value obtained. Odd's ratio was estimated for all the lifestyle risk factors of diabetes.

Results

The total population of the study area in both the districts was 44,305 (rural and urban) out of which 13,893 was the target population aged 40 years and more. The target population comprised 31.35% of the total population and out of this 4,000 (28.79%) people of both sexes were invited to participate in the study. 3,972 people (male and female) responded giving a response rate of 99.30% whereas 28 people did not respond to participate in the study (Table I). Subjects were divided into different age groups viz 40 - 49 years, 50 - 59 years and more than 60 years. 2,260 (56.89%) of the studied subjects were less than 50 years of age as compared with 1,712 (43.11%) people of more than 50 years. Males comprised 2,284 (57.50%) and females comprised 1,688 (42.50%) of the total population studied. The urban population studied was 1956 (49.24%) people whereas the rural population studied was 2,016 (50.76%) people . The total number of diabetics found in the study population was 251 out of 3,972 people giving an overall prevalence of 6.31%. Urban diabetics comprised 140 people whereas rural diabetics comprised 111 people thus constituting a prevalence of 7.15% and 5.50% respectively. The statistical difference between the two groups was significant (0.02). A higher prevalence of diabetics was noted in the age group of 50 - 59 years in both urban and rural groups (9.35% vs 8.58%), 60 years and above (7.55% vs 7.40%) and a comparatively lower prevalence was noted in the age group 40 - 49 years (5.55% vs 3.94%). Urban females in the age groups of 40 - 49 and 50 - 59 had a higher prevalence of diabetes than urban males of the corresponding age group (7.14%, 9.85% vs 4.51%, 8.91%) whereas urban males in the age group of 60 years and more had a slightly higher prevalence than urban females in the same age group (7.62% vs 7.37%). Overall urban females had a higher prevalence of diabetes than urban males (8.15% vs 6.52%). Regarding the rural group, females in the age group 40 - 49 years had a higher prevalence than males of corresponding age (4.14% vs 3.72%) whereas males in the age group 50 - 59 years and 60 years above had slightly

higher prevalence rates than females of their corresponding age groups (8.62% vs 8.53%) and (7.51% vs 7.14%) respectively. Regarding prevalence of diabetes in the age group of < 50 years it was seen that the number of diabetics was 151 and 100 in the age group > 50 years. Prevalence of diabetics recorded was 8.82% and 4.42% in the respective groups. The statistical difference between the two groups was highly significant (p value < 0.001). Overall the prevalence of diabetes was slightly more in females than males (6.45% vs 6.21%) and the statistical difference between the sexes was not significant (p value < 0.5). Prevalence of diabetes was more in people of social class I than social class V (10.08% vs 5.04%) and the statistical difference between the groups was highly significant (p value < 0.001). Prevalence of diabetes was noted to be higher in the literate group than the illiterate group (7.01% vs 5.24%) and both the urban literate and urban illiterate showed higher prevalence than the rural literate and rural illiterate groups (8.34%, 7.53% vs 5.43%, 3.61%). The statistical difference between the literate and the illiterate groups was significant (p value 0.02). Regarding prevalence of various risk factors it was noted that among 3,972 people screened 72 had family history of diabetes out of which 14 turned out to be diabetic in contrast with 3,900 people who had no family history of diabetes and 237 turned out to be diabetic. Thus the prevalence of diabetes in those with a family history and those without was 19.44% vs 6.07%. The statistical difference between the two groups was highly significant (p value < 0.001). Comparing the prevalence of diabetes in active and sedentary people it was found that 2,495 people were physically active and 1,477 were sedentary and the number of diabetics in each group was 111 and 140 respectively conforming to a prevalence rate of 4.44% and 9.47%. The statistical difference between the two groups was highly significant (p value < 0.001). Studying the effect of obesity on the prevalence of diabetes was astonishing. 1,172 people out of 3,972 people were obese giving figures of 29.50% people who qualified to be obese as per the revised guidelines for the Indian subcontinent. Out of the obese people 141 were diabetics and out of the 2,800 non obese people 110 were diabetics making a prevalence rate of 12.03% and 3.92% respectively. The statistical difference between the two groups was highly significant (p value < 0.0001). Continuing with the obesity effect it was notice that 131 people out of 251 diabetics fell into the obese category as per the waist hip ratio (WHR) of > 0.90 and 120 people had a WHR of < 0.90. Prevalence rate for obese diabetics as per the WHR was higher (11.02% vs 4.54%) than non obese diabetics. Urban obese diabetics had a higher prevalence than rural obese diabetics (12.50% vs 9.46%). The statistical difference between obese and non obese diabetics was highly significant (p value < 0.0001). Effect of smoking on diabetes did not show a reasonable association. Out of 3,972 people screened 1,236 were smokers and 2,736 were non smokers. In the smokers category 75 people and in the non smokers category 176 people turned out to be diabetics reflecting prevalence rates of 6.06% and 6.43% respectively. The statistical difference between the two groups was not significant (p value > 0.5). Regarding the prevalence of diabetics with dyslipidaemia it is obvious from our study that diabetics have a higher prevalence of dyslipidaemia as compared with people from the general population. All abnormalities of dyslipidaemia particularly hypertriglyceridaemia are seen in diabetics. All lipid abnormalities especially hypertriglceridaemia and hypercholesterolaemia showed a significant statistical difference in comparison to dyslipidaemia in the normal population. Odd's ratio as calculated for various lifestyle risk factors of diabetes showed the highest for those with a family history of diabetes (3.73) followed by BMI > 25 Kg/m^2 (3.34), hypertriglyceridaemia (2.68), hypercholesterolaemia (2.49), sedentary lifestyle (2.24), socio-economic status (2.11), age > 50 years (2.08), LDL > 100 (1.61), HDL < 40 (1.52) and lowest for smokers (0.93). Comparative studies of diabetes in India both rural and urban are reflected in Tables II and III.

Table I: Details of the population in the surveyed areas with the target and surveyed population.

Category	Area surveyed	Total population	Target population (40 yrs +) and % age	Population surveyed and % age	Persons responded (%)	Absentees (%)
Urban	Srinagar (Chattabal) (3 Mohallas)	13,393	3,214 (23.99)	910 (28.31)	900 (98.90)	10 (1.10)
Urban	Anantnag town (3 Mohallas)	11,000	3,979 (36.17)	1,061 (26.66)	1,056 (99.52)	05 (0.48)
Rural	Srinagar (Khonmoh, Zewan)	11,452	3,200 (27.94)	936 (29.25)	928 (99.14)	08 (0.86)
Rural	Anantnag (BBN, Nunwani Brakpora)	8,460	3,500 (41.37)	1,093 (31.22)	1,088 (99.54)	05 (0.46)
Both	Srinagar and Anantnag	44,305	13,893 (31.35)	4,000 (28.79)	3,972 (99.30)	28 (0.70)

Population Source: Directorate of Economics, Statistics, Planning and Development Department Srinagar, Govt. of Jammu and Kashmir.

Table II: Prevalence of diabetes and prediabetes in urban India since 2000 AD.

Location/author	Year of pub	Age group	Prevalence % of diabetes	Prevalence of IGF %	Prevalence of IGT %
Kashmir (Zargar)	2000	> 40	5.20		10.12
Kerala (Kutty VR)	2000	> 20	12.40		
Kerala (Joseph A)	2000	> 19	16.30		
Chennai (Ramachandran A)	2001	> 20	13.50		16.80
Chennai (Mohan V)	2001	> 20	12.40		7.50
Delhi (Ramachandran A)	2001	> 20	11.60		8.60
Delhi (Misra A)	2001	>18	10.30		
Bangalore (Ramachandran A)	2001	> 20	12.40		14.90
Kolkatta (Ramachandran A)	2001	> 20	11.70		10.00
Hyderabad (Ramachandran A)	2001	> 20	16.60		29.80
Mumbai (Ramachandran A)	2001	> 20	9.30		10.80
National (Ramachandran A)	2001	> 20	12.10		14.00
Jaipur (Gupta A)	2003	> 20	8.60	5.30	
Jaipur (Gupta R)	2004	> 20	16.80		
National (Sadikot S)	2004	> 20	5.90	4.80	6.30
Delhi(Prabhakaran D)	2005	20 - 59	15.00		37.00
National (Reddy K)	2006	20 - 69	8.40		6.40
Chennai (Mohan V)	2006	> 20	15.50		10.60
Kerala (Menon VU)	2006	> 19	19.50	7.10	4.10
Jaipur (Gupta R)	2007	> 20	20.10		
Chennai (Ramachandran A)	2008	> 20	18.60		7.40
Kolkatta (Kumar S)	2008	> 20	11.50	6.20	
Kashmir (Zargar)	2008	> 20	2.50	25.20	11.10
Kerala Urban (Thankappan KR)	2010	> 15 - 64	14.80		
Kerala Slum (Thankappan KR)	2010	> 15 - 64	13.10		
Kashmir (Current)		> 40	7.15		

Discussion

Epidemiological studies done on diabetes in India starting from Calcutta in 1938[17] to 2009[5,6] have reported gross prevalence rates of 1% to 20% though the study done in Calcutta was a hospital based one. This epidemiological study done to estimate the prevalence of type 2 diabetes in the Kashmir Valley of the Indian Sub-continent follows the earlier studies carried out by Zargar *et al*[7,8] which had reported gross prevalence rates of 1.89% (1.98% in males and 1.77% in females) in the year 2000 and 4% (in the year 2008) respectively. The latter study (2008) undertaken by Zargar *et al* was done in the age group of 20 - 40 years whereas the current study was done in the age group of 40 years and above. It can be seen that within one decade the prevalence of diabetes in the Kashmir Valley has risen more than three-fold (6.31%) reflecting the possible effects of lifestyle risk factors and changes in dietary habits and is in tune with what has been reported elsewhere in India, though the total prevalence is still lower when compared with other similar studies in the country (Table II, III). Preliminary reports in form of unpublished data coming from the state have suggested that the prevalence of type 2 diabetes may already have crossed the double digit mark. The gross prevalence of diabetes in Kashmir when compared with the study done by Zargar *et al* (2008) is

6.31% as against 2.40% but the study of 2008 was done in the age group of 20 - 40 years compared with the age group of 40 years and above. Though the burden of IGF and IGT in the 2008 study is quite high meaning thereby that the prevalence rates of diabetes are going to rise as has been shown in this current study. With the increase in the people with IGT and IGF the state seems heading for an explosive diabetes epidemic in the years to come.

Ramachandran *et al* 1997[18] has also reported a higher prevalence of diabetes in females (12.7% vs 10.4%) as compared with males in the age group of 40 (± 12) in an urban setting in Chennai. Purty *et al* in 2009 found a higher prevalence of diabetes in females (6.10% vs 5.31%) in an urban study of Puducherry in individuals aged 20 years and above[19]. Dhadwal *et al* in his study on the prevalence of type 2 diabetes in adults aged more than 40 years in Shimla

Table III: Prevalence of diabetes and prediabetes in rural India since 2000 AD.

Location/author	Year of pub	Age group	Prevalence % of diabetes	Prevalence of IGF %	Prevalence of IGT %
Kashmir (Zargar)	2000	> 40	4.00		7.56
Kerala (Kutty VR)	2000	> 20	2.50		
Rajasthan(Agrawal RP)	2004	> 20	1.60	9.20	6.50
National (Sadikot S)	2004	> 25	1.90	2.50	
National (Sadikot S)	2004	> 25	2.70		3.70
Tamil Nadu (Nirmalan PK)	2004	> 40	4.40		
Tamil Nadu (Ramachandran A)	2004	> 20	6.36		7.18
Mysore(BasavanagowdapaH)	2005	> 25	3.77	2.80	
Maharashtra(Deo SS)	2006	20 - 70	9.30	4.20	1.80
Andhra Pradesh (Chow CK)	2006	> 30	13.20	15.50	
Andhra Pradesh (Chow CK)	2007	20 - 90	3.70		
Vellore(Raghupathy P)	2007	26 - 32	2.10	3.40	14.30
Nagpur (Kokiwar PR)	2007	> 30	3.67	3.57	5.96
Ballabgarh (Prabhakaran D)	2007	35 - 64	2.80	3.70	
Ballabgarh (Baridalyne N)	2008	15 - 64	3.9 (M), 1.6 (F)		
Wardha (Khatib NM)	2008	45	8.50		
Tamil Nadu(Ramachandran A)	2008	> 20	9.20	1.90	5.50
Tamil Nadu (Balagopal P)	2008	10 - 92	5.10	13.50	
Kashmir (Zargar)	2008	20 - 40	2.40	11.10	1.60
Kerala(Vijayakumar G)	2009	> 18	12.50	4.60	
Kashmir(Current)		> 40	5.50		

Diabetes and gender

Prevalence rates of diabetes as seen in terms of gender show an almost equal prevalence in both sexes with females having a slightly increase prevalence than males (6.45% vs 6.21%) indicating thereby that diabetes is no longer a disease confined to males but with the modern sedentary stressful lifestyle more people of both sexes are becoming diabetic particularly females. Zargar *et al* (2008) has reported almost equal prevalence rates for females and males (2.2% vs 2.6%) though again in the age group 20 - 40 years. screened 1,195 subjects from seven randomly selected wards. The prevalence of diabetes was 4.86% (5.17% in males and 4.38% in females)[20]. Bharati *et al* in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes in males than females[25].

Diabetes and habitat

Coming to the prevalence of type 2 diabetes among urban and rural people in our study it was found that prevalence

was higher in urban areas as compared with the rural areas (7.15% vs 5.50%). Zargar *et al*[7] had found also found a higher prevalence in urban areas when compared with people from rural areas though the difference in the two groups was marginal (5.20% vs 4.00%). Most of the studies conducted in India have reported higher prevalence of diabetes from urban when compared with rural areas. Sadikot *et al* in their multicentric study (PODIS study) carried out in 77 centres (40 urban and 37 rural) in people aged 25 years and more all over India found that the total prevalence of type 2 diabetes in India using the 1999 WHO criteria was 4.3% with urban/rural prevalence at 5.9% and 2.7% respectively[21]. Sadikot *et al* again in their multicentric study (PODIS study) carried out in people aged 25 years and above in 108 centres in India (49 urban and 59 rural) in a population of 41,270 (20,534 males and 20,736 females) using the 1997 ADA criteria found the total prevalence of type 2 diabetes to be 4.6% urban and 1.9% rural respectively[22]. Singh *et al* in his study in Moradabad to assess the prevalence of type 2 diabetes and coronary heart diseae in a rural and urban population (1,769 rural and 1,806 urban) found that the prevalence of diabetes was more in urban (6%) as cimpared with rural (2.8%) areas[23]. Gupta *et al* has found a prevalence of 20.1% in an urban area of Jaipur in 2007[5], whereas the prevalence of diabetes in urban Kerala (2006) was 19.5% as reported by Menon *et al*[24]. Bharati *et al* in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report almost similar prevalence rates in both urban and rural areas (8.60% vs 8.04%) but report an overall increased age adjusted prevalence in urban than rural subjects (8.2% vs 2.4%)[25]. Mohan *et al* (2008) in his multicentric study has reported a higher urban prevalence of diabetes as compared to the rural prevalence in the age group of 15 64 years[26].

Diabetes and age

The importance of age on the prevalence of diabetes cannot be underestimated. Globally, the prevalence of diabetes is higher in men as compared with women but as age increases the difference between the two narrows significantly. The majority of diabetics globally are in the age group of 45 - 64 years and the most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people > 65 years of age[27]. The prevalence of diabetes in our study as correlated with age showed that as age increased the magnitude of diabetes increased as well. Prevalence of diabetes was shown to be the highest in the age group of 50 - 59 years with 9.35% in urban and 8.58% in rural areas. The age adjusted prevalence urban/rural 40 - 49 years was 5.55% and 3.94% and 60 years and above was 7.55% and 7.40% indicating thereby that middle-age was the most vulnerable segment for diabetes and its complications. Prevalence of diabetes in people aged > 50 years was almost twice than those aged < 50 years (8.82% vs 4.42%). Zargar *et al* (2000) in his study found that the prevalence of type 2 diabetes was the highest in the age group > 70 years and lowest in the age group 40 - 49 years (4.25% vs 0.93%). Zargar *et al* (2008) reported prevalence rates of 1.8% and 3.1% in young adults of the Kashmir valley in the age groups of 20 - 29 and 30 - 39 years respectively[7,8]. Anil J Purthy (2009) has reported that the prevalence of diabetes in his study from urban Puducherry was 8.2% after the age of 20 years[19]. Ramachandran *et al* (1997) has reported a significant increase in diabetes prevalence in urban Chennai with increase in various age groups (35 - 44 years 11.5%, 45 - 54 years 26.4% and 55 - 64 years 20% respectively[18]. Rao *et al* in their study on the prevalence of diabetes in coastal Karnataka in 2010 reported that the overall prevalence of diabetes was 16%, and increasing age showed two-fold, four-fold and six-fold higher odd's for 40 - 49, 50 - 59 and > 60 years age group as compared with the 30 - 39 years age group[28]. Bharati *et al* in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes (14.2%) in persons aged ≥ 50 years than in persons aged between 20 and 49 years (3.90%)[25]. Wijewardena *et al* (2006) in his study on the prevalence of diabetes in Sri Lanka conducted in the age group of 30 - 65 years reports a total prevalence of 14.2% in males and 13.5% in females indicating the influence of rising prevalence with age in both sexes[29].

Diabetes and socio-economic status

Socio-economic status in respect of developing countries forms an important risk factor in the development and progression of diabetes. People with higher socio-economic status are more likely to be sedentary, have higher rates of obesity, dyslipidaemia and thus are at greater risk of developing diabetes. In this study the impact of socio-economic status on the prevalence of diabetes has been profound. People belonging to social class I had twice the prevalence rates of diabetes as compared with people from social class V (10.08% vs 5.04%). Rao *et al* in their study on the prevalence of diabetes in coastal Karnataka in 2010 reported that the prevalence of diabetes was more in the high socio-economic strata 32% of the subjects had diabetes[28]. Vijayakumar *et al* (2009) has noticed a higher prevalence of diabetes in a rural community of Kerala with high socio-economic status[6]. Bharati *et al* (2011) reports similar association between high socio-economic status and increased prevalence of diabetes in a study from Puducherry[30]. Ram *et al* (2006) reports in his study on epidemiological risk factors in patients of diabetes attending a medical college hospital from Kolkatta that higher

prevalence of diabetes was associated with high socio-economic status[31].

Diabetes and literacy status

Diabetes and literacy status has been the subject of focus in a number of studies. Traditionally it was thought that people of low literacy levels would be more susceptible to develop diabetes because of ignorance and less knowledge about the disease. This study has shown that literate people have higher prevalence rates as compared with illiterate people (7.01% vs 5.24%) and urban literate have an even much higher prevalence than rural literate (8.34% vs 5.43%) meaning thereby that literate people whether urban or rural have higher prevalence rates as compared to their illiterate counterparts the possible explanation being that literate people are more sedentary, have less physical activity, belong to a higher socio-economic class and have more risk factors for diabetes. Bharati *et al* in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes in illiterate people than literate (10.0% vs 7.70%)[25]. This study is at variance with our study that reports a higher prevalence in literate subjects.

Diabetes and family history

A strong association between family history and the incidence/prevalence is well known and numerous studies have depicted the same. Over the years it has been considered that diabetes has a large genetic component as suggested by familial inheritance patterns. Diamond[32] initially commented on a high prevalence of diabetes in all ethnic groups worldwide and observed that there is a high prevalence in native communities in South Asia, Americas and the Pacific Islands but there is a low prevalence in the white population. The Asian phenotype is considered to be one of the major factors towards the increased risk for diabetes and nearly 75% of type 2 diabetics in India have a first degree family history indicating a strong familial aggregation in this population[33]. Recent genetic studies on Asian Indians indicate that certain genes appear to predispose Indians to diabetes[34]. In our study the prevalence of diabetes in those with a positive family history as compared with those without a family history was 19.44% vs 6.07% indicating the strong familial impact on prevalence. Bharati *et al* in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes in those with a family history and without (14.8% vs 6.6%)[25]. Vijayakumar G and Ram R report a similar association of increased prevalence in people with a strong family history[6,31]. Jali *et al* (2006) in a cross sectional hospital based study reports a total prevalence of 18.24% of diabetes in family members of known registered diabetics in Belagavi India with males/females showing prevalence rates of 10.38% and 7.69% respectively. He further observed that if both parents were diabetic the prevalence was 14.94%, if mother only then 10.0% and in case the father was diabetic then the prevalence was 6.48%[35]. This study though a hospital based one reveals the importance of family history on the overall prevalence of diabetes. Zargar *et al* (2008) in his study shows that the prevalence of diabetes was higher in those with a family history than in those without (13.3% vs 2.4%)[8]. It has been suggested that exposure to a high fat diet and low levels of physical activity are the common factors that trigger the gene environmental interaction in Asian Indians and both the thrifty genotype and the thrifty phenotype hypotheses appear to have aetiological roles in the development of diabetes in Asians. Genetic susceptibility to type 2 diabetes is unmasked by environmental changes that include urbanisation, dietary changes and physical inactivity[36].

Diabetes and physical activity

Prevalence of diabetes is directly correlated with physical activity and people who are physically active and exert bodily have less prevalence of diabetes as compared with those who are sedentary and physically inactive. Exercise is probably a protective factor against development of diabetes by way of increased insulin sensitivity in peripheral tissues especially muscle[37]. Studies in migrant Indians in Fiji and Tanzania have shown that despite correction of obesity, diabetes continued to increase in these populations showing thereby that diabetes is strongly associated with physical inactivity and is an independent risk factor for diabetes[38,39]. Most of the working population has now shifted to less demanding office jobs and sedentarism has crept into the society from children to the elderly leading to a spurt in the diabetic epidemic. In our study the prevalence of diabetes in those who were sedentary was 9.47% vs 4.44% in people who were physically active. Mohan *et al* in his study (CUPS 14, 15) has found that the prevalence of diabetes was three times higher in individuals with light or no physical activity compared to those having heavy physical activity (23.2% vs 8.1%)[40,41]. Bharati *et al* (2011) in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes in those with sedentary habits than physically active ones (10.1% vs 6.3%)[25]. Ram *et al* (2006) reports in his study on epidemiological risk factors in patients of diabetes attending a medical college hospital from Kolkatta for physical activity the estimated relative risk is maximum in case of sedentary workers where the odd's ratio was 9.4[31]. All these studies indicate that physical

inactivity is a major risk factor for development of diabetes.

Diabetes and obesity

Socio-economic growth in most of the developing nations particularly India has led to increased urbanisation, more office jobs, unhealthy diet practices, sedentary lifestyle, less physical activity and all these combined have enormously contributed to the increased prevalence of obesity in both urban and rural societies. Obesity is a major and proved risk factor in the development of diabetes and the term "diabesity " has been coined to underlie the interconnection and importance to this association. The metabolically obese phenotype among normal weight individuals in Asian Indians with a greater abdominal obesity and less muscle mass in spite of a normal BMI increases insulin resistance and consequently increases risk of diabetes at a younger age as compared with the western populations[36]. Risk of diabetes increases progressively from a BMI of > 23 kg/m^2 among Indians and BMI in > 23 kg/m^2 is considered overweight for most Asian populations. According to the WHO recommendation a BMI of 18.5 - 22 is considered healthy for the Asian population[42, 43]. Numerous studies have documented the increased prevalence of diabetes in the obese. Zargar *et al* (2000) in his study on the prevalence of type 2 diabetes in persons aged 40 years and more reports prevalence of diabetes is higher in the obese than in the non obese and that the obese subjects had a significantly higher basal as well as 2 hour blood glucose with GTT (6.57% and 13.34%) respectively[7]. Zargar *et al* (2008) has reported prevalence rate of 6.1% in obese subjects as compared with 2.3% in the non obese using a BMI of 25 kg/m^2 [8]. Our study shows that people with central obesity (BMI > 25 kg/m^2) have a much higher prevalence of type 2 diabetes than people who are not obese (12.03% vs 3.92%) and similarly people with abdominal obesity (WHR > 0.90) have higher prevalence of diabetes than those with a WHR < 0.90 (11.02% vs 4.54%). Ramachandran *et al* (1997) found that in an urban population in Chennai there was a strong association of increase in type 2 diabetes with higher BMI and WHR[18]. Bharati *et al* (2011) in their study on the prevalence of diabetes in people more than 20 years of age from Puducherry report a higher prevalence of diabetes in those with general obesity BMI > 30 kg/m^2 (13.8% vs 7.7%) and in those with with abdominal obesity WHR > 0.9 (10.9% vs 7.2%) [25]. Vijayakumar *et al* (2009) and Ram R in their study from Kerala and Kolkata report that central obesity was associated with a higher prevalence of type 2 diabetes (Odd's ratio 3.91 and 2.4) than in non obese people[6,31]. Despite a low BMI Asian Indians have more total abdominal and visceral fat with increased WHR leading to increased insulin resistance and consequently diabetes. McKeigue *et al* reported that in Asian Indians every 0.04 unit increase in WHR was associated with a four-fold rise in diabetes, two-fold higher post-glucose insulin levels, high triglycerides and low HDL[44]. The explosion of type 2 diabetes has been attributed to the fast food culture, migration from rural to urban areas particularly slums, sedentarism, a liking for white collar jobs, decrease in manual and agricultural labour leading to obesity, glucose intolerance and dyslipidemia[45, 46].

Diabetes and smoking

The risk of diabetes is said to be higher by 45% in smokers than smokers. A meta analysis of 25 studies found that active smoking was associated with a relative risk of 1.44 for type 2 diabetes[47]. Smoking increases insulin resistance due to increase in obesity. In most of the studies conducted the prevalence of diabetes is reported to increase than non smokers. In our study the prevalence of diabetes was equal in both smokers and non smokers (6.06% vs 6.43%) which is at variance with the study by Bharati *et al* who reported a prevalence of 10.3% in smokers vs 8.2% in non smokers[25].

Diabetes and dyslipidaemia

Dyslipidaemia and diabetes are two faces of the same coin. Diabetes is a strong factor for the development of dyslipidaemia particularly hypertriglceridaemia and hypercholesterolaemia and it has been observed that dyslipidaemics who are usually obese or overweight are at increased risk of development of diabetes and that the prevalence of diabetes is more in dyslipidaemic people than normal ones. In our study it was observed that the prevalence of diabetics was very high in dyslipidaemic people than in the non diabetic dyslipidaemics. WHO reports that a high saturated fat intake and high proportion of saturated fatty acids in serum lipids was associated with a higher prevalence of type 2 diabetes[48-50]. Prevalence of dyslipidaemic diabetics in people with hypertriglycerdaemia was an astounding 64.94% vs 38.26% in the general population. Similarly for cholesterol it was 38.85% vs 17.11%, HDL < 40 it was 38.24% vs 27.08% and for LDL > 100 it was 37.84% vs 25.67%. A number of studies have tried to find an association between dyslipidaemia and diabetes. Bharati *et al* (2011) found in his study on the prevalence and determinants of diabetes in Puducherry, South India, that prevalence of diabetes in people with cholesterol > 200 was 12.9% vs 5.97% in those with cholesterol < 200[25]. Kutty *et al* in his study on the prevalence of type 2 diabetes in an urban settlement in Kerala found greater prevalence is associated with advancing age, body mass index above 24.99, sedentary habits, serum total cholesterol > 239, serum

triglycerides > 149 as compared with people who had lower levels of these risk factors[51]. Vijayakumar *et al* (2009) in his study on the prevalence of type 2 diabetes in rural central Kerala reports that diabetes was significantly associated with hypercholesterolemia (Odd's ratio: 1.93)[6]. McKeigue *et al* in his study on migrant Indians in London has found increased prevalence of diabetes, hypertriglyceridaemia, low HDL and hyperinsulinaemia as compared with Europeans[52].

Conclusion

To conclude diabetes is a serious health issue and increasing prevalence rates in the young from 20 years of age, high rates of impaired fasting glucose and impaired glucose tolerance, a diminishing rural/urban and male/female difference, sedentary lifestyle, unhealthy dietary practices, high rates of obesity, dyslipidaemia and less physical activity all contribute to the enormity of the problem and unless concrete and definitive steps are taken to stop this epidemic it is bound to cause a great amount of morbidity and mortality more so at a young working productive age.

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INSTRUCTIONS TO AUTHORS

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Evaluation of primary tension type headache in school-going children

Umakant Anekar, Meenakshi Girish*, Nilofer Mujawar*, Vithalrao Dandge*, Girish Nanoti**

Abstract

We conducted a hospital based study to investigate children with chronic tension type headache (TTH) in order to evaluate the role of psychosocial stressors and the effect of psychotherapy. There were 85 children with chronic TTH diagnosed as per ICDH 2 criteria during the study recruitment period from January 2013 to June 2013. Psychosocial factors included 8 areas of stress in children, namely, school phobia, family phobia, over expectation, under expectation, emotional, environmental, social milieu, and parenting style. Internalising behaviour of children was found to be the most common stress factor 56 (65.9%). School absenteeism was found in only 11 (13%). All children responded well to multiple psychotherapy sessions. In conclusion, our study highlights the importance of psychosocial stressors in chronic TTH and the significant role of non-pharmacological therapy.

Key words: Chronic headache, psychological causes and psychotherapy.

Introduction

Chronic headaches constitute a significant, largely unaddressed burden of ill health and disability in children[1]. While the prevalence of migraine in paediatric age group is reported to be only slightly higher than the prevalence of chronic tension type headache (TTH)[2], migraine is much easier to identify and treat than TTH. Psychosocial stressors have been listed as one of the most common reasons for 'innocent' headaches in children[3]. Primary headaches interfere with school attendance and social activities, and significant parental anxiety related to the fear of brain tumours lead to multiple hospital visits and often unnecessary expensive investigations. Lack of studies in children to test the efficacy and safety of pharmacological treatment has placed non pharmacological treatment modalities in the form of psychotherapy, relaxation techniques, and biofeedback as first-line therapies. Our study was designed to explore the psychosocial stressors in chronic TTH and to evaluate the role of psychotherapy.

Objectives

1. To study the frequency of children with chronic TTH presenting at the out-patient department of a tertiary level hospital.
2. To identify the role of psychosocial stressors.
3. To determine the response to psychotherapy on follow-up at 6 months.

Material and methods

School going children in the age group between 6 and 16 years, attending the out-patient department of our hospital in the time period from January 2013 to June 2013 were included in the study if they presented with clinical history suggestive of chronic TTH as per the ICHD-2 criteria. Subjects not willing for long-term follow-up and those in whom TTH could not be clearly classified or had overlapping symptoms of migraine, were excluded. Organic causes were ruled-out clinically by assessment of their height/weight/head circumference, blood pressure and pulse, auscultation of neck, eyes and head for bruit, fundoscopy, and otoscopy. and examination and palpation of head, neck, shoulders, spine, and a thorough neurological examination. After taking written consent, an age appropriate prevalidated questionnaire, developmental psychopathological checklist, was administered to all the children. The questionnaire evaluated the children for eight stress factors, namely, school phobia, family phobia, over-expectation, under-expectation, emotional, environmental, social milieu and parenting style. All children were then referred to a psychologist for further management and followed for the next 6 months. Statistics were applied using SAS software and consisted of percentage analysis.

Results

There were 110 children who presented with symptoms of chronic primary headache during the study period. Only 85 children were enrolled for the final analysis, 10 were excluded as they were lost to follow-up and 15 had symptoms overlapping with migraine and hence were excluded.

Out of 85 cases of TTH, 32 (37.6%) were males, 53 females (62.4%). Majority of children were in the age group 11 - 13 years. 32 (37.6%), 43 (50.8%) were in the age group 6 - 10 years, and 10 (11.8%) in the 11 to 16 years age group

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(Table I). Duration of headache at the time of presentation ranged from 3 months to 2 years and each episode of headache lasted for an average range between 6 hrs to 2 days. In 22 cases (25.9%) headache was more often during school hours. School absenteeism was noted in 11 (13%). Parental anxiety was significant enough to enforce neuroimaging in 10 (11%). Table II shows age and sex-wise distribution of study subjects.

Tables I: Age and sex-wise distribution of participants.

Age group	Male (%)	Female (%)	Total (%)
Primary school	12 (14.10)	20 (23.52)	32 (37.70)
Middle school	17 (20)	26 (30.60)	43 (50.60)
High school	3 (3.60)	7 (8.24)	10 (11.80)
Total	22 (25.8)	53 (62.3)	85 (100)

Psychologic stressors were identified in 56 (65.9%) children (Table III). In all the 8 areas of stress, females were more affected than males, and middle-school children had more stressors than any other age group studied. Emotional stressor was recognised in all the 56 (65.9%) chidren. Medications were required in 9 (11%) cases, that too only in the initial week of counselling. Acetaminophen was the only drug prescribed. School phobia and fear of family member was identified in 54 (63.5%) children. Psychologic counselling in the form of relaxation therapy and in some, biofeedback therapy was done. All children were followed up with a headache diary. All 85 children (100%) achieved complete remission over a period ranging from 3 months to 6 months. All our patients belonged to the middle or lower socio-economic strata.

Table III: Frequency of psychological stressors in participants in both sexes.

	Male	Female	Total	Percentage
Family phobia	16	38	54	63.5
Educational phobia	19	35	54	63.5
Over-expectation	13	26	39	45.9
Under-expectation	17	27	44	51.8
Emotional	19	37	56	65.9
Environmental	17	33	50	58.9
Social milieu	18	34	52	61.8
Strict parental counselling	17	23	40	47.0

Discussion

Several studies have assessed the prevalence of primary headaches in the paediatric population[4] using the ICHD 2 criteria. The prevalence of TTH in our study was higher than that reported by others, although the increased prevalence in females in our study is similar to that reported in literature. The higher prevalence of TTH in younger children is also reported to be common in children belonging to the lower socio-economic strata[5]. Organic factors and heredity have been well-documented in the aetiopathogenesis of migraine[4]; in contrast, psychological factors have been found to be more relevant in TTH[6-10]. Internalising behaviour was judged as the emotional stressor in our tool and we found this to be a very common problem similar to other studies[11]. Educational pressures and family relations were the next common stressors found in our study, though there are conflicting reports regarding their role particularly in

Table II: Age and sex-wise distribution of cases in different stress areas.

Stress areas	Primary school age group N = 32		Middle school age group N = 43		High school age group N = 10	
	Males (%)	Females (%)	Males (%)	Females (%)	Males (%)	Female (%)
Family phobia	6 (18.7)	14 (43.7)	10 (23.2)	21 (48.8)	0	3 (30)
Education phobia	7 (21.8)	15 (46.8)	11 (25.5)	18 (41.8)	1 (10)	2 (20)
Over-expectation	5 (15.6)	10 (31.2)	8 (18.6)	14 (32.5)	0	2 (20)
Under-expectation	6 (18.7)	11 (34.3)	10 (23.2)	13 (30.2)	1 (10)	3 (30)
Emotional status	7 (8.25)	14 (43.7)	11 (25.5)	20 (23.5)	1 (10)	3 (30)
Environmental	6 (18.7)	12 (37.5)	10 (23.2)	18 (46.5)	1 (10)	3 (30)
Social milieu	7 (21.8)	13 (40.6)	11 (25.5)	15 (39.5)	0	4 (40)
Strict parenting style	4 (12.5)	7 (21.8)	12 (27.9)	14 (32.5)	1 (10)	2 (20)

chronic TTH[12]. Surprisingly, achievement orientation of parents was found to be more common with girls than with boys, but again there are conflicting reports on its role in the genesis of chronic headache[11]. School absenteeism was not found to be a major problem as majority of those abstaining did so for an average of 3 - 7 days/6 months. This is corroborated in another study[4] which found that school absenteeism was less common in children with TTH as compared to migraine.

The most gratifying part of our study is the effect of psychotherapy. To the best of our knowledge, no other study shows such a complete response to psychoptherapy, highlighting the need for greater emphasis in non pharmacological treatment, especially in children who have chronic TTH. A small number of patients (as some must have gone to medicine out-patient or neurological clinic), a lack of headache free controls in the study design, and the fact that ours was a clinic based study resulting in some selection bias constitute limitations in our study.

Conclusions

It is very important to evaluate for psychosocial stressors in all children with chronic primary headache and motivate parents to seek psychological therapy rather than pharmacological treatment for such headaches.

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"The only equipment lack in the modern hospital?
Somebody to meet you at the entrance with a handshake!."

– Martin H. Fischer.

ORIGINAL ARTICLE

JIACM 2015; 16(3-4): 201-3

Dyselectrolytaemia in acute myocardial infarction

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Abstract

The objective of this study was to estimate serum sodium and potassium concentration in patients of acute myocardial infarction, to compare electrolyte levels in cases and controls, and to correlate serum sodium and potassium concentration with prognosis of acute myocardial infarction. Seventy-five patients of acute myocardial infarction were studied with a mean age of 55 years. Twenty-five age and sex matched healthy controls were also included in the study. Serum sodium concentration was not affected in patients of acute myocardial infarction. In patients of acute myocardial infarction, hypokalaemia was present in 29.3% cases. Serum potassium concentration was decreased significantly in patients of acute myocardial infarction with arrhythmia (3.6 ± 0.87). Hypokalaemia was fairly common finding among acute MI patients, while serum sodium concentration showed no significant difference among the two groups. Mortality was more in males (31.4%) as compared to females (19%). Mortality was more in hypokalemic patients (27.2%). Therefore it is recommended that potassium levels which affect the clinical outcomes in patients of acute myocardial infarction should be monitored, and potassium replaced whenever required.

Key words: Myocardial infarction, serum sodium, serum potassium.

Introduction

Acute myocardial infarction is one of the commonest diagnosis in hospitalised patients. It is the leading cause of death worldwide. Sudden cardiac deaths occur worldwide – around 3 million per year[1]. The major determinants of electrophysiological peoperties of myocardial membrane are sodium and potassium. Electrolyte imbalances after acute myocardial infarction are common. Clinical importance of these imbalances in the era of primary intervention has not been fully understood[2]. In the resting state,the interior of the cell is negative, while outside is positive with a transmembrane potential of -80 to -100 mv.

The intracellular concentration of potassium ions is higher as compared to its extra-cellular concentration, while conversely, the extra-cellular concentration of sodium ions is higher than its intra-cellular concentration. There are four phases of action potential dependent on Na^+ K^+, and Ca^{++} [3]. Potassium ions play a very important role in the maintenance of normal cardiac function[4]. Hypokalaemia is seriously toxic to the heart[5]. The role of hypokalaemia in prognosis of myocardial infarction is under evaluation since a long-time[6]. There is a strong association between hypokalaemia and life-threatening arrhythmias[7]. After myocardial infarction, mortality is increased in hypokalaemic patients[8]. According to recent guidelines, we should monitor and replace K^+ in myocardial infarction even if initial K^+ appears normal[9]. In one study by Flear *et al*, hyponatraemia was a common finding among acute MI patients[10]. In some studies, it is mentioned that hyponatraemia is associated with poor outcomes in patients of STEMI[11]. In the era of primary interventions, the clinical outcomes of these electrolyte imbalances has to be fully understood especially in rural areas.

Aims and objectives

This study was taken to estimate serum sodium and potassium concentration in patients of acute myocardial infarction, to compare electrolyte levels in cases and controls, and to correlate serum sodium and potassium concentration with prognosis of acute myocardial infarction.

Material and methods

Twenty-five age and sex matched healthy controls were selected for estimation of the serum sodium and potassium concentration with electro-cardiographic recordings.

The seventy-five patients of acute myocardial infarction admitted to the intensive coronary care unit, irrespective of site of infarction and irrespective of type of arrhythmia were included in the study. The patients were of either sex, between the age group of 31 - 90 years. A detailed history of each patient was obtained. A thorough physical and systemic examination was done in all the patients. Routine blood and urine examinations were done. Blood urea, sugar, SGPT, serum creatinine, and cholesterol were estimated in all the patients.

The first electrocardiogram was taken at the time of admission. Serial electrocardiograms were taken till the patient remained in the hospital or expired. Serum sodium

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and potassium were estimated at the time of admission to ICCU.

The refrence values for serum sodium and potassium concentration were taken from clinical chemistry by TITZ.

Exclusion criteria: Patients with renal insufficiency, liver failure, chronic vomiting and diarrhoea patients, adrenal insufficiency, hyperglycaemic MI patients, hypertensive patients on potassium-sparing diuretics were excluded.

Results

In the study we have 25 controls and 75 cases with acute myocardial infarction. Table I shows the age and sex distribution of cases.

Table II compares the serum sodium and potassium concentration in the controls and cases. Out of 75 patients of AMI, 54 were males and 21 females with M: F of 18: 7. Serum sodium concentration was not affected in patients of acute myocardial infarction (139.7± 2.24) when compared with controls (140.4 ± 2.10). Serum potassium concentration was decreased in patients of acute myocardial infarction (3.6 ± 0.87) as compared to controls (4.4 ± 0.34).

Table I: Age and sex distribution of cases.

Age group in years	Males	Females	Total
31 - 40 yrs	8	0	8 (10.6)
41 - 50 yrs	16	5	21 (29.1%)
51 - 60 yrs	18	9	27 (36%)
61 - 70 yrs	9	7	16 (21.3%)
71 - 80 yrs	2	0	2 (2.6%)
81 - 90 yrs	1	0	1 (1.3%)
	54 (72%)	21 (28%)	100 (100%)

Occurrence of AMI was more in males as compared to females (M:F of 18:7) and between the age group of 51 - 60 yrs.

The lowest potassium level recorded in cases was 2.7 meq/l. Out of 75 patients; hyponatraemia was present only in 2 patients.

Seventy-three patients were normonatraemic. Hypernatraemia was not found in any patient. Out of 75 patients with acute myocardial infarction, hypokalaemia was present in 29.3%, hyperkalaemia in 4% of cases. Sixty-six per cent of cases had normokalaemia. Chart 1 shows the percentage of mortality in relation to serum potassium in patients of AMI. The mortality was more in hypokalaemic patients as compared to normokalaemic patients (27.2% vs 10.4%). There was no mortality in the hyperkalaemic group. The control group reported no mortality.

Discussion

Electrolyte imbalances are fairly common in acute myocardial infarction patients when sodium and potassium levels are measured within 48 hours of admission. Serum potassium concentration was significantly reduced in our study when compared to non-infarct control group.

Table II: Serum sodium and potassium concentration in controls and cases (patients of acute myocardial infarction).

Serum electrolyte concentration	Controls	Cases
Sodium ions		
Range (meq/l)	137 -144	136 - 144
Mean	140.2	139.9
SD	± 2.10	± 2.24
Potassium ions		
Range (meq/l)	3.9 - 5.0	2.7 - 5.7
Mean	4.4	3.6
SD	± 0.34	± 0.87

Serum potassium concentration was significantly decreased in patients of AMI when compared with controls. Statistical student "t" test was applied. p < 0.01 highly significant.

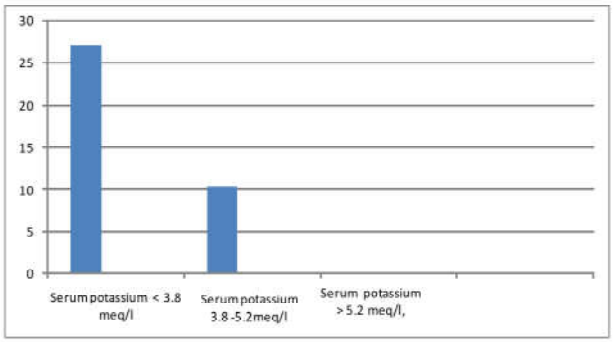

Chart 1: *Percentage of mortality in relation to serum potassium in patients of AMI.*

Hypokalaemia was present in a large number of patients. Hyperkalaemia was present in only 3 patients of myocardial infarction.

Hypokalaemia was found to be associated with increased risk of ventricular tachycardia in our study and in studies by Dyckner *et al* and Erik *et al*[7,8]. There is a five-fold increase in incidence of ventricular fibrillation in patients with low potassium[1].

This hypokalaemia is due to stress induced catecholamine reponse. In such patients this causes increased uptake of

K^+ into the cells[12]. Hyperkalaemia is found to be associated with reduced ventricular excitability and complete heart block.

In our study, hyponatraemia was present in only 2 patients. The patients who died were all normonatraemic. In contrast to our study, it is mentioned by Tang *et al* in his study that hyponatraemia was associated with increased morbidity and mortality in myocardial infarction patients[11].

A study conducted by Fear *et al* found hyponatraemia in 45% of patients of myocardial infarction and associated increased mortality[10]. On the contrary, in our study, hyponatraemia was present in only 2 out of seventy five cases; and all patients who died were normonatremic.

Conclusions

Hypokalaemia was present in large number of patients with acute myocardial infarction, mostly due to catecholamines response in such patients.

It has been associated with increased mortality in MI patients.

Hyponatraemia was not a common finding among acute MI patients.

Therefore it is recommended to monitor especially serum potassium levels and correct them as they have adverse effects on the disease outcome.

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Are creative minds hyper-sensitive?

It looks all creative minds are hyper-sensitive. That's why they create.

American novelist and Nobel laureate Pearl S. Buck (1892-1973) has this to say:

"The truly creative mind in any field is no more than this: A human creature born abnormally, inhumanly sensitive. To him... a touch is a blow, a sound is a noise, a misfortune is a tragedy, a joy is an ecstasy, a friend is a lover, a lover is a god, and failure is death. Add to this cruelly delicate organism the overpowering necessity to create, create, and create – so that without the creating of music or poetry or books or buildings or something of meaning, his very breath is cut off from him. He must create, must pour out creation. By some strange, unknown, inward urgency he is not really alive unless he is creating."

Courtesy: Journal of the Science of Healing Outcomes (JSHO) Vol. 7, No. 28 (July, 2015)

ORIGINAL ARTICLE

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Manifestations of dengue fever: A hospital based study

Payal Jain, Dheerendra Kuber*, Ajai K Garg*, GD Sharma**, AK Agarwal****

Abstract

Introduction: Dengue viral infection has become a significant tropical disease with increased recognition of atypical manifestations apart from the classical clinical features. This study outlines the evolving clinical spectrum of dengue with special emphasis on unusual manifestations.

Methodology: Data of 114 IgM dengue antibody-confirmed cases was collected, compiled, and analysed. Result: The outbreak was affecting mostly the younger age group with male preponderance. 7 cases had dengue without warning signs (D), 107 cases had dengue with warning signs (DW), and 16 cases had severe dengue (SD). Most common symptoms apart from fever and headache were gastrointestinal symptoms like abdominal pain, vomiting, and diarrhoea. Liver injury was almost universally present in the form of transaminitis. Atypical features were seen in 8.77% cases. Platelet count did not correlate exactly with severity of bleeding. Overall recovery rate was good. 2(1.75%) patients succumbed to multiorgan failure and shock.

Conclusion: Dengue illness may have a non-specific and varied presentation, thus mandating its screening in febrile illness especially during the post-monsoon period. The elucidation of the exact clinical profile is important for patient management.

Introduction

Dengue viral infection has grown dramatically around the world in recent decades. It has emerged as a serious international public health threat with almost half of the world's population at risk. Although the full global burden of the disease is uncertain; there are estimated 50 - 100 million cases every year with 500,000 people requiring hospitalisation annually and about 2.5% of those affected die[1]. In India the resurgence of dengue has led to frequent outbreaks in both urban and rural parts of the country. Interactions between crucial factors like environment, vector, virus, and ecology play an important role in dengue outbreaks.

Dengue presents with a range of clinical symptoms often with unpredictable clinical evolution and outcome. Infection by any of the four dengue virus serotypes may be asymptomatic or may lead to classic dengue fever (DF) or more severe forms of the disease namely dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)[1]. The 2009 WHO revised criteria classify dengue virus infection into dengue with or without warning signs and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure)[2]. A wide spectrum of unusual manifestations of dengue affecting various organ systems have recently become more frequent, which might be under-reported because of lack of awareness[3]. There are very few studies which have documented unusual clinical profile of dengue. The present study was conducted to assess the varied clinical profile of dengue patients admitted in a teaching hospital with special emphasis on unusual manifestations.

Methodology

The present study was conducted prospectively at Sharda Hospital, in the department of Medicine, School of Medical Sciences and Research, Greater Noida, during a dengue outbreak occurring between the months of August and November 2013.

The study was approved by the Institutional Ethics and Research Committee. Patients with clinically and serologically confirmed dengue virus infection, admitted in the medical wards of the hospital were included in the study. A proforma with detailed epidemiological, clinical, and laboratory parameters recorded during the hospital stay, was used as a tool for data collection. All clinical and laboratory details were reviewed daily and atypical manifestations were recorded. A positive serology was defined as the presence of IgM antibodies by ELISA at 5 or more days from the onset of fever with or without IgG antibodies. IgG antibody alone was not considered positive for the serological criteria because IgG antibodies could persist for more than 10 months. On the basis of their clinical presentation, the study subjects were classified and grouped as dengue without warning sign (D), dengue with warning signs (DW), and severe dengue (SD) according to WHO classification 2009 and treated as per standard WHO guidelines. The variables included as warning signs were persistent vomiting, restlessness, abdominal pain or tenderness, clinical fluid accumulation, mucosal bleed, liver enlargement, increase in haematocrit with concomitant drop in platelet count. Severe cases were defined as the following: severe plasma extravasation that led to dengue shock syndrome (DSS) or liquid accumulation with respiratory

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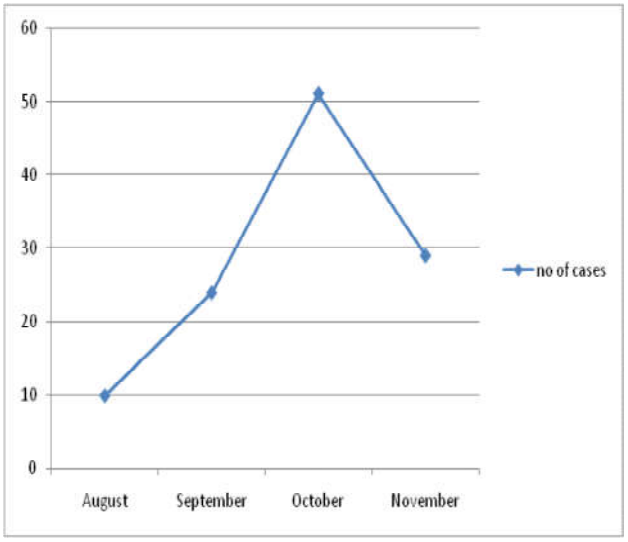

Fig. 1: *Month-wise distribution of serologically positive cases.*

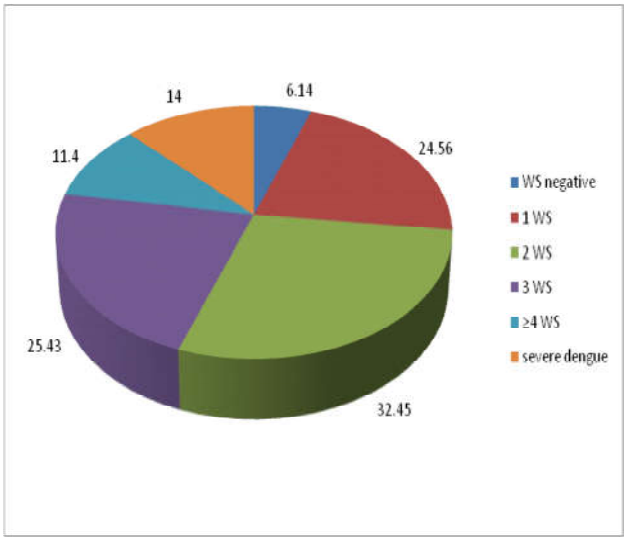

Fig. 4: *Dengue case categorisation according to 2009 revised criteria.*

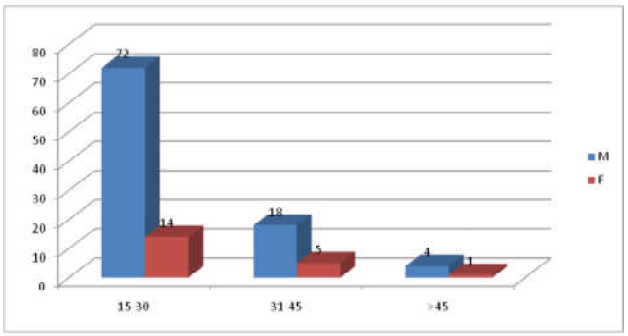

Fig. 2: *Distribution of patients according to age and sex.*

discomfort, severe haemorrhage, severe involvement of tissues, such as ≥ 1,000 IU/l levels of aminotransferases; and impairment of the central nervous system, heart, and other organs[2]. All categorical variables such as clinical characteristics and biochemical tests were expressed as numbers and percentages and continuous variables were expressed as mean ± SD.

Results

285 patients were admitted to the hospital with a clinical diagnosis of dengue fever, but only 114 patients have been

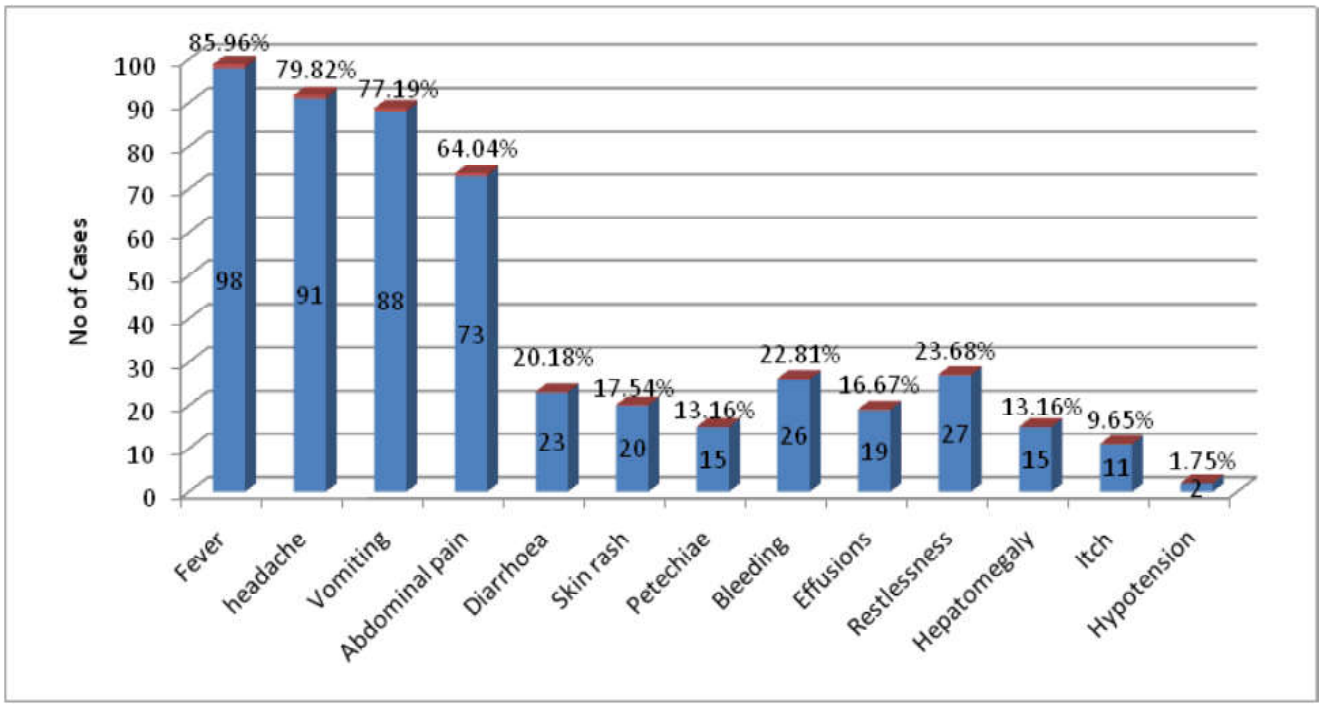

Fig. 3: *Clinical manifestations of dengue patients.*

included in this study as these cases fulfilled the standard serological criteria for the diagnosis of dengue infection.

Table I: Laboratory parameters of dengue patients.

Parameter	Number of patients	%
Haemoconcentration (HCT > 45%)	15	13.1
Thrombocytopenia (platelets ≤ 20,000/cu mm)	5	4.38
20,001 - 50,000/cu mm	42	36.84
50,001 - 100,000/cu mm	47	41.22
> 100,000/cu mm	20	17.54
High AST > 50 IU/l	97	85.1
High ALT > 50 IU/l	92	80.7
Bilirubin > 2 mg/dl	4	3.5
Creatinine > 1.2 mg/dl	3	2.63

Warning signs

Apart from the classical profile, we observed some atypical manifestations of dengue fever in this study. A total of 10 (8.77%) patients in the present study had atypical presentation.

Table II: Atypical clinical presentations of dengue patients.

Atypical clinical presentation	Number of patients
1. Hypokalaemic paralysis	3
2. Guillain-Barré syndrome	1
3. Encephalitis	2
4. Acute respiratory distress syndrome	2
5. Myocarditis	2

Discussion

Dengue is an important emerging problem of the tropical and sub-tropical regions today. The epidemics of dengue fever have been reported in the post-monsoon season, at every 2 - 3 year intervals. Majority of the patients in our study were diagnosed in the months of October and November than in August and September which was in accordance with various other studies[4,14] (Fig. 1). These findings indicate that preventive measures against dengue virus infection should come into full swing during water stagnation periods after the initial bouts of rainfall and at the end of monsoon. In this study, more than two-third of the study subjects were males. Various other Indian studies have also shown a male preponderance[4-6]. A recent study from eastern India by Chatterjee *et al*, however, found an equitable sex distribution[9].

The majority of the patients in the present study were young individuals, mean age being 27.13 years (Fig. 2). Patil from Maharashtra[5] and Chaturvedi *et al*[8] also reported a high incidence in young population.

Out of a total of 114 dengue sero-positive cases, 7(6.14%) cases were classified in group of dengue without warning signs, 107 (93.85%) cases in group of dengue with warning signs and 16 (14%) cases in severe dengue (Fig. 3). Early warning signs of dengue infection like pain in abdomen, persistent vomiting, hepatomegaly, haematocrit rise, and evidence of fluid leak should be observed carefully for timely intervention to prevent shock and severe complications. Although diarrhoea was not stated as a warning sign of dengue, the inclusion of diarrhoea was justified by the high frequency of the symptom.

The most common presenting symptoms were fever (85.96%), headache (79.82%) and vomiting (77.19%) (Table III). These results are in agreement with several studies in the literature. Abdominal pain was another frequent presentation seen in 64% subjects which was higher than that reported in previous dengue outbreaks. A high incidence of gastrointestinal symptoms was reported in a study from Kerala also and is attributed to hepatomegaly and serosal inflammation[10]. It is imperative to keep in mind that other infections causing fever and gastrointestinal symptoms such as *Salmonella typhi, Leptospira* and *Enterovirus* infections are common in India and may often lead to a diagnostic dilemma.

Cutanaeous manifestations can vary from maculopapular rash, petechiae, flushing and itching. In this study, rash was seen in 17.54%, petechiae in 13.16% and itch in 9.56% cases. A north Indian study by Karoli *et al*[6], reported rash in 26% cases and cutanaeous hypersensitivity in 16% cases, while a study from eastern India found rash in 37.84% cases[7]. Erythematous blanching rash during the initial phase of the illness was observed to be almost diagnostic of dengue fever.

Serositis in the form of ascites and pleural effusion from capillary leak are being frequently reported in recent outbreaks. In our study, radiological evidence of serositis was seen in 16.67% cases. Contrary to our findings, Chatterjee *et al*[9] found serositis in 43% subjects but was self-limiting and subsided within 2 - 3 weeks of recovery.

Bleeding diathesis is a known feature of dengue illness because of low platelet count and leakage from blood vessels. A significant proportion of patients (80%) in our study had platelet count below 100,000/cumm and 47 patients (41.2%) had platelet count below 50,000/cumm. Bone marrow suppression, immune mediated clearance, spontaneous aggregation of platelets to virus infected endothelium; all may contribute to thrombocytopenia. Bleeding manifestations were seen in 26 (22.8%) patients and were mainly in the form

of epistaxis, gum bleed, subconjunctival haemorrhage, and gastrointestinal bleed (Fig. 2). This is in contrast to 63% and 69% of bleeding manifestations reported by Horvath from Australia[11] and Sharma from India[12] respectively. Among 26 cases that had bleeding tendencies in our study, 11 cases showed normal platelet counts. In a Hyderabad based study by Khan *et al*[13], only 5% cases had bleeding while 40% had thrombocytopenia.

Type and severity of bleeding did not correlate with platelet count, signifying the fact that factors other than thrombocytopenia like platelet dysfunction, consumption coagulopathy, and endothelial dysfunction might be contributory. Likewise, many of the studies did not see any direct association between the platelet counts and bleeding diathesis.

Abnormal levels of AST and ALT were observed in 85.1% and 80.7% of the patients, respectively. The elevation of transaminases was usually mild to moderate in most cases (< 5-fold greater than the normal upper limit for AST and ALT) suggesting that liver involvement was mild-to-moderate in dengue infection. Anicteric hepatitis was commonly seen with elevated bilirubin in only 3.5% patients.

The mechanism of liver injury in dengue remains unclear. Liver cells may be damaged through one or more of the following mechanisms: (i) direct cytopathic effect of the virus; (ii) unregulated host immune response; and (iii) a non-specific effect of shock and hypotension[15].

Hepatic dysfunction was seen more in patients with severe dengue infections, similar to the study done by Roy *et al*[18]. Elevation of AST was more as compared to ALT in the present study and is consistent with other studies[16-18]. This differs from the pattern seen in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels. Though liver involvement is mild in majority of patients, fulminant hepatic failure may occur rarely leading to massive necrosis of the liver, hepatic encephalopathy, and even death[18]. Acalculous cholecystitis, acute pancreatitis, and acute parotitis are among the other gastrointestinal manifestations reported[3].

In our study, neurological involvement was seen in 5 (4.38%) patients in the form of hypokalaemic paralysis (3), encephalitis (2), and Guillain-Barré syndrome (1). The pathogenesis of neurological complications can be related to neurotrophic or systemic effect of the virus or can be immune mediated[19]. The exact incidence of various neurological complications is uncertain. Hypokalaemic quadriparesis is one of the manifestations for which only few case reports are present in literature[20,21]. Gupta *et al* reported that dengue fever can precipitate an attack of hypokalaemic paralysis; however, pure motor quadriparesis due to hypokalaemia was only occasionally reported. Our patients had pure motor quadriparesis and responded dramatically to potassium supplementation. Further documentation is required for such an association of acute pure motor reversible weakness to dengue fever.

Dengue fever as an antecedent infection in Guillain-Barré syndrome is uncommon. Some previous reports, as with our case, call attention to the possibility that Guillain-Barré syndrome may occur in association with dengue[6,7,23], although the mechanisms that relate to this infection are still not known. IV human immunoglobulin therapy resulted in total recovery in our case complicated by Guillain-Barré syndrome.

The reported incidence of encephalopathy and encephalitis has been found to vary between 0.5% and 6.2%[19]. Misra *et al* described 11 encephalopathic patients with confirmed dengue virus infection with lymphocytic pleocytosis in CSF, suggesting a viral meningoencephalitic process[24]. The primary features of dengue encephalitis are fever, headache, reduced consciousness, and seizures; although other neurologic manifestations may be evident.

Acute respiratory distress syndrome (ARDS) is one of the dreaded complications of dengue haemorrhagic fever, secondary to increased alveolar-capillary membrane permeability due to endothelial damage leading to interstitial and alveolar oedema. There are reports of ARDS with dengue fever (Sen *et al,* 1999; Wang Lin *et al,* 2007; Devarajan *et al,* 2008).

Two patients in our study developed sinus bradycardia and hypotension; there was some degree of myocardial damage causing impairment of the LV systolic function and elevation of the serum troponin T level. Both had favourable outcome with adequate and efficient supportive therapy. Clinical manifestations of cardiac complications vary considerably from tachy–brady arrhythmia to severe myocardial damage. Cardiac arrhythmia such as atrioventricular block and sinus node dysfunction, as well as reversible myocarditis has been reported in patients with dengue; most of these are self-limiting[28,30].

Renal impairment was seen in 3 (2.63%) patients. Shock-induced acute tubular necrosis is the main cause of renal failure in dengue patients apart from other rare causes like multi-organ dysfunction and rhabdomyolysis[30]. Descriptions of glomerular changes observed in DHF are scarce.

The outcome of the disease is variable as evidenced by various studies; however, overall patient outcome in our study was good, with majority of the patients recovering completely. During the study period, 2 (1.75%) patients died due to multiorgan failure and shock. The limitations of this study were that some cases exhibiting symptoms and signs suggestive of dengue illness were not included because they were sero-negative for dengue infection. Also,

specific serotype detection facility for dengue virus was not available at the institutional level.

Conclusion

The problem of dengue is enormous in our country. It is compounded by the huge population, poor medical and diagnostic facilities, inadequate mosquito control and all the ground conditions that favour multiplication of the vector. In view of the increase in the number of cases and the changing clinical spectrum of the disease, future studies should be designed to find predictive value of clinical and biochemical abnormalities that will help physicians in triaging patients in an outbreak situation. A high index of suspicion is required to detect and timely manage the atypical manifestations of dengue fever as these are no more a rare occurence.

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"To live by medicine is to live horribly."

– Carolus Linnaeus (1707 -1778).

ORIGINAL ARTICLE

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Haematological profile of *vivax* malaria patients

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Abstract

Introduction: Malaria is a common disease with a variety of manifestations. Plasmodium, being a parasite of red blood cells, haematological complications are not infrequent. Vivax malaria was supposed to be benign; however, major systemic involvement has been associated with falciparum malaria; recent observations suggest that haematological complications are frequently seen with vivax infection also.

Material and methods: Consecutive patients over the age of 18 years who tested positive for the malarial parasite P. vivax, were included in the study. The patients found to be having P. falciparum co-infection were excluded. A general and systemic examination was performed and the blood samples were examined for haemoglobin, total leukocyte count, platelets, red cell count, and red cell indices.

Results: A total of 79 vivax malaria patients were included in the study. The commonest abnormality seen in the patients was thrombocytopenia seen in 97.5% patients; however it recovered with chemotherapy for malaria. Second common abnormality was anaemia seen in 44.3% patients.

Conclusion: Haematological abnormalities are encountered in vivax malaria. Thrombocytopenia is the most common. A differential diagnosis of malaria should be considered in patients presenting with fever and thrombocytopenia.

Key words: Malaria, thrombocytopenia, vivax.

Introduction

Malaria is one of the most prevalent human infections in the world. More than 40% of the world population resides in malaria-endemic areas[1]. Almost all cases of malaria are caused by four species of the genus *Plasmodium* – namely *vivax, falciparum, malariae,* and *ovale*. Malaria infection imposes a great socio-economic burden on humanity, accounting for 85% of global infectious disease burden along with other diseases[2]. Approximately 1.2 billion people live in areas of high risk and 2.1 billion in low-risk areas, and each year, there are nearly 247 million cases and 1 million deaths.

Malaria has been a major public health problem in India. The reported incidence of malaria in India has been 1.5 - 2.6 million cases with 666 - 1,000 deaths per annum since 1990. The malaria caused by *P. vivax* is widely distributed around the world; and in the regions of South and South-east Asia, it represents almost 50% cases of malaria[3].

The malarial parasite, i.e., *Plasmodium*, is a parasite of blood and it may cause haematological alterations. Haematological changes that have been reported to accompany malaria are anaemia, thrombocytopenia, leucopenia, atypical lymphocytosis, and infrequently disseminated intravascular coagulation[4]. Leucocytosis, neutropenia, neutrophilia, eosinophilia, and monocytosis also have been reported[5,6].

The morbidity and sometimes mortality associated with malaria is high and these haematological parameters play an important role in it. Some recent studies have shown that *P. vivax* can also cause severe disease and the haematological parameters are usually affected in such cases. The present study was undertaken to identify the haematological alterations in *vivax* malaria patients.

Material and methods

The current observational study was performed at the School of Medical Sciences and Research, Sharda Hospital, Sharda University, Greater Noida during an outbreak of malaria between the months of April and November in the year 2011. All the patients over the age of 18 years who tested positive for malaria parasite – *P. vivax*, by blood smear examination (thick and thin) and underwent treatment at the Department of Medicine of the institute, either as in-patients or out-patients, were included in the study. The patients found to be having co-infection with *P. falciparum* were excluded. The exclusion was done on the basis of thick and thin film and malaria rapid card test; however, polymerase chain reaction (PCR) with deoxyribonucleic acid probe was not done for species identification.

A thorough general and systemic examination was performed and the blood samples were examined for haemoglobin, total leukocyte count, platelets, red cell count, and red cell indices (packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin

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concentration). Liver functions test, renal functions test, chest radiograph, and glucose-6-phosphate dehydrogenase (G6PD) activity were also performed. Haemogram was done with Sysmex-XT-1800i auto-analyser and liver functions test and renal functions test was done with Johnson and Johnson – Vitros 5.1/FS auto-analyser.

The patients presenting with clinical features mimicking malaria were excluded if they tested negative for malarial parasite tests but treated empirically for malaria; tested positive for *Plasmodium falciparum*; were co-infected with *Plasmodium falciparum* or had other infections proven either by serology or culture studies of blood and body fluids.

Anaemia was defined as haemoglobin level less than 12 gm/dl. It was further categorised as severe anaemia with a haemoglobin level of < 6 g/dl, and mild-moderate anaemia with haemoglobin level between 6 and 12 g/dl. Patients with platelet levels less than 150 x 10^9/l were designated as having thrombocytopenia. The platelet values at third day and seventh day were also recorded to assess the platelet recovery duration.

Results

A total of 79 patient of *vivax* malaria were included for the study. The average age of the patients in the study group was 29.8 ± 11.5 years; the male to female ratio being approx 2.5:1. Liver dysfunction was seen in 44.3% patients and renal dysfunction in 36.7% patients (Table I). Other haematological parameters are shown in Table II. The duration of admission was between 5 and 7 days and the patients were treated with artemisinin combinations (ACTs). All the patients who were G6PD sufficient were given primaquine for radical cure.

Table I: Demographic profile of malaria patients.

Parameters	Values
Age	29.8 ± 11.5
Sex	57:22 (approx 2.5:1)
Anaemia	35 (44.3%)
Liver dysfunction	35 (44.30%)
Renal dysfunction	29 (36.7%)

The mean haemoglobin of the study group was 12.17 ± 2.93 gm/dl. 44.3% patients had anaemia; however, severe anaemia was not observed in the study group. Majority of patients had haemoglobin levels between 10 - 12 gm/dl (Table III).

The mean platelet count of the patients at presentation was 77.1 ± 37.5 x10^9/l. Majority of patients had thrombocytopenia (97.5%), only two patients had normal platelet count at presentation. Only one patient had severe thrombocytopenia (< 20 x 10^9/l). 87.3% patients had normal platelet count at day 7. Only 3 (3.8%) patients had platelet count below 100 x 10^9/l on seventh day (Table IV).

Table II: Haematological profile of malaria patients.

Parameters	Mean ± SD
Haemoglobin	12.17 ± 2.93
Total leucocyte Count	6056.45 ± 2875.70
Total RBC Count	4.07 ± 0.73
Total platelet count	77.17 ± 37.51
MCV	86.5 ± 9.2
PCV	35.15 ± 5.85
ESR	19.69 ± 10.6

Table III: Haemoglobin levels in the study group.

Haemoglobin (gm/dl)	Number	Percentage
< 6	0	0
6 - 8	3	3.8
8 - 10	6	7.6
10 - 12	26	32.9
> 12	44	55.7

Table IV: Platelet values at presentation and after 7 days.

Platelet	Day 0 (no. of pts.)	Day 3 (no. of pts.)	Day 7 (no. of pts.)
< 20 x 10^9/l	1 (1.3%)	1 (1.3%)	0
20 x 10^9/l -50 x 10^9/l	18 (22.8%)	10 (12.7%)	0
50 x 10^9/l -100 x 10^9/l	43 (54.4%)	25 (31.6%)	3 (3.8%)
100 x 10^9/l -150 x 10^9/l	15 (19%)	31 (39.2%)	7 (8.9%)
> 150 x 10^9/l	2 (2.5%)	9 (11.4%)	69 (87.3%)

The mean total leucocyte count of the study group was 6,056.45 ± 2,875.70/l. The major changes in differential leucocyte count were seen in lymphocytes, neutrophils and monocytes. Eosinophils and basophils were normal (Table V).

Discussion

Although haematological changes are well-recognised with malarial infection, background haemoglobinopathy, nutritional status, demographic factors and malaria immunity play a major role in specific changes in that

geographical region[7]. These parameters are well studied in *P. falciparum* infection, but now recent studies have indicated that these changes do occur in *P. vivax* infection also.

Table V: Haematological parameters of malaria patients

Parameters		Number (n = 79)	Percentage
Haemoglobin	Normal	44	55.7
	Anaemia	35	44.3
Leucocyte count	Normal	60	75.9
	Leucopenia	17	21.6
	Leucocytosis	2	2.5
Platelet count	Normal	2	2.5
	Thrombocytopenia	77	97.5
Neutrophils	Normal	65	82.3
	Neutropenia	9	11.4
	Neutrophilia	5	6.3
Lymphocytes	Normal	64	81.1
	Lymphopenia	12	15.2
	Lymphocytosis	3	3.7
Monocytes	Normal	74	93.7
	Monocytopenia	0	0
	Monocytosis	5	6.3
Eosinophils	Normal	79	100
Basophils	Normal	79	100

The major haematological change seen in the present study was thrombocytopenia which was seen in 97.5% patients. Only 2 (2.5%) patients had normal platelet count at presentation. Severe thrombocytopenia (counts < 20 x 10^9/l) was seen only in one patient, while in majority of patients platelet count was between 50 x 10^9/l to 100 x 10^9/l. The pathogenesis of thrombocytopenia consists of a myriad of pathogenetic mechanisms involving splenic pooling of platelets, antibody (IgG) mediated platelet destruction, adenosine diphosphate (ADP) release following the haemolysis of parasitised RBCs, dysmegakaryopoiesis, platelet aggregation and activation, parasite invasion of platelets, platelet phagocytosis, platelet adhesion to erythrocytes, and oxidative stress[8,9]. Nevertheless, thrombocytopenia in malaria is observed to improve with disease resolution, and a normal platelet count is usually reported within 7 days after the initiation of antimalarial treatment[10]. A study from Uttarakhand region of India, which demonstrated manifestations of severe malaria in *vivax* infected patients had also shown thrombocytopenia as the major haematological change[11]. Thrombocytopenia with increased mean platelet volume can serve as an indicator for *vivax* malaria[12].

Malaria is the most common cause of severe anaemia in endemic areas[13]. Although *vivax* malaria is thought to be benign, some studies have shown that it can cause severe anaemia as well[11]. 44.3 % patients in the present study have anaemia; however severe anaemia was not seen. Anaemia in malaria is believed to occur due to haemolysis of parasitised and non-parasitised RBCs, peripheral sequestration of RBCs, and ineffective erythropoiesis. In malaria endemic areas, the prevalence and severity of anaemia are usually determined by a number of interacting factors. These include the level of parasitaemia, age of host, host genetic factors (e.g., co-existing RBC polymorphisms like haemoglobinopathies, G6PD), and non-malarial causes of anaemia (e.g., infections, malnutrition)[13].

Leucocytes play a vital role in the defense against malaria. Acuteness of infection, disease severity, parasitaemia, state of the host immunity to malaria, and concurrent infections play a major role in leucocyte changes of malarial infection[13]. The present study demonstrated that leucopenia is the commonest abnormality seen in 21.6% patients as compared to leucocytosis. The major changes seen in differential leucocyte count were in lymphocytes, neutophils and monocytes while eosinophils and basophils were normal. These changes are well reported in *falciparum* malaria but are seen in *vivax* malaria also. Lymphopenia was the commonest abnormality seen in 15.2 % cases as compared to lymphocytosis, which is well supported by literature that suggests that lymphopenia, sometimes profound but transient, is a common finding in acute malaria in nonimmune adults. The tissue redistribution of lymphocytes, from the free flowing pool to the marginal pool at the endothelial lining is usually responsible for transient malaria lymphopenia, particularly observed in T lymphocytes[14,15]. Sometimes lymphocyte destruction as a result of Fas-induced apoptosis is also a factor responsible for lymphopenia[16].

Activation of either phagocytes (neutrophils and macrophages) or natural killer (NK) cells is responsible for the innate immune response to blood borne pathogens. Thus reticuloendothelial hyperplasia involving macrophages, is one of the most important early pathological hallmarks in malaria. Hence, monocytosis has been one of the most consistent observations reported from prior studies done on the haematological changes that characterise malaria[17]. Although in majority of patients, monocytes were normal, 6.3% patients showed monocytosis.

The neutrophil count was normal for majority of patients

(82.3%) in this study. These findings are similar to those from two studies: one from India, in which about 85% of the patients had normal neutrophil counts[17] and another from Singapore where majority of the adults with acute uncomplicated malaria had normal neutrophil counts[18]. Some earlier studies had reported neutropenia or neutrophilia[19] among malaria cases, which was seen in 11.4% and 6.3% patients respectively in the present study. The mechanism of neutropenia in malaria has been postulated to involve increased margination and sequestration of neutrophils[15] as a result of the increased expression of cell adhesion molecules (ICAM-1 and VCAM-1)[20].

Although thrombocytopenia is the most common abnormality, it is largely asymptomatic. However, in a few cases, patients may have severe thrombocytopenia and can have bleeding requiring platelet transfusion. In the majority of cases, thrombocytopenia does not require any specific treatment, and improves with the antimalarial treatment only.

Anaemia is the second common abnormality in these cases and is mainly normocytic normochromic[17]. In the majority of cases, anaemia does not require any treatment and improves gradually; but in a few cases, blood transfusion (packed red blood cells) may be required.

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"Poisons and medicine are oftentimes the same substance given with different intents."

– Peter Mere Latham.

SHORT COMMUNICATION

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Clinical profile of dengue fever in a tertiary care centre in North India

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Abstract

Introduction: Dengue fever is one of the most common arbo virus mediated outbreaks, being reported from different parts of the world. Dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are different modes of presentation of the disease. Now as the outbreaks are hitting different geographic locations, different clinical manifestations are more and more being reported recently. The aim of this study is to document varied clinical manifestations of dengue patients in a tertiary care centre of Northern India.

Materials and methods: Total 137 patients were taken who were either the dengue NS1 Ag positive or had the presence of the IgM and the IgG Abs or both were included in this observational study and analysed.

Results: The most common clinical feature was fever (100%) followed by nausea and vomiting (67.15%), abdominal discomfort (59.12%) cases, and myalgia (57.66%). Ascitis and pleural effusion were also noted in the 2.92% cases and 2.19% cases respectively. Community awareness, early diagnosis and management and vector control measures need to be strengthened in order to reduce the increasing number of dengue cases.

Introduction

Dengue infection is a major health problem in our country. Globally, the incidence of dengue has increased in the recent years. The WHO estimates that presently about two-fifths of the world population is at risk for this viral infection[1]. Dengue was first reported in 1780, when Benjamin Rush described this condition as "break bone fever". It is a mosquito borne viral infection with four serotypes causing dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS)[2]. It is estimated that worldwide nearly 2.5 billion people continue to live at risk of contracting the infection while 50 million cases and 24,000 deaths tend to occur in 100 endemic countries. Risk of mortality in treated cases of DHF/DSS is 1% while mortality rate among untreated cases escalates to 20%[3]. India is one of the seven countries in the South-East Asia region regularly reporting the incidence of DF/DHF outbreaks due to its high incidence which constantly threatens the health care system. The first confirmed report of dengue infection in India dates back to the 1940s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality[4]. Several fatal forms of the disease, i.e., DHF, DSS have been reported in India from time to time in Kolkata, Delhi, and Chennai[5-8]. All the four serotypes of the virus have been in circulation and documented in Tamil Nadu[9]. During all these epidemics, infection occurred in active adults in the age group of 16 - 60 years[10,11]. The common signs and symptoms observed were fever, headache, myalgia, arthralgia, and bleeding manifestations have also been observed. The exact clinical profile is important for patient management and thus crucial for saving lives. The present study is an attempt to describe the salient clinical as well as laboratory findings of serologically confirmed hospitalised cases of dengue fever during the study period. The study group represented the adult population.

Material and methods

This is an observational study. The patients were selected were from the admitted patients in the Rajindra Hospital, Patiala, a tertiary care centre in the State of Punjab. We included 137 patients suffering from dengue fever in the study period from September 2013 to November 2013. All the patients who presented with fever and who were either the Dengue NS1 Ag positive or had the presence of the IgM and the IgG Abs or both, were included in the present study. But patients with other co-infections like malaria, typhoid, etc, or with any other co-morbid diseases were excluded from the study. A detailed history was taken and a careful clinical examination was performed. The laboratory investigations like haemoglobin (Hb), the total and the differential leucocyte counts (TLC and DLC), platelet count, haematocrit (Hct), liver function tests (LFT), urea, creatinine, chest X-ray, and ultrasonography of abdomen were done in all the patients. Other relevant investigations were performed according to the clinical condition of the patients.

Results

Patients of different ages – from 16 years to 80 years – presented to the hospital varying. The Table I shows

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distribution of patients according to age group. Male to female ratio was found to be1.2:1.

Table I: Age-wise distribution of patients.

Age (Years)	Male (N = 75)	Female (N = 62)	Total (137)
16 - 20	10	7	17
21 - 30	26	19	45
31 - 40	11	12	23
41 - 50	9	10	19
51 - 60	6	9	15
> 60	5	3	8

Fever was the most common clinical presentation which was found among all the presenting patients (100%). The fever was of a mild-to-moderate degree in a majority of the patients and it had no specific pattern. The other main complaints besides fever were vomiting, nausea, rash, petechiae, itching, myalgia, and upper abdominal pain. Among the 20 patients with bleeding manifestations, 6 patients had both gum bleeding and gastrointestinal bleeding in the form of malena, 6 patients had gum bleeding only, and 8 patients had only malena. Among the 50 patients with rash, 30 patients had an erythematous hue of the skin and the rest had purpuric spots. 4 patients also had subconjuctival haemorrhage.

Table II: Symptomatology with percentage.

Symptoms	Patients (N=137)	Percentage
Fever	137	100%
Myalgia	79	57.66%
Rash	50	36.49%
Abdominal discomfort	81	59.12%
Vomiting, nausea	92	67.15%
Headache	15	10.94%
Bleeding	20	14.59%
Diarrhoea	13	9.48%
Itching	27	19.78%
Ascites	10	7.29%
Retro-orbital pain	8	5.8%
Pleural effusion	9	6.5%

Out of 137 patients, 50 had platelet count below 50,000/cumm of blood and the rest 87 patients (62.16%) had more than 50,000/cumm of blood. And among the 50 patients with below 50,000 platelet count, 22 patients had both rash and bleeding,10 had rash only, and 10 had bleeding episode only without any rash in spite of having a low platelet count, while the other 8 had neither rash nor bleeding. Considering the rest 87 patients, only 14 patients had rash, but none had bleeding episodes. Various biochemical parameters were depicted in Table III. One interesting finding in this table was transaminitis in these patients without elevation of bilirubin.

All the patients who were suspected to have the dengue infection were admitted. The average duration of their hospital stay was 10 - 14 days. The average duration of the fever was found to be 7 - 10 days. No mortality was reported during the study.

Table III: Biochemical/laboratory parameters.

Parameters	Mean ± SD
Haemoglobin (gm/dl)	12.6 ± 3.41
Total leucocyte count (cumm)	4,819 ± 1,578
Platelet count (cumm)	9,899 ± 7,105
PCV	39.9 ± 4.9
Urea (mg/dl)	39.99 ± 17.67
Creatinine (mg/dl)	1.17 ± 0.41
Bilirubin (total) (mg/dl)	0.89 ± 0.43
Bilirubin (direct) (mg/dl)	0.46 ± 0.24
Bilirubin (indirect) (mg/dl)	0.49 ± 0.20
AST (IU/ml)	157.8 ± 111.0
ALT (IU/ml)	115.4 ± 108.6
ALP (IU/ml)	209.34 ± 99.98

Discussion

Dengue is emerging as a major health problem in India. Since the first epidemic in 1963 - 64 in Kolkata, many places, including the rural areas of north India, have been experiencing regular outbreaks of the dengue infection. In the present outbreak, dengue cases showed a male to female ratio as 1.2:1 respectively. Congruent pattern was also seen in the retrospective analysis of the 2006 North Indian dengue outbreak[12]. The study revealed that majority of the cases were in the age group of 15 - 40 years. The clinical profile of dengue revealed that fever was the most common presenting symptom (100%). Similar studies in and around India have also substantiated fever as being the most common presenting symptom. Abdominal pain and vomiting were due to the liver injury caused by the dengue virus. Other infections that cause fever and gastrointestinal symptoms such as typhoid, leptospirosis, and enteroviral infections are common in India and may often lead to a

delay in the diagnosis of dengue.

In a study of 62 patients in Japan, by Itoda *et al*[13], rash was more frequent in 82% cases. In a north Indian study by Karoli *et al*[14], rash was present in 26% cases, while 16% had cutaneous hypersensitivity. Rahim *et al*[15] also found rash in high frequency of 78.5% in a Bangladesh based study. Thrombocytopenia is one of the important causes of developing petechial rash, but 14 patients out of 46 patients with platelet count more than 50,000/cumm of blood, developed rash in our study. So, other mechanism like immunologic cause may be an explanation for developing these rashes. Dengue virus, when it interacts with the host cells, causes a release of cytokines and stimulation of immunologic mechanism by which vascular endothelial changes, infiltration of mononuclear cells, and perivascular oedema occurs.

Ascites and pleural effusion from capillary leak syndrome are one of those features, more and more reported in recent years of outbreaks, by the help of technological advances like ultrasonography. We have detected 3rd space collection in the form of ascites and pleural effusion in 7.29% and 6.5% of cases. In a Bangladesh based study by Mia *et al*[16], 41% patients developed ascites and 42% had pleural effusion.

Dengue fever can cause hepatic injury and transaminase elevation similar to viral hepatitis. We found that in 60.49% patients, ALT was raised, while AST raised in 78.81%. Among them, 84.63% patients had more AST than ALT and only 15.37% patients had the reverse. In the study by Khan *et al*[17], serum ALT was > 40 U/l in 40% cases. In a study by Kularatne *et al*[18], 88% patients showed elevated ALT and AST, with 122 of them having a two-fold increase. Sedhain *et al*[19] have reported a case of fulminant hepatic failure from dengue fever in young girl from Nepal. Kuo *et al*[20] from Taiwan found raised AST and ALT in 93.3% and 82.2% cases.

In our study, the serological diagnosis of dengue was based on the identification of either the dengue NS1 Ag or the presence of the IgM and the IgG Abs or both; hence, only a few cases showed serological positivity. However, in the present study, all the cases were clinically suspected to be dengue fever and they responded accordingly.

Conclusion

All the patients were treated symptomatically and all improved, with no mortality. In the recent few years, the world has seen varied clinical presentations of the dengue fever in different epidemics, even in the same regions and even in the same period of time. Where some known features are still manifesting, few atypical features are noted from several parts of the world. So a continuous seroepidemiological surveillance and timely interventions are needed to indentify the cases, so that its complications, outbreak, and mortality can be minimised.

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SHORT COMMUNICATION

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Clinical, laboratory, and radiological features of patients with cerebrovascular accident at a tertiary care centre

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Abstract

India is a developing nation with more than 1.25 billion inhabitants and is undergoing remarkable economic and demographic changes in recent years resulting in a transition from poverty-related infectious and nutritional deficiency diseases toward lifestyle-related cardiovascular and cerebrovascular diseases. Defined risk factors mentioned in literature cannot be directly applied to the Indian population, keeping in mind that most of the studies available on risk factors causing cerebrovascular accidents are based upon a different population, demography, and race. Given the anticipated increase in the burden of stroke in the coming years due to lifestyle modification, we have tried to find out an association between the various risk factors, co-morbid conditions, and onset of stroke in our population at a tertiary care hospital.

Methods

75 patient were enrolled in this study and various parameters according to our questionnaire were analysed. A logistic regression analysis was used to determine the factors associated with outcome. A p value of less than or equal to 0.05 was considered significant.

Results

In our study of 75 acute onset stroke patients, 58 were ischaemic (41 males, 17 females) stroke and 17 were haemorrhagic (10 males and 7 females) stroke. Out of all stroke patients, 24 patients were females and 51 were males. Mean age of presentation was 58.6 ± 11.6 years which is much earlier than reported in western[1] population and comparable to African[2] population. Maximum number of stroke patients reported within 12 - 24 hours. None reported within the crucial first 6 hours. The most common complaint of stroke patients was sensory impairment, motor weakness, and facial deviation. 24 patients were febrile at the time of presentation, out of which 14 had haemorrhagic stroke, and 10 had ischaemic stroke. None of our patients had cardioembolic stroke. 48 patients had stage 2 hypertension (SBP) and only 11 patients were in stage 1 hypertension (SBP) (ESH/ESC 2013 criteria). Mean GCS score at presentation was 11.6 ± 3.2, this was relatively higher in ischaemic stroke in comparison to haemorrhagic ones, a well established scale of neurological status and prognostication[3].

In our study population, 29 patients were diabetic, 31 hypertensive, and 23 patients had both diabetes and hypertension. 15 patients consumed alcohol daily, 39 were smokers, and 6 were tobacco chewers.

Mean blood glucose in haemorrhagic stroke patients at presentation in the emergency room was 190 ± 107 mg/dl, whereas in ischaemic stroke patients it was 202 ± 112 mg/dl. Mean HbA1C value in all stroke patients was 6.8 ± 2.4% and in ischaemic stroke patients it was 7.1 ± 2.6% (significantly more than those of haemorrhagic stroke, i.e., 5.9 ± 1.8). These observations point towards a greater association of ischaemic stroke with diabetes mellitus[4] (probably because of increased atherosclerosis). Mean creatinine value in all stroke patients was 1.4 ± .95 mg/dl, and values in ischaemic and haemorrhagic stroke patients were 1.5 ± 1.1 and 1.3 ± .3 mg/dl, respectively. There was no statistically significant difference in mean glomerular filtration rates among type of stroke.

Mean total cholesterol, LDLC, VLDLC, and triglyceride values were higher in males than in females, in both ischaemic as well as haemorrhagic stroke, although the value was statistically not different in both groups. Mean HDL values were 36.2 ± 10 mg/dl in ischaemic stroke patients and 39 ± 9 in haemorrhagic stroke patients. Although the difference was statistically non significant.

In patients who consumed alcohol daily, their total cholesterol, LDL and triglyceride values were higher as compared to those who took alcohol 3 times/week. Alcohol intake was positively correlated with levels of total (P = 0.007) and LDL cholesterol (P = 0.004).

The most common side of lesion was the left. The most common topographic location for ischaemic as well as haemorrhagic stroke was the left basal ganglia. In 17 haemorrhagic patients, 9 patients (54%) had left-sided lesion out of which 8 had basal ganglia lesion, and 1 patient had left occipital involvement. 8 patients had right cerebral hemisphere involvement, out of which 5 patients had basal ganglia bleed.

40 of 58 ischaemic stroke patients and 13 of 17 haemorrhagic stroke patients had basal ganglia involvement. Out of these 40 patients who had ischaemic

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stroke, 13 patients had right basal ganglia involvement whereas 27 patients showed left basal ganglia involvement. In 13 patients who had haemorrhagic stroke, 5 patients had right basal ganglia involvement, 8 patients had left basal ganglia involvement.

To our surprise, NCCT head[5] was predictive of a disease pattern in all patients probably because of late presentation (> 12 hours).

Carotid Doppler imaging[6] of common carotid, internal carotid, and vertebral artery was done in 58 ischaemic cerebrovascular accident patients (Table I). Mean values of R IMT (intima-media thickness) and L IMT was .98 ± .19 mm and 1.04 ± .23 mm respectively in 58 ischaemic stroke patients which was much higher as compared to the general population. IMT generally increases with age, but values < 0.8 mm correlate well with lack of atherosclerotic disease, e.g., CVA[7] and MI[8].

Vertebral artery imaging of both sides showed normal ante-grade flow pattern, except in two cases in which one case showed reversal of flow on the right side and the other case showed reversal on the left. One patient died during the course of stay in hospital and the other was diagnosed as subclavian steal syndrome on CT angiography.

In patients with diabetes alone, and in patients who had both DM and HTN, the mean values of IMT, ICA and ICA/CCA in both right and left sides were significantly increased, than in those patients who were only hypertensive although the difference was not statistically significant.

Table I: Results of carotid Doppler in patients with ischaemic stroke

Ischaemic cerebrovascular accident (n = 58)				
	Minimum	**Maximum**	**Mean**	**SD**
R IMT (mm)	.6	1.3	.98	.19
L IMT (mm)	.6	1.4	1.04	.23
R ICA PSV (m/s)	74	139	103	17.3
L ICA PSV (m/s)	72	160	108	21.8
R ICA/CCA PSV	1.0	2.1	1.48	.24
L ICA/CCA PSV	1.0	2.4	1.57	.36

Table II: Doppler diagnosis of stenosis, 50% and 70%[7]

Diameter stenosis (%)	PSV ICA (m/s)	EDV ICA (m/s)	IC/CC systolic ratio
50	> 1.25	> 0.4	> 2
70	> 2.3	> 1.0	> 4

In our study only 9 patients had a ratio > 2 of IC/CC, 8 on left side and one on right side. Smoking showed a linear dose-dependent relationship of pack years of smoking with CIMT and also incidence of ischaemic stroke. 2-D echo-cardiography of all patients showed that left ventricular hypertrophy was present in 30 out of 58 ischaemic stroke patients and in 16 out of 17 haemorrhagic stroke patients, indicating more association of hypertension with haemorrhage also projecting LVH as marker of HTN comparable to previous studies[9].

Diabetic retinopathy was found only in 17 ischaemic stroke patients. Hypertensive retinopathy was found in both ischaemic and haemorrhagic stroke patients, but more so in ischaemic stroke patients. No statistically significant correlation could be established between grade of retinopathy and type of stroke.

Left ventricular hypertrophy and retinopathy on fundus evaluation were significantly associated with incidence of stroke. On regression analysis, diabetes mellitus and smoking were strong predictors of ischaemic stroke.

Age and hypertension were independent predictors of CIMT and stroke (both ischaemic and haemorrhagic). Alcohol intake was not associated with either stroke type.

Conclusion

Diabetes mellitus and smoking were the strongest independent risk predictors for stroke along with LVH and retinopathy. Diabetes mellitus and smoking were strongest risk factor for IMT thickness followed by HTN and age. High CIMT is directly correlated with incidence of ischaemic stroke ($P < 0.05$) and may serve as a surrogate marker towards this disease.

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REVIEW ARTICLE

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Lupus pregnancy

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown aetiology which is characterised by the presence of multiple autoantibodies. It predominantly affects young women of reproductive age. Pregnancy and its outcome is a major concern to most SLE patients. However, there seems to be little consensus about the effects of SLE on pregnancy and vice-versa. Early studies report an increased foetal and maternal risk, but recent prospective studies do not indicate such a relationship. A variety of factors, such as disease activity, renal involvement, history of foetal loss, antiphospholipid antibodies, lymphotoxic antibodies, and possibly antibodies to Ro/SSA have been implicated in the pathogenesis of adverse outcome in pregnant SLE patients. The literature is controversial regarding the frequency of lupus flares during pregnancy and the organ systems in which flares occur. So, queries regarding the risk of disease flares during pregnancy, chances of foetal loss, and the safety of various drugs during ante-partum and post-partum period are often raised.

Childbearing is the right of women and the patient with SLE should not be deprived of it. In recent years, with the improvement in understanding of the pathogenesis of SLE and the judicious use of immunosuppressive drugs, better disease control can now be achieved. Pre-pregnancy counselling and close collaboration between specialists such as obstetricians, paediatricians, and rheumatologists is essential in optimising the maternal and foetal outcome in lupus pregnancies. In this review, important issues regarding fertility rates, risk of disease flares during lupus pregnancy, pregnancy course, foetal outcome, safety of various drugs used for disease control during pregnancy and lactation, and contraceptive advice are discussed.

Fertility rate

Fertility of patients with SLE is usually unaltered by the disease. A pregnancy rate of 2.0 to 2.4 pregnancies per patient has been described, not only during disease remission but also during periods of disease activity[1,2]. Various factors contributing to lower fertility in some patients are menstrual abnormalities with anovulatory cycles during active disease and high dose corticosteroid treatment, end-stage renal failure secondary to lupus nephritis resulting in amenorrhoea and ovarian failure secondary to cyclophosphamide therapy[3,4].

Pregnancy and SLE flares

It is controversial as to whether there is an increased risk of lupus flares occuring during pregnancy as compared to nonpregnant lupus patients. Various well-designed prospective studies have yielded contradictory results. Studies done by Lockshin *et al*, Mintz *et al*, and Urowitz *et al*, did not find any increased incidence of flares during pregnancy when compared with controls, while Wong *et al*, Petri *et al*, and Ruiz–Irastorza *et al*, reported that pregnancy was associated with more lupus flares[5-10].

Some physiological changes during pregnancy may be misinterpreted as flares, for example, palmer erythema, transient facial blush, increase in proteinuria due to an increase in GFR, post-partum alopecia, and bland synovial effusions. For this reason, modification of the commonly used disease activity indices has been proposed for the assessment of lupus activity during pregnancy[11].

Despite the inconsistent results, a common agreement from these studies is that lupus flares during pregnancy are fairly common, with a frequency of more than 57% and flare rates ranging from 0.06 to 0.136 per patient month[12]. Prediction of a lupus flare during the course of pregnancy is difficult. SLE may flare at any trimester of pregnancy and in the post-partum period. Various indices have been created, e.g., SLE Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG), to monitor the activity (flare) and severity of disease during pregnancy.

Lupus flares during pregnancy tend to be mild. Arthralgia, arthritis, skin lesions, and fever with or without infection, are the most prominent clinical manifestations. Exacerbation of SLE with major organ involvement such as kidneys and the central nervous system may occur in up to 46% and 5% respectively, of patients[2,6,9,10,13].

Overall, studies do not suggest that lupus flares during pregnancy are exceedingly more serious than those occurring otherwise.

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Optimal timing for conception

A number of studies have demonstrated that active lupus at the time of conception was associated with a higher risk of disease flare during pregnancy[14-17]. Renal flares, especially, run an aggressive course during pregnancy with development of acute renal failure and even to maternal death.

Thus, in SLE patients, pregnancy is best undertaken during periods of quiescence. Nephritis, if present, should be in remission for at least six months before conception. As proposed by Boumpas and Balow, patients with stabilised renal function, resolution of urinary sediment abnormalities, proteinuria of less than 1 gm/day, and normalisation (ideally) of the C3 level for at least six months should be regarded as having renal remission[12].

As a general rule, the longer the patient is in remission before of conception, the better the chances of successful pregnancy without lupus exacerbations.

Obstetric outcome

Patients with SLE have an increased risk of pre-eclampsia during pregnancy, incidence ranging from 5% to 38%. Apart from general risk factors such as primigravida, pre-existing systolic hypertension, smoking, obesity, and previous history of pre-eclampsia, miscarriages, or abortions, the presence of aPL is an additional factor for early onset pre-eclampsia[18,19].

Differentiation between pre-eclampsia and renal flare is difficult, as both conditions can cause hypertension, proteinuria, oedema, and worsening of renal function, and may co-exist in the same patient. But, the distinction between the two conditions is important as management is different. Serum C3 and C4 levels steadily rise during pregnancy and pre-eclampsia. A drop in C3 and C4 levels coupled with rising anti-dsDNA points towards disease flare in SLE patients with proteinuria. The presence of active urinary sediments (white cell, RBCs, or granular casts) and disease activity in other organs such as arthritis, cutaneous vasculitis, oral ulcers, and lymphadenopathy in patients with worsening proteinuria points to lupus flare. Importantly, steroid treatment will typically worsen pre-eclampsia while renal flare will respond to increasing dose of steroid.

Foetal outcome

SLE does not decrease the chance of conception but significantly diminishes the chances of a successful outcome. Lupus pregnancies are characterised by an increased incidence of foetal wastage (abortions and still births), prematurity, and intrauterine growth retardation (IUGR)[20]. The incidence of abortions and still births in lupus pregnancies varies from 6 - 35% and 0 - 22%, respectively, which is higher than in normal pregnancy[6,21]. Active lupus nephritis, previous history of foetal death, and the presence of aPL have been shown to be predictive factors for foetal wastages in lupus pregnancies[14-16, 22-26]. Foetal loss related to the antiphospholipid syndrome usually occurs in the second and third trimesters[25]. The presence of both the lupus anticoagulant and high titre IgG anticardiolipin antibodies (aCL) are associated with the highest risk of foetal wastage[26,27].

Following recent trials involving aCL associated lupus pregnancies, use of combinations of aspirin with subcutaneous unfractionated heparin/low molecular weight heparin (LMWH), live births have been achieved[28-30].

Neonatal lupus erythematosus (NLE) is a syndrome consisting of congenital heart block (CHB), transient cutaneous lupus lesions, cytopenia, hepatic and other systemic manifestations in children born to mothers with SLE with the presence of anti-Ro or anti-La antibodies. The occurrence and severity of neonatal lupus are unrelated to maternal disease activity or severity. Screening for anti-Ro and anti-La antibodies is recommended for SLE patients who plan to be pregnant. Foetal echocardiography should be done during the 16th to 24th week of gestation by a specialist. Besides accurately diagnosing CHB in-utero, foetal echocardiography is also useful in following the course of the disease and detecting foetal myocarditis, pericardial effusion, and valvular regurgitation. A deteriorating serial foetal echocardiogram (for example, development of heart failure and hydrops) warrants use of maternal dexamethsone or betamethasone[12,31].

Antenatal care

Pre-conceptional counselling should be done in all patients with SLE. Patients should be advised to have regular antenatal check-up, i.e., once in 2 weeks till 32 weeks of gestation and thereafter, weekly. During each visit careful monitoring of blood pressure and weight should be done. Complete blood picture, liver function, renal function, 24-hour protienuria and creatinine clearance should be evaluated every month. All patients on long-term steroids should undergo the 1-hour 50 gm oral glucose challenge test at 20, 28, and 32 weeks of gestation. Glucose tolerance test is done when screening test is abnormal or if there is evidence of foetal macrosomia. Serum C3 and C4 complement levels are estimated once in 6 weeks. Because of the chances of foetal growth retardation, serial ultrasound examination is done in the first visit (1st trimester) for accurate gestational dating, next at 18 to 20 weeks of gestation to rule-out foetal anomaly and for an early evidence of foetal heart block. Foetal

echocardiography at 20 to 24 weeks of gestation if there is evidence of foetal heart block (foetal heart rate less than 60 beats per minute with poor beat to beat variability) can be performed. Doppler blood flow velocimetry is done if there is suspicion of foetal growth retardation[12].

Safety of medications in lupus pregnancy

High dose aspirin (> 80 mg/d) and NSAIDs should be avoided in the last two weeks of pregnancy as they may be associated with prolonged gestation and labour, increased risk of bleeding during delivery, oligohydramnios, premature closure of ductus arteriosus, and pulmonary hypertension[32].

Corticosteroids and hydroxychloroquine have not been shown to be teratogenic. Prednisone, prednisolone, and methylprednisolone have minimal placental transfer and are the steroids of choice during pregnancy. Use of high dose corticosteroids during pregnancy is associated with premature rupture of membranes (PROM), IUGR, and precipitation of maternal complications such as gestational diabetes, hypertension, osteoporosis, and avascular bone necrosis[29, 33-36].

Hydroxychloroquine – the commonest antimalarial – is used in SLE. No reports of hydroxychloroquine associated congenital malformations have been described so far in the literature[37-39]. There is good evidence that withdrawal of hydroxychloroquine may lead to lupus flares[38-39], so this drug should not be stopped unnecessarily during pregnancy in patients with SLE.

Azathioprine and cyclosporin A are two cytotoxic agents that may be considered during pregnancy, when intense immunosuppression is deemed necessary. Cyclophosphamide, another commonly used cytotoxic agent in SLE, is teratogenic and should be avoided during pregnancy. Treatment with cyclophosphamide may be considered in the second half of pregnancy in case of severe life-threatening disease of mother. Methotrexate is contraindicated during pregnancy. Strict contraception is needed when patient is on methotrexate. Methotrexate should be stopped 4 - 6 months prior to conception[40].

Regarding IVIg, it is used in lupus pregnancy in case of APLS, autoimmune thrombocytopenia, and myositis. It crosses placenta after 32 weeks of gestation. Teratogenicity reports are limited. No harmful effects to the foetus have been reported. Care has to be taken to prevent hepatitis virus transfer to foetus through the infusion[40].

Lactation

Most drugs used for treatment of SLE are secreted in breast milk. High doses of aspirin should be avoided in nursing mothers. The American Academy of Pediatrics (AAP) considers ibuprofen, indomethacin, and naproxen to be safe with breast-feeding. NSAIDs are contraindicated in nursing mothers with jaundiced neonates because of increased risk of kernicterus[12,40].

Maternal intake of prednisolone up to 30 mg/day is considered safe. If dose of prednisolone is greater than 30 mg/day, feeding should be avoided for 4 hours after ingestion of morning dose of steroid[12,40].

Regarding hydroxychloroquine, although AAP classifies this drug as compatible with breast-feeding, it should be used cautiously because of its slow elimination rate and potential accumulation to toxic amounts in infants[12, 40].

Breast-feeding should not be contemplated in mothers who are taking cytotoxic agents such as cyclophosphamide, cyclosporin A, azathioprine, and methotrexate[12-40]. IVIg is compatible with breast-feeding.

Contraception issues

A number of anecdotal case reports have associated oestrogen-containing combined oral contraceptive pills (OCPs) with lupus exacerbation[42-46]. The ongoing Safety of Estrogens Lupus Erythematosus National Assessment (SELENA) trial conducted in the United States may hopefully provide more information on this aspect[47]. As there is some evidence that the risk of thromboembolism related to OCPs use may be higher in SLE patients, particularly with positive aPL, OCPs should be avoided in these subset of patients. Low dose of oestrogen containing OCPs may be considered for those with stable disease and without history of thromboembolism or aPL[46,49]. Barrier methods and progestogens are alternatives if oestrogens are contraindicated.

Intrauterine contraceptive devices are associated with increased risk of infections, especially in those SLE patients who are under heavy immunosuppression; so these devices should be discouraged among SLE patients. Mechanical barrier methods such as condoms with spermicides and diaphragms are safe and effective.

Conclusion

Patients with SLE have normal fertility and should not be discouraged from having children. What is required is planning, i.e., when to conceive. A close collaboration with the obstetrician, rheumatologist and paediatrician is required in optimising the maternal and foetal outcome in lupus pregnancy. Pregnancy is best undertaken when general health of the patient is at its best and when the disease, especially lupus nephritis, is in clinical remission for at least six months. Appropriate counselling regarding

risk of NLE in the offspring, especially patients with positive anti-Ro and anti-La antibodies, is required. In patients with APLS and bad obstetric history, aspirin and subcutaneous heparin should be considered. Judicious monitoring and management of disease flares and thromboembolic phenomena during the pregnancy course and the puerperal period is mandatory. Blood pressure, urine protein, creatinine clearance, complements concentrations, anti dsDNA titres, and blood counts should be obtained at each antenatal visit. Regular surveillance, by foetal ultrasonography and echocardiography is useful in picking up CHB during the second trimester of pregnancy and monitoring for progress.

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REVIEW ARTICLE

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Evaluating and Managing Sepsis

*MPS Chawla**

Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year (Fig. 1), killing one in four (and often more), and increasing in incidence[1]. In North America 7,50,000 individuals with severe sepsis are hospitalised annually and 2,15,000 of them die. These figures may be much higher in developing countries which lack the advanced microbiologic services necessary to quantify the extent of devastation secondary to infection. It is the commonest cause of noncardiac ICU deaths and eleventh overall cause of death. The patients who survive have a high-risk of morbidity and mortality even after 2 - 5 years of discharge. Besides its clinical challenge, the treatment of sepsis imposes a large economic burden on healthcare systems worldwide.

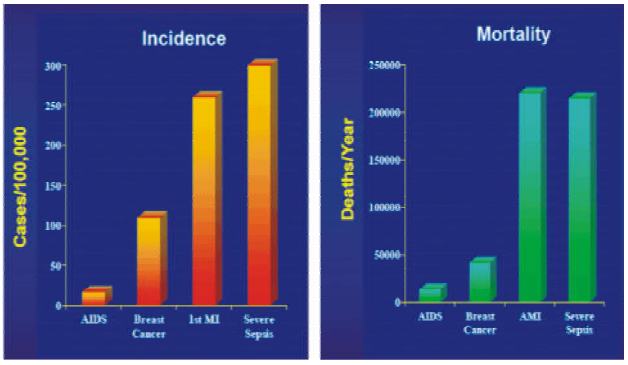

Fig. 1: *Incidence of sepsis and mortality caused by severe sepsis and septic shock.*

Similar to polytrauma, acute myocardial infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcome.

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection[2]. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Tables I and II).

Table I: Diagnostic criteria for sepsis.

General variables

- Fever (> 38.3° C)
- Hypothermia (core temperature < 36° C)
- Heart rate > 90/min –1 or more than two sd above the normal value for age
- Tachypnoea
- Altered mental status
- Significant oedema or positive fluid balance (> 20 ml/kg over 24 hr)
- Hyperglycaemia (plasma glucose > 140 mg/dl or 7.7 mmol/l) in the absence of diabetes

Inflammatory variables

- Leukocytosis (WBC count > 12,000 cu mm)
- Leukopenia (WBC count < 4,000 cu mm)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein more than two sd above the normal value
- Plasma procalcitonin more than two sd above the normal value

Haemodynamic variables

- Arterial hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or an SBP decrease > 40 mmHg in adults or less than two sd below normal for age)
- Organ dysfunction variables
- Arterial hypoxaemia ($PaO_2/FiO_2 < 300$)
- Acute oliguria (urine output < 0.5 ml/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dl or 44.2 μmol/l
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 1,00,000 cu mm)
- Hyperbilirubinaemia (plasma total bilirubin > 4 mg/dl or 70 μmol/l)

Tissue perfusion variables

- Hyperlactataemia (> 1 mmol/l)
- Decreased capillary refill or mottling

WBC = White blood cell; SBP = Systolic blood pressure; MAP = Mean arterial pressure; INR = International normalised ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° or < 35° C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxaemia, increased serum lactate level, or bounding pulses.

Adapted from Levy MM, Fink MP, Marshall JC et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31: 1250-6.

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Table II: Severe sepsis.

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output < 0.5 ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation
- Acute lung injury with PaO_2/FiO_2 < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FiO_2 < 200 in the presence of pneumonia as infection source
- Creatinine > 2.0 mg/dl (176.8 μmol/l)
- Bilirubin > 2 mg/dl (34.2 μmol/l)
- Platelet count < 1,00,000 cu mm
- Coagulopathy (international normalised ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC et al: 2001 SCCM/ESICM/ ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250-6.

Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mmHg or a SBP decrease > 40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension.

Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.

Factors responsible for increasing incidence of sepsis

- Patient's age – incidence increases with age.
- Increased use of cytotoxic/immunosuppressive drug therapy.
- Increased incidence of concomitant medical illnesses.
- Increased use of invasive devices for diagnosis and therapy.
- Rising incidence of infections due to organisms other than Gram-negative bacteria (Gram + bacteria, fungi, and possibly viruses).
- Perhaps, the emergence of antibiotic resistant organisms, e.g., ESBL, VRE.

Causes

Infections of chest, abdomen, genitourinary system and primary bloodstream infections are responsible for 80% of the cases. Incidence of Gram-negative infections has decreased over the years to 25 - 30%, Gram-positive organisms (30 - 50%) and polymicrobial organisms (25%) are responsible for majority of cases. One should keep in mind viruses, parasites and fungi as a cause in relevant cases.

Pathophysiology

In recent years, a significant body of literature has been published in an attempt to understand the complex and dynamic pathophysiologic mechanisms that underlie the heterogeneous sepsis syndrome. Sepsis has been shown to develop when the initial, appropriate host response to an infection becomes amplified and subsequently dysregulated, leading to an imbalance between proinflammatory and anti-inflammatory responses. It has been reported that the innate immune response, which unlike the adaptive immune response, is able to immediately respond to invading pathogens, plays a major role in the initiation of sepsis pathophysiology[3]. The activation of this "first line of cellular defense" results in an excessive release of cytokines, chemokines, and other inflammatory regulators. Cytokines regulate a variety of inflammatory responses, including the migration of immune cells to the locus of infection, which is a crucial step in containing a localised infection and preventing it from becoming systemic. However, a dysregulated cytokine release may lead to endothelial dysfunction, characterised by vasodilation and increased capillary permeability. The resulting leakage syndrome is clinically associated with hypotension, hemoconcentration, macromolecular extravasation, and oedema, which are frequent findings in septic patients[4]. The dysfunctional epithelial barriers enable pathogens and their products to further invade the host organism, to disturb regulatory mechanisms, and ultimately, to cause remote organ dysfunctions . Moreover, increasing evidence has indicated that immune and inflammatory responses are tightly interwoven with different physiologic processes within the human host, such as coagulation, metabolism, and neuroendocrine activation. An inflammation-induced dysregulation of the coagulation system, for instance, significantly aggravates the deleterious effects of sepsis and can result in lethal disseminated intravascular coagulation. The innate immune system detects invading microorganisms via pathogen recognition receptors (PRRs), which are expressed on epithelial barriers as well as on immune cells such as dendritic cells and macrophages (Figs 2 and 3). A specific family of PRRs named Toll-like receptors (TLRs) recognises conserved macromolecular motives from microorganisms, called pathogen-associated molecular patterns (PAMPs). Examples of bacterial PAMPs include lipopolysaccharide (LPS; the main virulence factor of Gram-negative bacteria), peptidoglycan, lipoteichoic acid (a cell wall component of Gram-positive bacteria), flagellin, and bacterial DNA. The stimulation of TLRs or the NOD-like receptor (NLR) family of intracellular PRRs results in the triggering of downstream signaling cascades. Depending on the particular receptor engaged, this process leads to the activation of a transcriptional response programmme that includes nuclear factor κB (NF-κB), followed by the

production and secretion of cytokines, chemokines, and nitric oxide (NO).

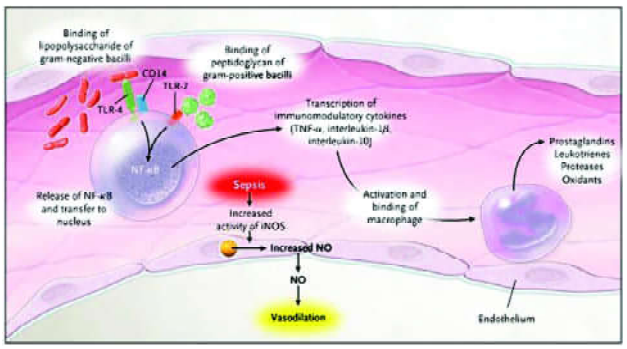


Fig. 2: *See text for details.*

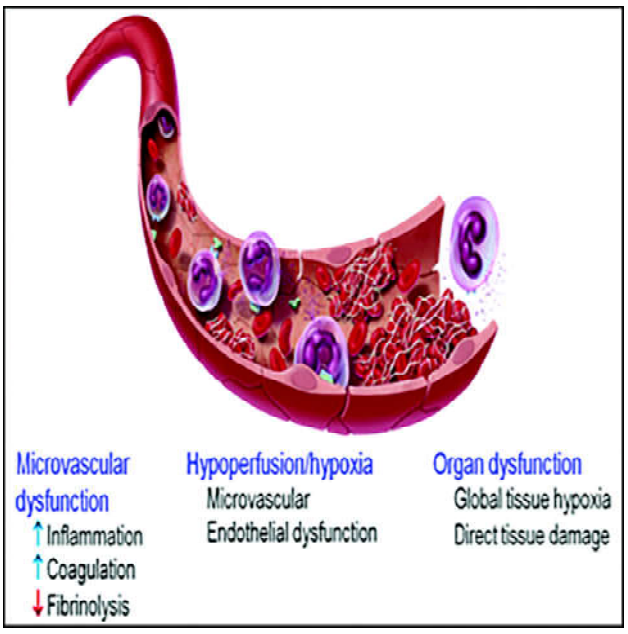


Fig 3: *See text for details.*

Management of severe sepsis

In a randomised controlled trial published in NEJM, 2001, Rivers *et al* demonstrated the time critical nature of severe sepsis and septic shock, establishing the efficacy of a protocol for ED resuscitation known as Early Goal-Directed Therapy[5]. The trial included 263 subjects randomised to conventional and intensive management arms and found a 16 % absolute reduction in in-hospital mortality in the EGDT arm vs the standard therapy arm. This mortality benefit remained at 28 and 60 days.

The first set of Surviving Sepsis Campaign guidelines were issued in 2004 which were revised in 2008. Recently these guidelines were updated[6] (2012 guidelines) using the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[7] system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2).

Table III: Determination of the quality of evidence.

Underlying methodology

A (high) RCTs

B (moderate) Downgraded RCTs or upgraded observational studies

C (low) Well-done observational studies with control RCTs

D (very low) Downgraded controlled studies or expert opinion based on other evidence

Factors that may decrease the strength of evidence

1. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias
2. Inconsistency of results, including problems with subgroup analyses
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Main factors that may increase the strength of evidence

1. Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradient

Table IV: Surviving sepsis campaign bundler.

To be completed within 3 hours

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate 4 mmol/l

To be completed within 6 hours

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/l (36 mg/dl):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO2)*
7. Remeasure lactate if initial lactate was elevated*

**Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mmHg, ScvO2 of 70%, and normalisation of lactate.*

Adapted from Dellinger et al. Surviving sepsis campaign: International Guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41(2): 580-637.

Initial resuscitation and infection issues (Table V)

A. Initial resuscitation

1. It is recommended to initiate the protocolised,

quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/l). This protocol should be initiated as soon as hypoperfusion is recognised and should not be delayed pending ICU admission. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as a part of a treatment protocol (grade 1C):

CVP 8 - 12 mmHg

MAP ≥ 65 mmHg

Urine output ≥ 0.5 ml/kg/hr

Superior *vena cava* oxygenation saturation (Scvo2) or mixed venous oxygen saturation (Svo2) 70% or 65%, respectively.

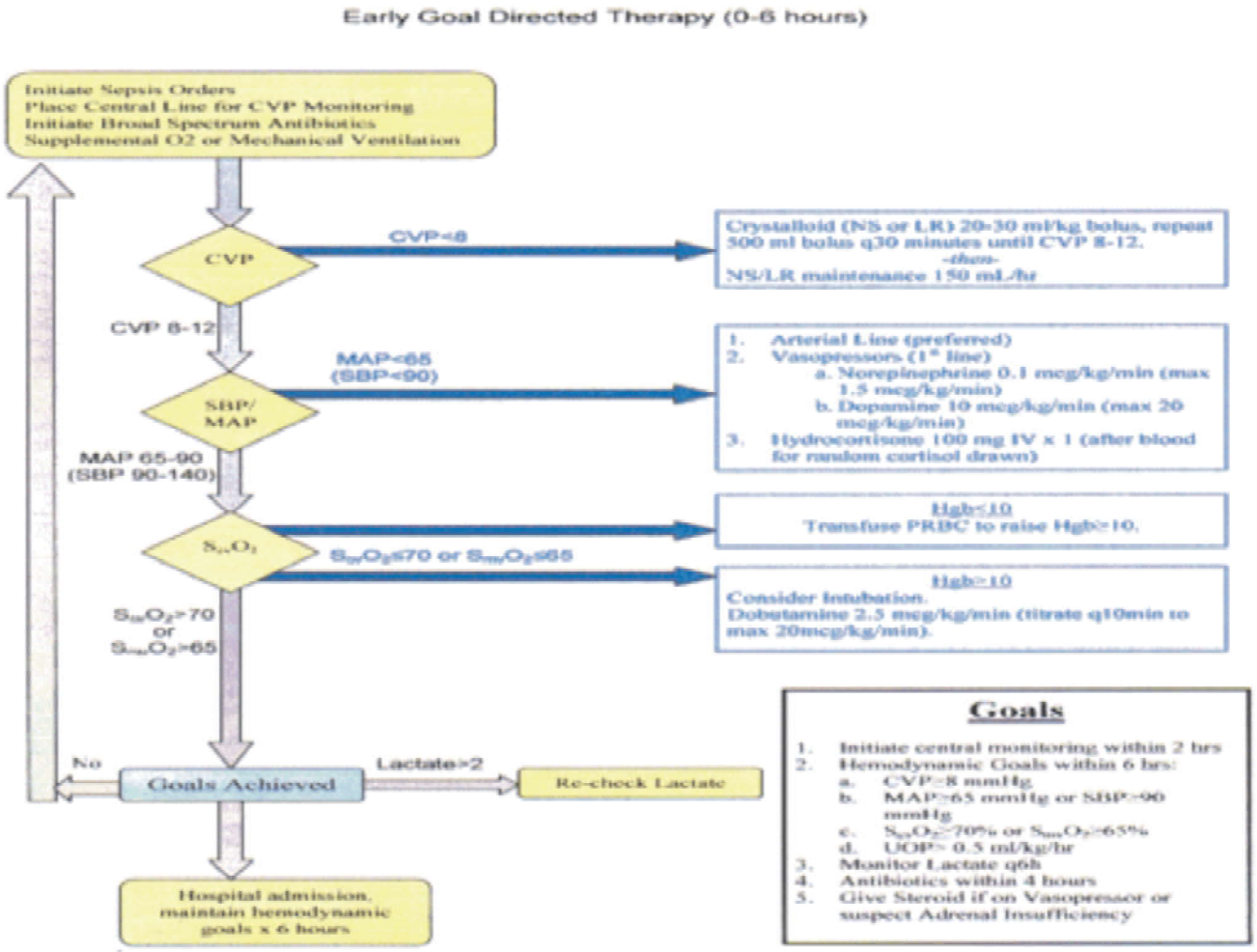
2. Target resuscitation to normalise lactate in patients with elevated lactate levels[8] as a marker of tissue hypoperfusion (grade 2C).

B. Screening for sepsis and performance improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis should be done to increase the early identification of sepsis and allow implementation of early sepsis therapy (grade 1C).
2. Performance improvement efforts in severe sepsis should be used to improve patient outcomes (UG).

C. Diagnosis

1. Obtain appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (> 45 minutes) in the start of antimicrobial(s) administration (grade 1C). To optimise identification of causative organisms, obtain at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial



therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (< 48 hours) inserted. These blood cultures can be drawn at the same time if they are obtained from different sites. Cultures of other sites (preferably quantitative where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection, should also be obtained before antimicrobial therapy if doing so does not cause significant delay in antibiotic administration (grade 1C). One should remember that in as many as 30% of the cases, no organism may be cultivated.

2. Use the 1,3 β-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (grade 2C) when invasive candidiasis is in the differential diagnosis of infection.

3. Availability of several new commercial kits such as septifast has helped in recognition of causative organisms[9].

4. Imaging studies should be performed promptly in attempts to confirm a potential source of infection. Potential sources of infection should be sampled as they are identified and in consideration of patient risk for transport and invasive procedures, (e.g., careful co-ordination and aggressive monitoring if the decision is made to transport for a CT-guided needle aspiration). Bedside studies, such as ultrasound, may avoid patient transport (UG).

D. Antimicrobial therapy[10,11,12]

1. The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) should be the goal of therapy.

2a. Initial empiric anti-infective therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

2b. The antimicrobial regimen should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1B).

3. The use of low procalcitonin levels[13] or similar biomarkers is recommended to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient's presenting illness and local patterns of infection. Combination empiric therapy should be used for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For selected patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is suggested for *P. aeruginosa* bacteremia (grade 2B). Similarly, a more complex combination of beta-lactam and a macrolide is suggested for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

4b. Combination therapy, when used empirically in patients with severe sepsis, should not be administered for longer than 3 to 5 days. De-escalation to the most appropriate single-agent therapy should be performed as soon as the susceptibility profile is known (grade 2B). Exceptions would include aminoglycoside monotherapy, which should be generally avoided, particularly for *P. aeruginosa* sepsis, and for selected forms of endocarditis, where prolonged courses of combinations of antibiotics are warranted.

5. The duration of therapy typically should be 7 to 10 days if clinically indicated; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with *S. aureus;* some fungal and viral infections, or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of of noninfectious cause (UG).

E. Source Control[14]

1. It is recommended that a specific anatomical diagnosis of infection requiring consideration for emergent source control, (e.g., necrotizing soft

tissue infection, peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible and intervention be undertaken for source control within the first 12 hours rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used, (e.g., percutaneous rather than surgical drainage of an abscess) (UG).

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

F. Infection prevention[15,16]

1a. Selective oral decontamination (SOD) and selective digestive decontamination (SDD) should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia (VAP).

1b. Oral chlorhexidine gluconate (CHG) should be used as a form of oropharyngeal decontamination to reduce the risk of VAP in ICU patients with severe sepsis (grade 2B).

Table V: Recommendations: Initial resuscitation and infection issues.

A. Initial resuscitation

1. Protocolised, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/l). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8 - 12 mmHg
   b) Mean arterial pressure (MAP) ≥ 65 mmHg
   c) Urine output ≥ 0.5 ml/kg/hr
   d) Central venous (superior *vena cava*) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalise lactate (grade 2C).\

B. Screening for sepsis and performance improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital-based performance improvement efforts in severe sepsis (UG).

C. Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (< 48 hrs) inserted (grade 1C).
2. Use of the 1, 3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

D. Antimicrobial therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrugresistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteraemia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

4b. Empiric combination therapy should not be administered for more than 3 - 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7 - 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

E. Source control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used, (e.g., percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

F. Infection prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

Adapted from Dellinger et al. Surviving sepsis campaign: International Guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41(2): 580-637.

Haemodynamic support and adjunctive therapy (Table VI)

G. Fluid therapy of severe sepsis

1. Crystalloids should be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Hydroxyethyl starches (HES) should not be used for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP, CRYSTMAS[17], 6S[18], and CHEST[19] trials. The results of the recently completed CRYSTAL trial were not considered).
3. The use of albumin may be considered in the fluid resuscitation of severe sepsis and septic shock[20] when patients require substantial amounts of crystalloids (grade 2C).
4. An initial fluid challenge is recommended in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolaemia to achieve a minimum of 30 ml/ kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (see Initial Resuscitation recommendations) (grade 1C).
5. A fluid challenge technique should be applied wherein fluid administration is continued as long as there is hemodynamic improvement[21] either based on dynamic, (e.g., change in pulse pressure, stroke volume variation) or static, (e.g., arterial pressure, heart rate) variables (UG).

H. Vasopressors[22-25]

1. Vasopressor therapy should initially target a MAP of 65 mmHg (grade 1C).
2. Norepinephrine is recommended as the first-choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) should be used when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG).
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03 - 0.04 U/min should be reserved for salvage therapy (failure to achieve an adequate MAP with other vasopressor agents) (UG).
6. Dopamine is used as an alternative vasopressor agent to norepinephrine only in highly selected patients, (e.g., patients with low-risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in the following circumstances: (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/ vasopressor drugs and low-dose vasopressin have failed to achieve the MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic therapy

1. A trial of dobutamine infusion up to 20 μg/kg/min is administered or added to vasopressor (if in use) in the presence of: a) myocardial dysfunction, as suggested by elevated cardiac filling pressures and low cardiac output, or b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).

2. There is no recommendation for the use of a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids[26,27]

1. It is suggested not to use intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore haemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, use intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. There is no indication for using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).
3. Clinicians should taper the treated patient from steroid therapy when vasopressors are no longer required (grade 2D).
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When low-dose hydrocortisone is given, use continuous infusion rather than repetitive bolus injections (grade 2D).

Table VI: Recommendations: Haemodynamic support and adjunctive therapy.

G. Fluid therapy of severe sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolaemia to achieve a minimum of 30 ml/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is haemodynamic improvement either based on dynamic, (e.g., change in pulse pressure, stroke volume variation) or static, (e.g., arterial pressure, heart rate) variables (UG).

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mmHg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03 - 0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients, (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore haemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

Adapted from Dellinger et al. Surviving sepsis campaign: International Guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41(2): 580-637.

Supportive therapy of severe sepsis (Table VIII)

K. Blood product administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischaemia, severe hypoxaemia, acute haemorrhage, or ischaemic coronary artery disease, red blood cell transfusion is recommended when

the haemoglobin concentration decreases to < 7.0 g/dl to target a haemoglobin concentration of 7.0 to 9.0 g/dl in adults (grade 1B).

2. Erythropoietin should not be used as a specific treatment of anemia associated with severe sepsis (grade 1B).

3. Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).

4. There is no recommendation for antithrombin administration for the treatment of severe sepsis and septic shock (grade 1B).

5. In patients with severe sepsis, platelets should be administered prophylactically when counts are ≤ 10,000/mm^3 (10 × 109/l) in the absence of apparent bleeding, as well when counts are ≤ 20,000/mm^3 (20 × 109/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50 × 109/l]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

L. Immunoglobulins[28]

1. Intravenous immunoglobulins should not be used in adult patients with severe sepsis or septic shock (grade 2B).

M. Selenium

1. There is no recommendation for using intravenous selenium to treat severe sepsis (grade 2C).

N. History of recommendations regarding use of recombinant activated protein C

1. Recombinant human activated protein C (rhAPC) was approved for use in adult patients in a number of countries in 2001 following the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial, which enrolled 1,690 severe sepsis patients and showed a significant reduction in mortality (24.7%) with rhAPC compared with placebo (30.8%, p = 0.005)[29]. The 2004 SSC guidelines recommended use of rhAPC in line with the product labeling instructions required by the U.S. and European regulatory authorities with a grade B quality of evidence . By the time of publication of the 2008 SSC guidelines, additional studies of rhAPC in severe sepsis (as required by regulatory agencies) had shown it ineffective in less severely ill patients with severe sepsis as well as in children. The 2008 was also downgraded from 2004, from B to C). The 2008 guidelines also recommended against use of rhAPC in low-risk adult patients, most of whom will have APACHE II scores ≤ 20 or single organ failures (grade 1A), and against use in all paediatric patients (grade 1B). SSC recommendations reflected these findings, and the strength of the rhAPC recommendation was downgraded to a suggestion for use in adult patients with a clinical assessment of high-risk of death, most of whom will have Acute Physiology and Chronic Health Evaluation (APACHE) II scores ≥ 25 or multiple organ failure (grade 2C; quality of evidence. Results of the PROWESS SHOCK trial (1,696 patients) were released in late 2011, showing no benefit of rhAPC in patients with septic shock (mortality 26.4% for rhAPC, 24.2% placebo) with a relative risk of 1.09 and a p value of 0.31[30]. The drug was withdrawn from the market and is no longer available, negating any need for an SSC recommendation regarding its use[31].

O. Mechanical ventilation of sepsis-induced acute respiratory distress syndrome[32]

1. It is recommended that clinicians target a tidal volume of 6 ml/kg predicted body weight in patients with sepsis induced acute respiratory distress syndrome (ARDS) (grade 1A vs. 12 ml/kg).

2. It is recommended that plateau pressures be measured in patients with ARDS and that the initial upper limit goal should be less than 30 cm water (grade 1 B).

3. Positive end-expiratory pressure (PEEP) should be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).

4. Strategies based on higher rather than lower levels of PEEP are suggested for patients with sepsis-induced moderate-to-severe ARDS. (grade 2 C).

5. Recruitment measures should be used in sepsis patients with severe refractory hypoxaemia due to ARDS (grade 2C).

6. Prone positioning should be used in sepsis-induced ARDS patients with a PaO_2/FiO_2 ratio ≤ 100 mmHg in facilities that have experience with such practices (grade 2B).

7. It is recommended that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP (grade 1B).

8. It is suggested that noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).

9. It is recommended that a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low FiO_2 requirements which can be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, extubation should be considered (grade 1A).

10. Routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS is not recommended (grade 1A).

11. A conservative fluid strategy is recommended for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).

12. In the absence of specific indications such as bronchospasm, the recommendation is against the use of β_2-agonists for treatment of patients with sepsis-induced ARDS (grade 1B).

P. Sedation, analgesia, and neuromuscular blockade in sepsis

1. Either continuous or intermittent sedation should be minimised in mechanically ventilated patients.

2. NMBAs should be avoided if possible in the septic patient *without ARDS* due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).

3. A short course of an NMBA ($\leq$48 hours) is suggested for patients with early, sepsis-induced ARDS and $PaO_2/FiO_2 < 150$ mmHg (grace 2C).

Q. Glucose control[33]

1. A protocolised approach to blood glucose management is recommended in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dl. This approach should target an upper blood glucose level $\leq$ 180 mg/dl rather than an upper target blood glucose $\leq$ 110 mg/dl (grade 1A).

2. It is recommended that blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter (grade 1C).

3. It is recommended that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

R. Renal replacement therapy

1. Continuous renal replacement therapies and intermittent haemodialysis are equivalent in patients with severe sepsis and acute renal failure because they achieve similar short-term survival rates (grade 2B).

2. The use of continuous therapies is suggested to facilitate management of fluid balance in haemodynamically unstable septic patients (grade 2D).

S. Bicarbonate therapy

1. It is recommended against the use of sodium bicarbonate therapy for the purpose of improving haemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidaemia with pH $\geq$ 7.15 (grade 2B).

T. Deep vein thrombosis prophylaxis

1. It is recommended that patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). It should be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus unfractionated heparin [UFH] twice daily and grade 2C versus UFH given thrice daily). If creatinine clearance is < 30 ml/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).

2. It is suggested that patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).

3. It is recommended that septic patients who have a contraindication to heparin use, (e.g.,

thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral haemorrhage) not receive pharmacoprophylaxis (grade 1B). Rather they should receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases, start pharmacoprophylaxis (grade 2C).

U. Stress ulcer prophylaxis

1. Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor should be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).
2. When stress ulcer prophylaxis is used, it is suggested to use proton pump inhibitors rather than H2 receptor antagonists (H2RA) (grade 2C).
3. Patients without risk factors should not receive prophylaxis (grade 2B).

V. Nutrition

1. Oral or enteral (if necessary) feedings is recommended, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hrs after a diagnosis of severe sepsis/septic shock (grade 2C).
2. Avoid mandatory full caloric feeding in the first week, but rather suggest low-dose feeding, (e.g., up to 500 kcal per day), advancing only as tolerated (grade 2B).
3. Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).
4. Use nutrition with no specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

W. Setting goals of care

1. Goals of care and prognosis should be discussed with patients and families (grade 1B).
2. The goals of care should be incorporated into treatment and end-of-life care planning, utilising palliative care principles where appropriate (grade 1B).
3. Goals of care should be addressed as early as feasible, but no later than within 72 hrs of ICU admission (grade 2C).

Table VIII: Recommendations: Other supportive therapy of severe sepsis.

K. Blood product administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischaemia, severe hypoxaemia, acute haemorrhage, or ischaemic heart disease, it is recommended that red blood cell transfusion occur only when haemoglobin concentration decreases to < 7.0 g/dl to target a haemoglobin concentration of 7.0 - 9.0 g/dl in adults (grade 1B).
2. Not using erythropoietin as a specific treatment of anaemia associated with severe sepsis (grade 1B).
3. Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).
4. Not using antithrombin for the treatment of severe sepsis and septic shock (grade 1B).
5. In patients with severe sepsis, administer platelets prophylactically when counts are < 10,000/mm^3 (10 x 109/l) in the absence of apparent bleeding. Prophylactic platelet transfusion to be done when counts are < 20,000/mm^3 (20 x 109/l) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50 x 109/l]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

L. Immunoglobulins

1. Not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).

M. Selenium

1. Not using intravenous selenium for the treatment of severe sepsis (grade 2C).

N. History of recommendations regarding use of recombinant activated protein C (rhAPC)

A history of the evolution of SSC recommendations as to rhAPC (no longer available) is provided.

O. Mechanical ventilation of sepsis-induced acute respiratory distress syndrome (ARDS)

1. Target a tidal volume of 6 ml/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs. 12 ml/kg).
2. Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be ≤ 30 cm H20 (grade 1B).
3. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
4. Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis-induced moderate-or-severe ARDS (grade 2C).
5. Recruitment maneuvers be used in sepsis patients with severe refractory hypoxaemia (grade 2C).
6. Prone positioning be used in sepsis-induced ARDS patients with a PaO_2/FiO_2 ratio ≤ ? 100 mmHg in facilities that have experience with such practices (grade 2B).
7. That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30 - 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
8. That noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).

9. That a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable; b) haemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilator and end-expiratory pressure requirements; and e) low FiO_2 requirements which can be met safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).
10. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).
11. A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).
12. In the absence of specific indications such as bronchospasm, not using beta 2-agonists for treatment of sepsis-induced ARDS (grade 1B).

P. Sedation, analgesia, and neuromuscular blockade in sepsis

1. Continuous or intermittent sedation be minimised in mechanically ventilated sepsis patients, targeting specific titration end-points (grade 1B).
2. Neuromuscular blocking agents (NMBAs) be avoided if possible in the septic patient without ARDS due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).
3. A short course of NMBA of not greater than 48 hours for patients with early sepsis-induced ARDS and a $PaO_2/FiO_2 < 150$ mm Hg (grade 2C).

Q. Glucose control

1. A protocolised approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are > 180 mg/dl. This protocolised approach should target an upper blood glucose ≥ 180 mg/dl rather than an upper target blood glucose ≤ 110 mg/dl (grade 1A).
2. Blood glucose values be monitored every 1 - 2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

R. Renal replacement therapy

1. Continuous renal replacement therapies and intermittent haemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).
2. Use continuous therapies to facilitate management of fluid balance in haemodynamically unstable septic patients (grade 2D).

S. Bicarbonate therapy

1. Not using sodium bicarbonate therapy for the purpose of improving haemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidaemia with pH ≥ 7.15 (grade 2B).

T. Deep vein thrombosis prophylaxis

1. Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). This should be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus twice daily UFH, grade 2C versus three times daily UFH). If creatinine clearance is <30 ml/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).
2. Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
3. Septic patients who have a contraindication for heparin use (e.g., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral haemorrhage) not receive pharmacoprophylaxis (grade 1B), but receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases start pharmacoprophylaxis (grade 2C).

U. Stress ulcer prophylaxis

1. Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).
2. When stress ulcer prophylaxis is used, proton pump inhibitors rather than H2RA (grade 2D).
3. Patients without risk factors do not receive prophylaxis (grade 2B).

V. Nutrition

1. Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock (grade 2C).
2. Avoid mandatory full caloric feeding in the first week but rather suggest low dose feeding (e.g., up to 500 calories per day), advancing only as tolerated (grade 2B).
3. Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).
4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

W. Setting goals of care

1. Discuss goals of care and prognosis with patients and families (grade 1B).
2. Incorporate goals of care into treatment and end-of-life care planning, utilising palliative care principles where appropriate (grade 1B).
3. Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (grade 2C).

Adapted from Dellinger et al. Surviving sepsis campaign: International Guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41(2): 580-0637.

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UPDATE ARTICLE

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Stem cell transplantation: Where do we stand now?

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Introduction

Stem cells are the cells which have the ability to divide (clonogenic ability) and self-renew indefinitely as well as to differentiate into one or more cell types[1]. Adult human stem cells that are intrinsic to various tissues have been described. These cells are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiologic cell turnover or tissue damage due to injury[1]. Haematopoietic stem cells that give rise to blood cells and move between bone marrow and peripheral blood are the best-characterised adult stem cells in humans. Mature blood cells are produced continuously by less-differentiated precursors that are in turn descended from more primitive progenitors and, originally, from haematopoietic stem cells. Recent data suggest that adult stem cells generate differentiated cells beyond their own tissue boundaries, a process termed "developmental plasticity". In fact, a single stem cell can restore the entire lymphohaematopoietic system of a lethally irradiated animal.

Haematopoietic stem-cell transplantation (HSCT) was originally conceived more than 50 years ago as a treatment for injury from irradiation and, later, for cancer. Associated problems needed to be solved before the procedure could be used clinically. HSCT is usually carried out for one of two purposes: (1) to replace an abnormal but nonmalignant lymphohaematopoietic system with one from a normal donor; or (2) to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. The use of HSCT has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors[1].

Definitions

Totipotency: Ability to regenerate an organism in total. E.g., zygote, 1st cleavage blastomeres → organism.

Pluripotent: Ability to form all lineage of the body. E.g., embryonic stem cell.

Multipotent: Adult stem cell (haematopoietic stem cell) → multiple cell types of one lineage.

Unipotent: Cells form only one cell type. E.g., spermatogonial stem cell → sperms

Types of extrinsic stem cells

Extrinsic stem cells are further classified in two subtypes[1,2]:

1. **Adult stem cells:** These stem cells can give rise to specialised cell types of the tissue from which they came (i.e., a heart stem cell can give rise to a functional heart muscle cell). They can be harvested from bone marrow, adipose tissue, and umbilical cord blood.
2. **Embronic stem cells:** They are self-renewing (can replicate itself), pluripotent (can form all cell types found in the body) and theoretically is immortal. They are derived from the inner cell mass of developing blastocysts.

Embryonic stem cell versus adult stem cell[1,2]

Embryonic stem cell (ESC)	Adult stem cells (ASC)
• High malleability	• Limited developmental potential
• Potential for undesired development (teratomas)	• Better behaved, easier to manage
• Infinite lifespan, unlimited supply	• Lose their ability to proliferate or differentiate after a time in culture
• High ethical burden	• Less moral ambiguity
• Uncertain legal status	• Less legal controversy

Haematopoietic stem cell transplantation (HSCT)[1, 3,7]

The transplantation of multipotent haematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood[1] is called haematopoietic stem cell transplantation. It has a proven role in haematologic malignancies, e.g., multiple myeloma, leukemias, lymphomas, anaemias such as aplastic anaemia, thalassaemia, sickle cell anaemia and germ cell tumour autoimmune disorders such as systemic lupus erythematosus, or amyloidosis[1,4].

Types of stem cell transplantation

Allogeneic transplantation: Cell, tissue or organ transplant from one member of a species to a genetically different member of the same species (HLA matched).

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Advantages

- No tumour contamination of the graft and no prior marrow injury from chemotherapy (less risk of later myelodysplasia)
- Graft versus tumour effect
- Can be used for patients with marrow involvement by tumour or with bone marrow dysfunction, such as aplastic anaemia, haemoglobinopathies or prior pelvic radiation

Disadvantages

- Dose intensive regimen limited by toxicity (usually limited to patients < age 55)
- Time needed to identify donor if no sibling donor avaliable
- Higher early treatment-related mortality from GVHD (graft versus host disease) and infectious complications (20 - 40%)
- Allogeneic transplant costlier than autologous transplantation (Rs. 500,000 - 100,000 for allogeneic while 300,000 - 500,000 for autologous HSCT in India).

Autologous transplantation: Cell, tissue, or organ transplants from one individual back to the same individual. Such transplants do not induce an immune response and are not rejected.

Advantages

- No need to identify donor
- No immunosuppression
- Lesser risk of infection
- No GVHD
- Dose intensive therapy can be used for older patients (usually upto age 70)
- Low early treatment related mortality (2 - 5%)

Disadvantages

- Not feasible if peripheral blood is involved
- Possible marrow injury leading to myelodysplasia
- No graft vs host reaction

Indications for bone marrow/blood stem cell transplantation[3-7]

Indications	Allogeneic	Autologous
Severe aplastic anaemia	+	-
Beta-thalassaemia	+	-
Fanconi anaemia	+	-
Sickle cell anaemia	+	-
Immunodeficiency disease		
– Severe combined	+	-
– Wiskott-Aldrich syndrome		+ -
– Chediak-Higashi disease	+	-
Inborn error of metabolism	+	-
Acute myeloblastic leukaemia		+ +
Acute lymphocytic leukaemia (experimental)		+ +
Chronic myeloid leukaemia (experimental)	+	+
Chronic lymphocytic leukaemia (experimental)	+ (experimental)	+
Myelodysplastic syndrome (experimental)	+	+
Multiple myeloma	+ (experimental)	+
Hodgkin's lymphoma	+ (experimental)	+
Non-Hodgkin's lymphoma	+ (experimental)	+
Neuroblastoma	-	+
Germ cell tumour of testis (experimental)	-	+

Harvesting stem cells

Stem cells can be harvested from bone marrow, peripheral blood, and umbilical cord.

Bone marrow

It is done under general anaesthesia by repeated aspiration from posterior iliac crest. It can also be obtained from anterior iliac crest or sternum. In allogeneic haematopoietic stem cell transplantation with major ABO incompatability between the donor and recipient, mature RBCs are removed from the graft as it avoids haemolytic transfusion reaction[1].

Peripheral blood stem cells

Peripheral blood stem cells have to be mobilised from the marrow. It is done by giving the donor G-CSF (5μ/kg/day in 2 divided doses, s.c., for 5 days). On day 5 - 6 after drug administration, peripheral blood stem cells are collected by leucopheresis using an apheresis machine. Peripheral blood stem cells are cryopreserved at -80°C using 7.5% dimethylsulfoxide or liquid nitrogen. Patient is then administered high dose chemotherapy. Peripheral blood stem cells are then infused 24 - 48 hrs later (depending

upon half-life of the agents). Primary concern with autologous HSCT is re-infusion of malignant cells along with progenitor cells[1,8-11].

Umbilical cord

Umbilical cord blood (UCB) is a rich source of primitive stem cells. It has certain distinct advantages over other types such as[1,9,10]:-

- Relative immaturity of immune system at birth → lower risk of acute graft versus host reaction.
- Easy procurement
- No risk to donors
- Reduced risk of transmiting infections
- Immediate avaliability of cryopreserved unit
- Acceptable partial HLA mismatches

It also has certain shortcomings such as[10] :-

- Higher primary graft failure (10 - 20%)
- Delayed myeloid recovery (smaller number of stem cells in UCB)

Due to limited yield of stem cells from a single UCB donor, UCB stem cells from single donor have been in children < 25 kg. weight while in adults – double UCB donor stem cells transplant may be used.

Pre-transplant issues for all transplant patients

- Fertility counselling/sperm banking is advised to the patients before chemotherapy administration.
- Well-balanced diet and mild exercise are found to be helpful.
- Smoking is best avoided.
- Counselling about quality of life post-transplant
- Dental examination: dental cavities can be a serious source of infection after transplant. Therefore, these need to be treated before commencing conditioning.
- Bone marrow transplantation is a long process involving unpleasant treatments and side-effects. In some centres, a psychologist is available to help the patient cope and come to terms with this experience.
- Females who have reached puberty are asked to have a pregnancy test as part of routine pre-transplant preparation.

Transplant process (5 steps)

1. Conditioning
2. Stem cell infusion
3. Neutropenic phase
4. Engraftment phase
5. Post-engraftment period

1. Conditioning phase

The conditioning period typically lasts 7 - 10 days. The purposes is to eliminate malignancy and to provide immune suppression to prevent rejection of new stem cells. It is done by delivery of chemotherapy and/or radiation.

2. Stem cell processing and infusion

Infusion – 20 minutes to an hour, varies depending on the volume infused. The stem cells may be processed before infusion, if indicated. Depletion of T-cells can be performed to decrease GVHD. Premedication is done with acetaminophen and diphenhydramine to prevent reaction. It is infused through a central venous line, much like a blood transfusion. Anaphylaxis, volume overload, and rarely a transient GVHD are the major potential complications involved. Stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO) as a preservative and potentially can cause renal failure, in addition to the unpleasant smell and taste.

3. Neutropenic phase

During this period (2 - 4 weeks), the patient essentially has no effective immune system. Healing is poor, and the patient is very susceptible to infection. Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase.

4. Engraftment phase

During this period (several weeks), the healing process begins with resolution of mucositis and other lesions acquired. In addition, fever begins to subside, and infections often begin to clear. The greatest challenges at this time are management of GVHD and prevention of viral infections (especially CMV).

5. Post-engraftment phase

This period lasts for months to years. Hallmarks of this phase include the gradual development of tolerance, weaning-off of immunosuppression, management of chronic GVHD, and documentation of immune reconstitution.

Post-transplant care[14]

General care

- Masks are mandatory for these patients.
- Patient has to avoid crowds and public places.
- For the first 100 days after transplant, the patient will not return to work or school.
- Avoid all contact with animals and their droppings/ waste.
- Avoid gardening, mowing the lawn, and other activities that stir-up the soil or the ground.
- Avoid swimming in lakes, public pools, and sitting in hot tubs.
- Stay away from dusty, dirty, moldy things (construction areas, remodelling areas, vacuum cleaner bags, etc.).
- Avoid stagnant water (flower vases, vaporisers, de-humidifiers, etc.).
- Family members and people in close contact should receive the influenza (flu) vaccine.
- Maintain proper hygiene, esp. oral care, skin care.

Sexual activity

- Precautions are advised, e.g., barrier method to avoid STD.
- Water-based lubricant to combat vaginal dryness (which results because of chemotherapy and radiation).

Notification of communicable diseases like measles, chicken pox, etc., in community.

- Avoid contact with children who have received a live immunisation (such as the chicken pox vaccine).

Re-immunisation: The immune system may no longer "remember" its previous exposures to childhood vaccinations. Therefore, the patient will have to be re-immunised with several of the childhood vaccines one to two years after transplant.

Drugs to avoid: Especially aspirin and ibuprofen have to be avoided because of their antiplatelet activity.

Complications following stem cell transplantation[13-15]

Acute

- Infection
- Graft rejection
- Acute graft versus host reaction[15]
- Regimen related complications
- Gastrointestinal – nausea/vomiting, diarrhoea, mucositis, pulmonary, and cardiac
- Haemorrhagic cystitis
- Veno-occlusive disease
- Chronic graft versus host reaction
- Relapse
- Sterility
- Cataract
- Secondary leukaemia

HSCT in haematological disorders – present scenerio

Severe aplastic anaemia: Treatment of choice in < 40 yrs is allogeneic HSCT. 3 years probability of survival is 83% for < 20 years of age, 70% for > 20 years of age. There is a small risk of development of solid organ tumour. Older patients can be managed with ATG ± CSA; 50% survive 15 years after therapy.

Thalassaemia: For children born with severe forms of thalassaemia, chronic transfusions will lead to normal growth and development. However, without aggressive iron chelation, endocrine failure will ensue, and most will die in the second or third decade of life from iron overload. Aggressive iron chelation will prevent or delay these complications. Stem-cell transplantation, if available, is the best treatment option: In young patients, there will be fewer complications than with other treatments, and if transplantation is successful, there is no need for lifelong therapy with transfusion and chelation.

Hodgkin's lymphoma (HL): Relapsed HL or HL refractory to primary chemotherapy is managed with high-dose chemotherapy (HDCT) + autologous HSCT. 3 yrs probability of survival is 78% for patients in CR (complete remission) and 68% for patients in sensitive relapse and 57% for resistant relapse. Allogenic HSCT for this diseae is experimental.

Non-Hodgkin's lymphoma (NHL): Diffuse large B-cell lymphoma are managed with HDCT + autologous HSCT in case of relapse, in those who have achieved second complete remission and good partial response after salvage chemotherapy. Patient with high risk International Prognostic Index (IPI) score 4 - 5 benefit from HDCT + autologous HSCT.

Multiple myeloma (standard of care in patients < 65 yrs of age): Initial induction therapy is given with thalidomide/lenalidomide/bortezomib + dexamethasone

followed by autologous PB HSCT and then maintenance therapy using lenalidomide or bortezomib or thalidomide in low dose for 1 year. Outcome is superior if HSCT is performed within 12 - 18 months of diagnosis[12].

Myelodysplastic syndrome (MDS): It is treatment of choice for patients with IPSS intermediate -2 and high risk MDS[1].

Chronic myeloid leukaemia (CML): Allogenic HSCT is considered for all patients who fail to achieve remission after 3 months of Imatinib therapy, or those who fail to achieve complete cytogenetic remission after 12 - 18 months of imatinib therapy; relapse after initial response and in advanced disease (accelerated phase or blast crisis). LFS (leukaemia free survival) (5 yr) in chronic phase > 50%. DFS (disease free survival) in accelerated phase – 15 - 25%, and in blast crisis < 15% of cases.

Chronic lymphoid leukaemia (CLL): Autologous HSCT is done in young patients with high risk CLL. Allogenic HSCT in CLL is associated with increased failure rates; it is still under research.

Acute lymphoid leukaemia (ALL)

Use of the antileukemic agents together with a stringent application of prognostic factors for risk-directed therapy in clinical trials, has resulted in a steady improvement in treatment outcome in children and adolescents. Unfortunately, the experience with adult ALL has been far less rewarding: reported cure rates seldom exceed 40 per cent. The poor outcome in adult ALL has been variously attributed to an increased frequency of high-risk leukaemia with greater drug resistance, poorer tolerance of and compliance with treatment, reluctance to accept certain temporary toxic effects, and less effective treatment regimens, as compared with childhood ALL. Allogeneic transplantation is the ultimate form of treatment intensification. Among adults with ALL, long-term disease-free survival rates of 30 to 40 per cent have been obtained with the use of chemotherapy, as compared with 45 to 75 per cent with the use of allogeneic transplantation.

Even so, allogeneic transplantation clearly benefits certain very high-risk paediatric and adult patients, such as those with BCR-ABL+ ALL or those with a poor initial response to treatment. The procedure also appears to improve the clinical outcome among adults who have ALL with t (4; 11), but whether it is beneficial for infants with the same genotype remains controversial.

HSCT in paediatric solid tumours

Primary HDCT+ HSCT reserved for patients who are poor risk patients with an expected survival rate < 20% at 3 years with conventional therapy.

Stem cell therapy in non-haematological conditions

Stem cell therapy is still under research for its therapeutic potential in the following conditions[4-7]:-

Pulmonology: ARDS, emphysema, lung fibrosis, pulmonary arterial hypertension – endothelial progenitor cells transducted with nitric oxide synthetase, lung cancer – targeting endogenous stem cells with potential.

Neurology: with spinal cord injury[7], amyotrophic lateral sclerosis (ALS), stroke, traumatic brain injury, and Parkinson's disease sp.

Endocrinology: Type 1 diabetes.

Hepatology: Liver failure, cirrhosis – it potentially can substitute for organ transplantation.

Peripheral artery disease: Chronic limb ischaemia.

Nephrology: End-stage renal disease[6].

Umbilical cord banks in India

The following umbilical cord banks are operational in India.

- Life cell
- Public stem cell bank – Jeevan
- Cryosave
- Cord life
- ReeLabs

Stem cell transplantation in India

HSCT is being done at 37 centres in India, e.g.:-

- Tata Memorial Hospital, Mumbai, Maharashtra
- Institute Rotary Cancer Hospital, New Delhi
- Adyar Cancer Institute, Chennai, Tamil Nadu
- Apollo Speciality Hospital, Chennai, Tamil Nadu
- Tata Memorial Rural Cancer Project, Barshi, Solapur, Maharashtra
- R and R Army Hospital, New Delhi
- Cancer Care Trust and Research Foundation, Indore, Madhya Pradesh
- Inlaks Hospital, Pune, Maharashtra
- Gujarat Cancer and Research Institute, Ahmedabad, Gujarat
- Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh
- Armed Forces Medical College and Command Hospital

(SC), Pune, Maharashtra.

Ethical concerns

They are mostly related to embryonic stem cells. Adult stem cells such as those derived from bone marrow harvested as autologous cells and are generally free of ethical controversy.

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"A vigorous five-mile walk will do more good for an unhappy but otherwise healthy adult than all the medicine and psychology in the world."

– Paul Dudley White.

CASE REPORT

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Pure red cell aplasia in tuberculosis

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Abstract

A case of disseminated tuberculosis presented with fever, cough, severe anaemia and jaundice. He was diagnosed to have pure red cell aplasia on bone marrow examination. The hematological abnormalities reverted with anti-tuberculous treatment. This is case is presented because of its rarity.

Key words: Pure red cell aplasia, tuberculosis.

Introduction

Pure red cell aplasia (PRCA) is a selective depression of erythroid cell line (severe anaemia, reticulocytopenia, and marrow containing < 0.5% mature erythroblasts in an otherwise normal marrow). PRCA is either acute or chronic. Acute PRCA can arise during the course of a number of infectious processes, in association with thymomas, rheumatoid arthritis, lymphoproliferative disorders, autoimmune haemolytic anaemias, insect-bites, protein energy deprivation (Kwashiorkor), hypothermia, with myelodysplastic syndrome, after the exposure to several drugs and chemicals, or as an idiopathic disorder. The infectious causes of PRCA include parvo virus B19, viral hepatitis, mumps, infectious mononucleosis, cytomegalovirus, human immunodeficiency virus, tuberculosis (TB), typhoid, etc. Haematological abnormalities are well recognised in TB[2]. However, PRCA in association with TB is very rare. We report a case of disseminated TB presenting as anaemia due to PRCA.

A 14-year-male presented with fever of moderate grade with yellowish discoloration of urine since 1 month; nonproductive cough - 15 days, and swelling of both feet - 3 days. History of loss of weight and appetite was present. No history of drug intake, toxic exposure was present. Past and family history was negative for TB. Physical examination showed a moderately built, poorly nourished, febrile, severely anaemic, and icteric patient. Right supraclavicular lymphadenopathy was present which was tender and nonmatted. Firm, nontender hepatosplenomegaly was present. Decreased vocal fremitus and resonance, dull percussion note and absent breath sounds in the right axillary, infra-axillary and infra-scapular area were noted. There were no added sounds. Hb - 4 gms/dl, TLC - 7,200/cumm, DLC-P - 67%, L - 30%, M - 2%, E - 1%, B - 0%. RBC count - 1.79 millon/cumm, reticulocyte count < 0.1%, platelet count - 1.5 lakh/cumm and ESR 50 mm 1st hr. PBF showed macrocytic normochromic RBCs with moderate degree of anisocytosis and poikilocytosis. Urine examination – NAD, Mantoux test – positive, total serum proteins - 5 gms/dl, albumin - 2.8 gms/dl, globulin - 2.2 gms/dl, serum bilirubin - 3 mg%, SGOT - 96 IU/l, SGPT - 75 IU/l, renal functions – normal. Chest X-ray revealed right-sided pleural effusion. Pleural fluid was straw coloured. Microscopic examination showed predominantly lymphocytes, small number of mesothelial cells and many RBCs. No malignant cells present. TLC - 2,050/cumm, DLC - L - 98%, P - 02%. Proteins - 3.5 gms/dl, sugar - 95mg/dl. Gram's and Ziehl-Neelson staining – negative. Bone marrow aspiration smears revealed a normocellular marrow. M:E ratio was were markedly increased (99.1). Erythroid series of cells were markedly depressed with a rare basophilic normoblast, proerythroblast, and absent mature normoblasts. Myeloid series of cells showed mild increase in eosinophilic precursors. Megakaryocytes were unremarkable. Differential count showed myeloblasts/promyelocytes - 0% myelocytes N - 12%, E - 10%, B - 0%. Metamyelocyte - 11%, neutrophils - 51%, eosinophils - 4%, basophil - 1%, lymphocytes - 9%, monocytes - 0%, plasma cells - 2%, erythroblasts - 1%. FNAC from the supraclavicular lymph node showed many reactive lymphoid cells with polymorphic leucocytes in the background of amorphous material. No granuloma seen. Biopsy from lymph node showed areas of necrosis, acute inflammation, dystrophic calcification with haemorrhage and congestion. No definite granuloma seen. Patient was diagnosed as pulmonary TB with dissemination to liver and spleen with acute PRCA. He was given 2 units of blood transfusion and was put on ATT. There was improvement in the haemogram with Hb - 8 gms%, RBC count 2.5 million/cumm, reticulocyte count - 1.5% after 10 days. Patient showed regular improvement in haematological parameters thereafter.

Disseminated TB can give rise to striking blood changes so much so that a primary blood disorder is mistakenly

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diagnosed[2]. The reported haematological abnormalities include anaemia, leucopenia, monocytosis, leukemoid reactions, granulocytic leukocytosis, pancytopenia, and very rarely PRCA[2,3]. Peripheral blood film shows no specific abnormalities. There is a complete absence of polychromatic cells and the reticulocyte count is zero or virtually zero. In bone marrow cytology, cellularity is somewhat reduced with a striking reduction of maturing erythroid cells. Proerythroblasts are present in normal numbers and sometimes may be increased. Other lineages are normal. In bone marrow histology, the cellularity is reduced with striking lack of erythroid islands and maturing erythroblasts. PRCA involves a selective failure of erythroid progenitors with relatively unaffected granulopoiesis and megakaryopoiesis. Absence of history of drug use, toxic exposure, autoimmune illness with a 3 gm% increase of haemoglobin following ATT strongly suggest an aetiological role of the infection in the haematological abnormality. The various theories put forward to explain the haematological manifestations of TB include abnormal splenic function[2], direct invasion of bone marrow[3] and the allergic action of products of tubercle bacilli on sensitive haemopoietic tissue[2]. In a study of IgG inhibitors of burst forming units – erythroid and colony forming units – erythroids could be identified in a majority of these patients. These inhibitors have no effect on erythroid precursor cells, erythropoietin or myeloid progeniotors[1].

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REBLET

CASE REPORT

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Cerebral venous sinus thrombosis

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Introduction

Intracranial sinovenous occlusive disease is an infrequent condition (0.5 - 1% of all strokes) with a variety of causes [5]. The increasing recognition of this condition is probably due to an enhanced clinical awareness and the use of MRI. Intracranial venous thrombosis can be aseptic or septic. Intracranial venous thrombosis may occur at any time from infancy to old age, but most reported modern cases have been in adult women in association with the puerperium. Onset of symptoms may be acute, subacute, or chronic. Cerebral venous infarction is the most serious consequence of cerebral venous thrombosis. High index of suspicion is required in appropriate clinical settings to diagnose this entity at the earliest and ensure prompt treatment with anticoagulants, which can result in almost complete neurological recovery. We report two such male cases, which presented to us with varying manifestations, and briefly discuss this entity.

Case report 1

A 35-year-old male presented with complaints of multiple episodes of recurrent generalised tonic-clonic seizures (GTCS), followed by state of altered sensorium for about two days. The illness was preceded by headache and fever (mild-to-moderate grade) for about fifteen days. There was no history of, vomiting, blurred vision, ear discharge, or head injury. There was no past history of any major illness or symptoms suggestive of TIA. On examination, he was febrile with pulse 88/min, regular; blood pressure of 126/78 mmHg, and respiratory rate of 30/min. There was no pallor, icterus, tremors or signs of hepatic dysfunction. Neurological evaluation revealed an unconscious patient, hypereflexic upper and lower limbs, and bilateral extensor plantars. There was no papilloedema, or signs of meningeal irritation. The chest auscultation revealed crackles on all sites bilaterally, raising suspicion of aspiration pneumonitis. Examination of the other systems was normal. Investigations revealed Hb 11.8 g/dl; total leukocyte 15,600/dl and platelet count of 1,80,000; serum bilirubin 1.2; SGOT/SGPT of 36/47 and serum creatinine of 1.2; blood sugar level at 92 mg/dl. The CSF examination was unremarkable. NCCT brain showed bilateral parietal lobe haemorrhagic infarcts. MRI of the brain showed evidence of superior sagittal sinus (SSS) thrombosis and venous infarcts in both parietal lobes. The patient was managed with parenteral antibiotics, antiepileptics, anticerebral oedema measures, subcutaneous low molecular weight (LMW) heparin (enoxaparin) 40 mg SC twice daily. Oral anticoagulation (tab warfarin 3 mg OD) was started simultaneously. His condition failed to respond to the regimen and the patient expired after three days of admission.

Case report 2

A 50-year-old chronic alcohol abuser and smoker, presented with complaints of altered sensorium since 5 days which was preceded by an episode of binge drinking. The illness was preceded by headache. There was no history of fever, vomiting, blurred vision, ear discharge, or head injury. He denied past history of any major illness or symptoms suggestive of TIA. On examination, he was afebrile with pulse 88/min; regular, blood pressure of 118/70 mmHg, and respiratory rate of 16/min. There was no pallor, icterus, tremors, diaphoresis, or signs of hepatic dysfunction. Neurological evaluation revealed a confused male with spasticity of both lower limbs and bilateral extensor plantars. There was no papilloedema, or signs of meningeal irritation. Examination of the other systems was normal. Investigations revealed Hb 11.8 g/dl; total leukocyte 7,200/dl; and platelet count of 2,02,000; serum bilirubin 1.2, SGOT/SGPT of 52/45; and serum creatinine of 1.2; blood sugar level at 102 mg/dl. NCCT brain showed diffuse hypodensity seen in bilateral thalamus and globus pallidus region and midbrain region. MRI findings (Fig. 1 and 2) were in favour of deep cerebral venous thrombosis involving the inferior saggital sinus, internal cerebral vein, straight sinus and venous confluence with diffuse oedematous hyperintensity of mid brain and thalamus.

The patient was managed with parenteral vitamins (vitamin B1, B6, and B12), subcutaneous low molecular weight (LMW) heparin (enoxaparin) 40 mg SC twice daily for seven days. Oral anticoagulation (tab warfarin 3 mg OD) was started simultaneously. His neurological deficit recovered gradually.

Discussion

CVST is reported to be commoner in developing countries,

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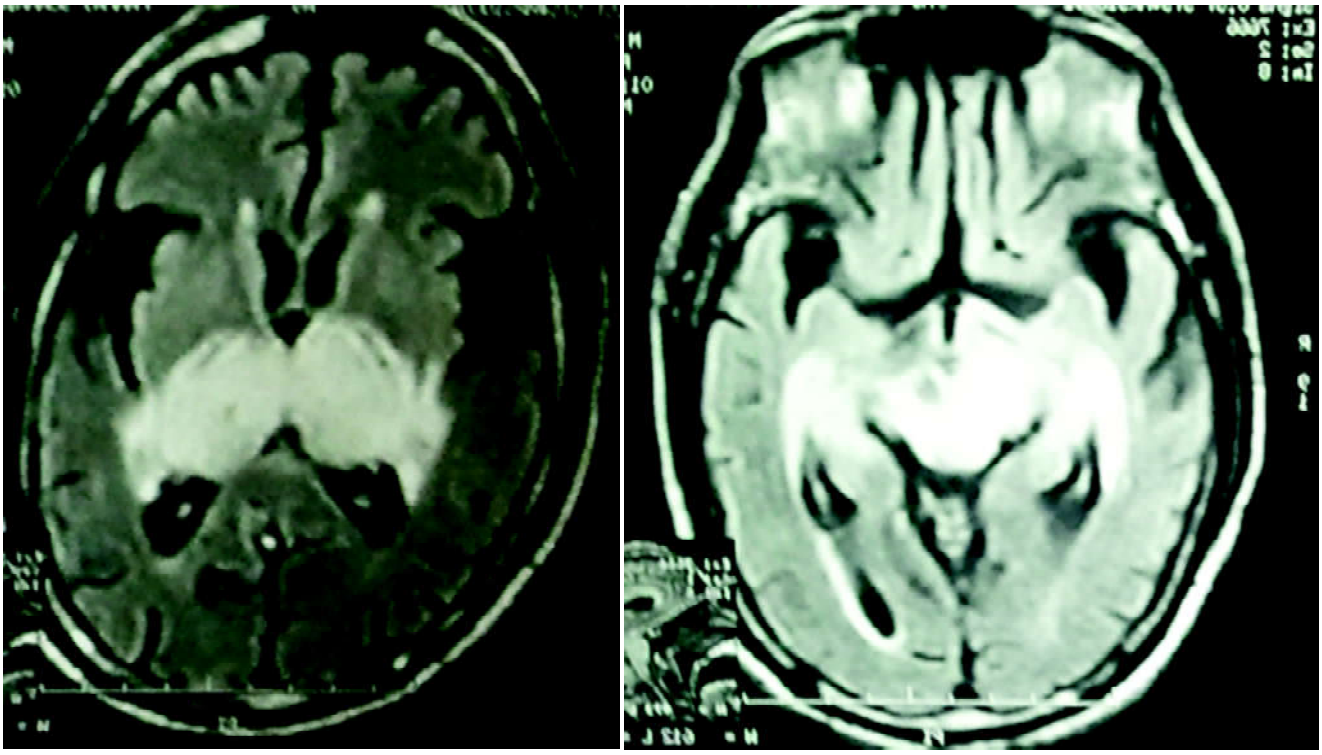

Fig. 1: *MRI findings: Hyperintensity of mid-brain and thalamus.*

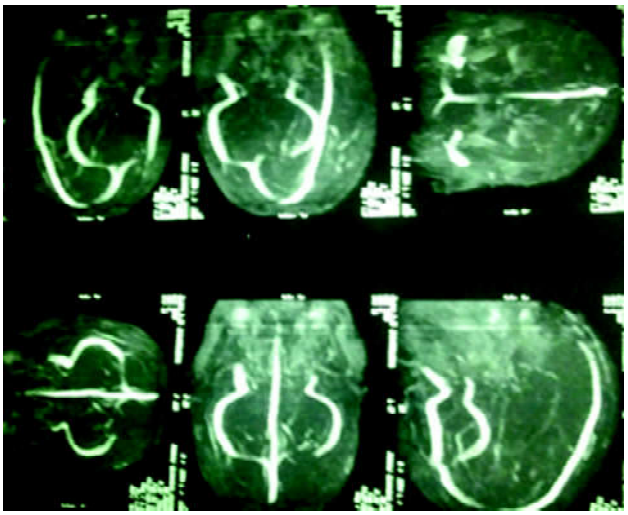

Fig. 2: *MR venography: Deep cerebral venous thrombosis involving the inferior saggital sinus, internal cerebral vein, straight sinus, and venous confluence.*

and has been linked to pregnancy, multiparity and infection. Nearly 40% of patients with CVT have seizures at presentation and data shows that 7% of CVT patients experience seizures within 2 weeks of diagnosis. Majority of these early seizures are recurrent, but 40% of them occurred *de novo*. The prevention of early seizures is a relevant clinical problem. Such seizures can cause neurologic and systemic deterioration, status epilepticus, and death. The risk of seizures was increased in patients with motor deficits, again pointing to the relevance of damage to the motor cortex[1]. Multiple factors have been associated with CVT, but only some of them are reversible. Prior medical conditions (e.g., thrombophilias, inflammatory bowel disease), transient situations (e.g., pregnancy, dehydration, infection), selected medications (e.g., oral contraceptives, substance abuse), and unpredictable events (e.g., head trauma) are some predisposing conditions[8]. CVST is a great masquerader as it can present in various forms and confuse the clinician. It manifests as a stroke with seizures confusing it with arterial strokes. It may present with headache and papilloedema, the clinical *sine qua non* of ICSOL. It may also present with pleomorphic seizures occasionally with fever suggesting encephalitis[2].

Presence of bilateral haematoma in CT may be a clue for CVST. Haemorrhagic infarction is common in CVST and is reported in 35 - 50% of patients, which is attributed to blockade of venous sinuses. There is increase in venous and capillary pressure resulting in diapedesis of RBCs and subsequent rupture of small vessels[3]. Presence of ICH may be an extension and exaggeration of the above-mentioned sequence. Rapidity of venous thrombosis and lack of fibrinolysis may contribute to occurrence of ICH[3]. Neuroimaging modalities of choice in CVST are computerised tomographic (CT) scan and MRI with MR venogram (MRV). CT scan may be normal in 15 - 30% cases

but MRI with MRV is almost 100% diagnostic[4]. CT scan pictures suggestive of CVST are infarcts, which may not conform to an arterial territory, extensive cerebral oedema, haemorrhagic infarcts, falcine and tentorial enhancement and thrombosed cortical vein (cord sign). Thrombosis of the deep venous system presenting with bilateral thalamic infarction or oedema is a common finding, but unilateral venous thrombosis presenting with unilateral thalamic oedema is extremely rare[7]. MRI with MRV is the investigation of choice, which shows absence of flow void in the thrombosed sinuses[4]. That most patients with cerebral vein thrombosis have a more benign prognosis than previously suspected: 5.6% of patients died during the acute phase, and 9.4% of patients had died at the end of the follow-up period. Conversely to the acute phase, where most patients died due to cerebral herniation, during the follow-up period most patients had died due to underlying conditions such as cancer rather than as a result of direct consequences of their CVT. Most surviving patients recovered completely or had only mild functional or cognitive deficit; less than 1 in 5 surviving patients were dependent or had a permanent disability at the end of the follow-up period. Patient characteristics likely to be associated with an adverse outcome include: age older than 37; presence of focal deficit at presentation; altered consciousness, including coma, at presentation; intracranial haemorrhage; involvement of cortical veins; and underlying cancer.

Conclusion

CVST is not an uncommon cause of stroke in our country. Puerperal CVST accounts for a majority of these cases. The main causes of non-puerperal CVST are dehydration, antiphospholipid antibody syndrome, hyper-homocysteinaemia, Factor V Leiden, malignancies, paraproteinaemia, paroxysmal nocturnal haemoglobinuria and certain drugs like oral contraceptives and L-asparginase. The cases reported above demonstrate a need for maintaining suspicion of CVST in male patients with appropriate clinical presentation. In the first case, the cause of CVST was infection, while in the second case dehydration was the most likely culprit. Also, dehydration (even subclinical) assumes importance in the aetiology and management of these patients.

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"Today's medicine is at the end of its road. It can no longer be transformed, modified, readjusted. That's been tried too often. Today's medicine must DIE in order to be reborn. We must prepare for its complete renovation."

– Maurice Delort.

CASE REPORT

JIACM 2015; 16(3-4): 247-49

Acute nitrobenzene intoxication

Tej Pal Singh, Manaswi Choubey**, Mahendra Dogiwal***

Introduction

Intentional exposure is a major cause of premature mortality globally and 1,13,914 suicides are recorded annually from India for which a variety of chemicals have been used[1]. Nitrobenzene also known as nitrobenzole or oil of mirbaine is used in dyes, paints, lubricating oil and synthetic rubber. The lethal dose is reported to range from 1 to 10 grams by different studies[2,4]. Nitrobenzene ingestion primarily causes methaemoglobinaemia. Acute poisoning with nitrobenzene causing significant methaemoglobinaemia is an uncommon but life-threatening emergency. Early aggressive management of severe poisoning, strongly suspected on clinical grounds may change the outcome of the patient.

Case report 1

A 17-year-old unconscious male presented to our emergency department with cyanosis and a grayish-brown hue, laboured respiration of 30/min, BP 60 mmHg systolic, pulse rate of 150/min, pupils with normal size and sluggish reaction, and SpO_2 of 60% on air. His chest was clear. The patient was immediately administered on 100% O_2 by high-flow mask. Dopamine support was started at inotropic dose. There was a history of ingestion of shoe paint remover solvent followed by severe pain in the abdomen, nausea, vomiting, and dizziness, after which he was brought to the hospital. His arterial blood sample was found to be chocolate brown in colour which was suspected to be due to methaemoglobinaemia. His ABG was suggestive of metabolic acidosis with pH 7.12, PaO_2 130 mmHg, $PaCO_2$ 44 mmHg and HCO_3 13.3 meq/l. Gastric lavage was done via naso-gastric tube with sodium bicarbonate, followed by administration of activated charcoal (1 g/kg of 20% suspension) and started with IV fluids. His SpO_2 became 86% and he had respiratory distress. BP was 90/60 mmHg. X-ray chest and ECG were within normal limits. WBC was 14,000/dl, serum bilirubin was 1.8 mg/dl (conjugated 1.0, unconjugated 0.80), SGOT 23 and SGPT 21. Urine was dark colored. Serum creatinine and electrolytes were within normal limits. A clinical diagnosis of acute nitrobenzene poisoning with severe methaemoglobnaemia was made.

Due to non availability of intravenous methylene blue, specific antidote could not be given. Haemodialysis was done and slow IV infusion of ascorbic acid 1 gm in 5% dextrose thrice a day was given. His SpO_2 after 2 hours of dialysis became 92% and patient became stable. He became fully conscious after 4 hrs of dialysis and was discharged on the 5th day.

Case report 2

A 21-year-old male was brought to the emergency department with alleged ingestion of some unknown chemical substance. He worked in a printing press. On admission, he was in an unconscious state, not responding to verbal commands and pain. There was history of an episode of vomiting. On examination, the pupils were found dilated, reacting sluggishly to light. Heart rate was 63/minute, BP - 76/34 mmHg, SpO_2 70%, respiratory rate was 38/min. On examination, cyanosis was present, with marked bluish discoloration of nail beds, finger tips, and lower palpebral conjunctiva. Chest auscultation was normal. Abdomen was found soft to palpation. The patient was immediately intubated. Inotropic support was given. Gastric lavage was done and 100% oxygen was begun. The blood sample withdrawn for investigations revealed severe brownish discoloration. Electrocardiograms recorded at the time of admission and thereafter were normal. Blood investigation revealed leucocytosis, elevated liver enzymes with mildly deranged renal profile. The urine was dark brown coloured. The Hb was 6.6 mg/dl, TLC was 12,600 count/mm^3, blood sugar (mg/dl) 121, and blood urea (mg/dl) 56, SGOT (U/L) 159, SGPT (U/L) 118, creatinine (mg/dl) 2.1. He was given antibiotics, pantoprazole, and ondansetron. One unit of whole blood was transfused. A clinical diagnosis of acute severe methaemoglobinaemia of unknown origin was made. From the information provided by the attendants it was derived that the substance consumed was most likely nitrobenzene solution which was used in the printing process as a reducing agent. The patient was put on conservative treatment. The patient failed to respond to the treatment administered and expired the next day.

Discussion

Acute poisonings due to ingestion of nitrobenzene present in consumer products have occurred frequently in the past

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and are accidental or suicidal[5]. The first report of nitrobenzene poisoning came in 1886[6] and subsequent fatality reports followed[5,6].

The symptoms which were present were non-specific except for cyanosis which is a typical finding in cases of nitrobenzene poisoning, as methaemoglobinaemia commonly occurs. This happens when nitrobenzene oxidizes the ferrous ion of haemoglobin to the ferric state (Fe^{+++}), resulting in decreased binding and delivery of oxygen by red blood cells[7].

Acute intoxication is usually asymptomatic up to the level of 10 - 15% of methaemoglobinaemia, showing only cyanosis. Beyond 20% headache, dyspnoea, chest pain, tachypnoea and tachycardia develop. At 40 to 50%. confusion, lethargy and metabolic acidosis occur leading to coma, seizure, bradycardia, and ventricular dysrythmia. Anaemic and G6PD patients suffer more severe symptoms[2-4].

Nitrobenzene is metabolised to p-nitro phenol and aminophenol and excreted in urine up to 65%, and in stools up to 15% after 5 days of ingestion. Liver, stomach, brain, and blood may act as stores and release it gradually[7].

Symptoms of nitrobenzene ingestion include burning sensation in the mouth, numbness of the tongue, salivation, nausea, vomiting, diarrhoea, giddiness, throbbing headache, marked cyanosis, cold and moist skin, weak and rapid pulse, hurried breathing, drowsiness and coma. The blood is likely to be chocolate-coloured due to the presence of methaemoglobin. The pupils get constricted at first, and then dilated. Urine becomes dark coloured. Convulsions may occur before death. Gastrointestinal toxicity may result in hepatosplenomegaly, jaundice, and altered liver functions. Haematological toxicity may show methaemoglobinaemia, haemolytic anaemia, and Heinz bodies[8-10].

The fatal dose of nitrobenzene is said to be about fifteen drops, and the MAC in air is about 1 ppm. Death usually occurs within six to seven hours of ingestion[9].

Chemically induced methaemoglobinaemia is a life-threatening condition which requires immediate and definitive management. Methaemoglobinaemia management can be classified into five categories: (1) reducing the toxin's systemic absorption by induction of emesis with ipecac syrup/salt water and facilitating removal of toxin from gastrointestinal tract by gastric lavage, activated charcoal, and a purgative; (2) reduction of methaemoglobin to haemoglobin via reducing agents; (3) treatment of the "functional anaemia" (hypoxic state) with hyperbaric oxygen; (4) extracorporeal removal of the chemical; and (5) replacement of metheamoglobin with a functional oxygen-carrying pigment[11].

The definitive treatment of methaemoglobinaemia is the use of the reducing agent methylene blue, whose action is dependent on production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) by the hexose phosphate shunt and the activity of the enzyme, NADPH-methaemoglobin reductase. NADPH is necessary for the reduction of methylene blue to leukomethylene blue, which is responsible for the reduction of methaemoglobin into haemoglobin[10,12]. The role of ascorbic acid in reducing methaemoglobinaemia is controversial as its action is slow and offers little advantage over normal endogenous reduction of methaemoglobin. Methylene blue is available as 1% 10 ml vial and for the initial management of methaemoglobinaemia. Its recommended dose is 1 to 2 mg/kg to a maximum of 5 to 7 mg/kg/day. Since maximal response to methylene blue usually occurs within 30 to 60 minutes, methaemoglobin levels should be monitored and repeat doses of methylene blue should be spaced at least one hour apart and after evaluating the response to the last dose. G6PD deficiency should be considered if a patient has a negligible initial response to a therapeutic dose of methylene blue[13]. Methaemoglobin levels should be continuously monitored as nitrobenzene has the potential for continued methaemoglobin production[11,14]. N-acetylcysteine has a controversial role in reducing methaemoglobin, so its use is not yet approved[15]. Exchange transfusion is indicated in severe cases[16]. Hyperbaric oxygen is reserved for patients who have a methaemoglobin level > 50% and or those who do not respond to standard treatment[10].

The patients were unconscious with respiratory distress and hypotension. Due to non availability of methylene blue, specific treatment was not possible at our centre. The patients were treated with supportive therapy. Both patients were posted for dialysis as a desperate measure. The first patient improved but the second patient failed to respond to the treatment and expired.

Conclusion

Acute methaemoglobinaemia is usually associated with high mortality. Methylene blue and ascorbic acid are the treatment of choice. Blood exchange transfusion and hyperbaric oxygen therapy are usually reserved for patients who are resistant to standard treatment. Forced diuresis led to a rapid fall in methaemoglobinaemia and improved outcome[2].

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"The physician should look upon the patient as a besieged city and try to rescue him with every means that art and science place at his command."

– Alexander of Tralles (AD 525 - 605), Physician.

CASE REPORT

JIACM 2015; 16(3-4): 250-2

Purpura fulminans in a case of complicated *falciparum* malaria

Debaprasad Chakrabarti, Mukut Roy**, Soma Saha**, Gautam Mazumder***, Amrit K Bhattacharyya*****

Abstract

Dermatological manifestations are relatively rare in falciparum malaria. Here, we report a elderly male with falciparum malaria who presented with purpura, severe cutaneous haemorrhagic necrosis and gangrenous plaques. He was successfully managed with antimalarials and anticoagulants. The case is presented because of its rarity.

Key words: Purpura fulminans, malaria.

Introduction

Malaria is a mosquito borne disease caused by protozoa plasmodium. Most life-threatening cases of malaria with multiorgan dysfunction are caused by *Plasmodium falciparum*. Cutaneous manifestations, although noted, are rarely reported and have included jaundice[1], petechiae[1], vasculitis[2], purpura[2,3], and gangrene[4,5].

Purpura fulminans is a term used to describe a condition of rapidly progressive necrosis of skin associated with haematological features of DIC[6] (disseminated intravascular coagulation).

In this paper, a case of purpura fulminans in a patient of *falciparum* malaria is presented.

Case report

A 60-year-old male was brought to the emergency medical services of our hospital with a history of high grade fever with chills and rigors for 4 days, and altered sensorium for 1 day. There was no history of convulsion, cough, respiratory distress, or reduced urinary output. No complaint of photosensitive rash, arthralgia, bleeding from any site or focal neurological deficit was reported. There was no significant medical illness in the past.

On examination, the patient was febrile, drowsy, and poorly responding to painful stimuli with pulse rate 112/min, regular. All the peripheral pulses were palpable. His BP was 130/70 mm of Hg and respiratory rate was 24/ min. Physical examination revealed deep jaundice and bluish-blackish gangrenous discoloration of distal areas of both feet and toes with some purpuric spots (Fig. 1a). Some of the acral parts showed haemorrhagic bullae formation with crusts.

Besides this, peeling of skin with serosanguinous discharges was noted. Purpuric lesions were also present on the bridge of the nose (Fig. 1b). There were no signs of meningeal

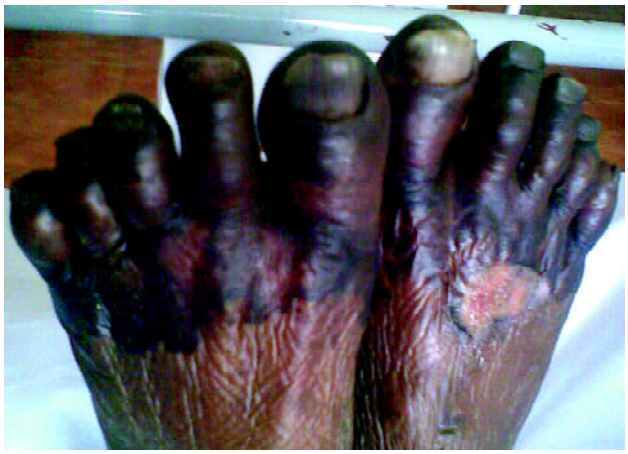

Fig. 1a: *Haemorrhagic cutaneous necrosis of distal aspect of foot.*

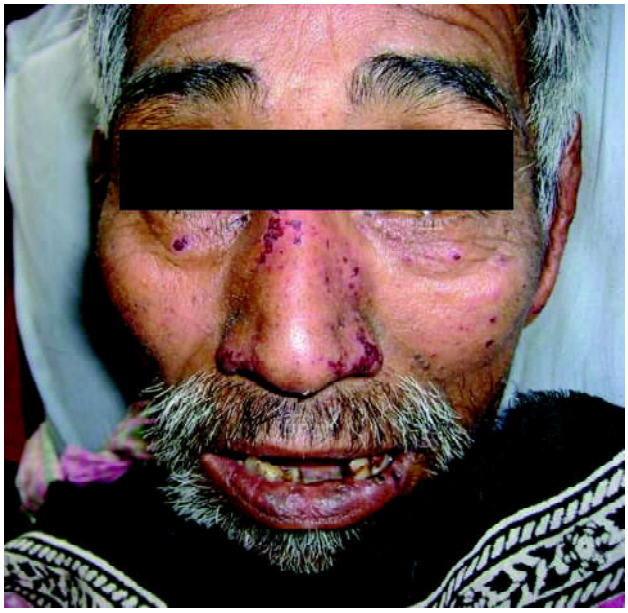

Fig. 1b: *Purpuric lesions over the nose.*

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irritation or papilloedema, and rest of the systemic examination was normal.

Investigations revealed anaemia (Hb - 8.9 gm/dl), leucocytosis (TLC - 11,100) thrombocytopenia (platelets - 82,000), and increased prothrombin time (38 sec.) with ESR of 30 mm/hr. Random blood sugar was 110 mg/dl, serum urea was 56 mg/dl and creatinine was 1.7 mg/dl. His liver function test showed serum bilirubin of 4.5 mg/dl with predominant unconjugated hyperbilirubinaemia and mildly evelated transaminases. CSF analysis was non contributory. PBS examination revealed trophozoites of *Plasmodium falciparum,* and rapid antigen test for malaria was positive. Chest X-ray, ECG, and USG of abdomen was normal.

HIV, HBV, HCV serology and ANA, ANCA were negative. Blood and urine culture was sterile. Patient was subjected to D dimer assay which was positive, and skin biopsies revealed extensive red cell extravasation with epidermal necrosis consistent with thrombo-occlusive disease.

The patient was put on IV artesunate and IV heparin along with other supportive measures. Over the next 48 hrs, he became alert, afebrile, and improved clinically. The cutaneous lesions resolved remarkably over the next ten days (Fig. 2) and he was sent home in a stable condition.

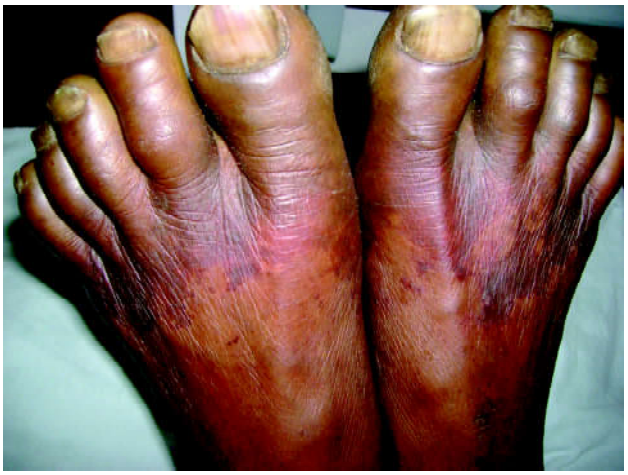

Fig. 2: *Improvement of the gangreneous lesions of both feet following treatment.*

Discussion

Malaria is the most important parasitic disease known to mankind. Most severe life-threatening cases of malaria with multiorgan system involvement are caused by *Plasmodium falciparum*. Skin findings seen in malaria are rarely reported[1]. We present a rare case of purpura fulminans with features of DIC in a patient of complicated *falciparum* malaria.

Calverly[7] states that the diagnosis of purpura fulminans should not be made without DIC and at least one positive test for excessive thrombin generation. Two such tests are the D dimer assay and the more difficult to perform fibrin monomer assay.

In our patient, the positive D dimer assay with other evidence of DIC including thrombocytopenia, raised prothrombin time, and more specifically the skin biopsy allowed us to make a diagnosis of purpura fulminans in a case of *falciparum* malaria.

Purpura fulminans can be classified into three categories:-

a) Acute infectious purpura fulminans.

b) Secondary to hereditary or acquired dysfunction of protein C or other haemostatic regulatory mechanism.

c) Idiopathic purpura fulminans which could be unknown post-infectious in aetiology[5].

Purpura and cutaneous gangrene have been reported in the past as rare dermatological symptoms. However, there was no evidence of DIC in those cases and hence the diagnosis of purpura fulminans could not be entertained[5]. With our extensive search of review of literature we could find only two such case reports till date mentioning it an extremely uncommon dermatological manifestation of malaria.

The exact mechanism responsible for purpura fulminans in malaria is still not understood. It is thought to result from cytoadherence and rosetting of parasite leading to obstruction in microcirculatory bed. CD-36, thrombospondin (TSP), endothelial leukocyte adhesion molecule-1 ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intra-cellular adhesion molecule-1 (ICAM-1), and histidine-rich protein (HRP) have been identified as the various receptors which may cause adhesion of the infected red cells to the vascular endothelium[8].

Management of purpura fulminans include early and aggressive treatment of associated infection and supportive treatment with vasodilators, heparin, and aspirin. Our patient responded to IV artesunate and supportive drugs.

Thus we present a case of purpura fulminans, a rapidly progressive skin necrosis associated with DIC in a patient of complicated *falciparum* malaria. It emphasises the high index of suspicion to be kept to differentiate it from meningococcaemia and other causes of vasculitis and the need for prompt treatment to avoid limb amputation. This case report also highlights the importance for a careful search to the presence of malarial infection in any given case of purpura fulminans.

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"When a lot of remedies are suggested for a disease, that means it cannot be cured."

– *Anton Chekhov,* The Cherry Orchard.

CASE REPORT

JIACM 2015; 16(3-4): 253-4

Unexplained delirium in dengue fever

M Chaturvedi, PM Jha**, A Pandey***, P Kumar***

Abstract

Dengue fever is the most important mosquito-borne, arbo-viral infection of man, that causes a severe flu-like illness. During the last few years, there have been increasing reports of dengue fever with unusual manifestations like neurological and psychiatric. There has not been any systemic study mentioning the prevalence and pattern of psychiatric sequelae. We report a 50-year-old male who after an acute dengue infection developed an episode of delirium and was successfully treated. Most of these patients required reassurance and support except a few who required a short course of anxiolytics. These symptoms generally resolve within one week of onset of dengue fever.

Key words: Dengue, Delirium, Psychiatric manifestations.

Introduction

During the last few years, there have been increasing reports of dengue fever with unusual manifestations[1], primarily with neurological as well as psychiatric symptoms. The neurological features include headache, seizures, neck stiffness, depressed sensorium, paralysis, and cranial nerve palsies[2-5]. Among the most prominent psychiatric symptoms encountered in the acute phase of dengue fever are fear of death, anxiety, insect phobia, behavioural disorders, delirium, depression, and mania[6]. Psychiatric morbidity during acute dengue infection has rarely been reported. There has not been any systemic study mentioning the prevalence and pattern of psychiatric sequelae. We report a 50-year-old male who after an acute dengue infection developed an episode of delirium which was successfully treated.

Case report

A 50-year-old male was admitted to Post-Graduate Department of Medicine, SNMC, Agra with c/o high grade fever without chills and rigors, associated with loss of appetite, generalised myalgia, nausea, headache, and arthralgia of 3 days duration. There were no associated symptoms of sore throat, cough, dysuria, expectoration, seizures, head trauma, haemorrhagic manifestation or rash. Since the second day of admission, the patient showed altered and hyperactive behaviour, started using abusive language, picking threads from hypothetical clothes, and altered sleep-wake cycle. There was no previous history of similar episode in the past. Family history was not significant.

Examination revealed a conscious ill looking male with mild pallor, no icterus, cyanosis, clubbing, oedema, or lymphadenopathy. His BP was 114/76 mmHg, pulse rate was 110 bpm and patient was afebrile. On systemic examination of respiratory system - normal broncho-vescicular breath sounds heard bilaterally with no added sounds; cardiovascular system - S1 S2 heard normally with no audible murmur; abdomen – soft, non tender, non distended, with no palpable organomegaly; and on CNS examination – patient was conscious, co-cooperative and oriented to time, place, and person. Neck rigidity and Kernig's sign were absent. Fundus examination did not reveal any sign of raised ICP. Investigations on day of admission showed: Hb - 10.8 gm/dl, haematocrit - 43, TLC - 2,700, differential count – neutrophils 52%, lymphocytes 48%. His platelet count was 76,000 (56,000 on 2nd day; 46,000 on 3rd day; 88,000 on 4th day). Blood sugar, urine (routine and microscopy), serum creatinine and electrolytes were normal during his complete course of admission. SGOT/SGPT was slightly deranged - 86/75 and serum bilirubin was 0.8 mg/dl. Peripheral smear for malaria and malaria ELISA test were negative. His IgM ELISA and NS1 antigen for dengue was positive. On the third day of admission, MRI head was done and was found to be normal; CSF was drawn and was sent for cytology, biochemistry, and ADA to rule-out tubercular antigen, encephalitis, etc., but was reported normal. USG -abdomen and chest X-ray PA view were also normal.

Psychiatric opinion was taken and a clinical diagnosis of dengue fever with delirium was made. The underlying cause was treated and injection haloperidol and promethazine i/m were given for 4 days. Platelets and liver transaminases returned to normal after five days of conservative management. On the 5th day, the patient was afebrile and his behaviour was near-normal.

Discussion

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As psychiatric manifestations are difficult to estimate in acute dengue cases, their exact prevalence is still unknown, but the most prevalent psychiatric symptom encountered in the acute phase of dengue was fear of death followed by anxiety and associated symptoms.

Most of these patients with psychiatric symptology required reassurance and support, except for a few who required a short course of anxiolytics. These symptoms generally resolve within one week of onset of dengue fever. However, delirium in the afebrile phase of dengue is quite an unusual manifestation as reported in our case. Delirium with high-grade fever may be possible in an elderly person but relatively rare in the afebrile phase. Delirium, or acute confusional state, is a syndrome that presents as severe confusion and disorientation, developing with relatively rapid onset and fluctuating in intensity. Delirium represents an organically caused decline from a previously attained baseline level of cognitive function. It is typified by a fluctuating course, attention deficitsm and generalised severe disorganisation of behaviour. It typically involves other cognitive deficits, changes in arousal (hyperactive, hypoactive, or mixed), perceptual deficits, altered sleep-wake cycle, and psychotic features such as hallucinations and delusions. Our patient suffered from dengue fever as diagnosed from the positive dengue IgM antibody against NS1 antigen of dengue virus which is a quite sensitive and specific laboratory test for clinical diagnosis of dengue fever and delirium as evidenced by altered behaviour, hyperactive state, using abusive language, picking threads from hypothetical clothes, altered sleep-wake cycle and normal MRI brain, CSF study. The patient's past and family history was found to be unremarkable for any episode of a distinct mood disorder. In our patient the platelet count on admission was 76,000/cumm and thereafter decreased slightly. There was no evidence of DHF or dengue shock syndrome.

This case illustrates a clear temporal relationship between the onset of dengue fever and the emergence of delirium symptoms. In view of the above-mentioned facts, a possible organic aetiology (dengue infection) for the delirium episode was entertained. Similar kinds of symptoms have been seen in cases of dengue encephalitis earlier, but MRI and CSF were not normal in those cases[7]. In our case, MRI, CSF, and electrolytes were normal.

The present case was successfully treated. A systematic study is needed to find out the prevalence and pattern of associated psychiatry disorders as dengue is a major health problem in some parts of Asia.

Conclusion

As in our country, dengue is becoming endemic and in almost every year in the months of September to November, in monsoon period, cases of dengue fever are being reported from different parts of the country. Because numbers of cases are quite high, many patients may present with unusual and atypical manifestations. Therefore, any patient at the time of epidemic with a history of short duration fever (< 7 days), with atypical manifestations can be suspected as dengue fever in delirium.

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"Hope costs nothing."

– SIDONIE GABRIELLE.

CASE REPORT

JIACM 2015; 16(3-4): 255-6

A case of non tubercular mycobacterial (NTM) pulmonary infection

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Abstract

Non tubercular mycobacterial (NTM) pulmonary infection is a well known entity in medical literature. In suspected cases — at least before starting treatment for multi-drug resistant tubercular cases — NTM infection should be ruled out either by conventional or new rapid diagnostic techniques. Therefore NTM pulmonary infection should be considered in the differential diagnosis of MDR TB pulmonary infection.

Introduction

Many acid-fast organisms may be found in sputum sample causing pulmonary infection. The most common being mycobacterium tuberculosis complex (MTBC which includes, *M. tuberculosis, M. africanum, M. bovis subsp. bovis, M. bovis subsp. caprea, M.bovis BCG, M. microti, M. canettii and M. pinnipedii*), non tubercular mycobacteria (NTM) and other microorganisms like actinomyces(*Nocardia*, rhodococcus) and fungal yeast forms (blastomyces, histoplasma).

There is continued growth in the number and prevalence of mycobacterial species other than the *Mycobacterium tuberculosis* complex causing human disease[1,2]. Non-tubercular mycobacteria (NTM) like all the other mycobacteria can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease. Chronic pulmonary disease is the most common localised clinical manifestation of NTM[3,4,5].

The isolation rate of NTM from India has been reported as ranging from 0.5% to 8.6%. The incidence of NTM is still unknown; even though being isolated from the cultures, it has been neglected or considered as a contaminant, thus not recorded. NTM infections have frequently been overlooked in developing countries like India because of high incidence of tuberculosis infection, unfamiliarity of clinicians with non tubercular mycobacterial infection due to nonspecific clinical manifestations and inadequacy of laboratory services[6]. Treatment guidelines for both the diseases — caused by *M. tuberculosis* complex *and non-tubercular mycobacteria — are* different. Mycobacterium can be differentiated from other acid-fast organisms by microscopic examination, but to differentiate MTBC from non tubercular mycobacteria (NTM), culture, colony characteristics, biochemical tests, and various molecular tests are required.

Case report

A 40-year-old male patient was found to be sputum AFB positive at a peripheral health institution. He was put on regular anti-tubercular therapy (ATT) since September 24, 2012. He completed his ATT course of 8 months in May 2013. At the end of 8 months regular treatment, the patient's sputum sample was found to be AFB positive. Due to treatment failure, he was suspected to be a multi-drug resistant tuberculosis (MDR-TB) case and referred to the Intermediate Reference Laboratory (IRL), Dharampur (Kasauli, Himachal Pradesh) for drug susceptibility testing (DST). At IRL, his sputum smear was found to be AFB positive and subjected to Line Probe Assay (LPA) for DST; but the LPA test result was negative, i.e., MTBC not detected. The decontaminated sputum sample was then inoculated on LJ drug-free media as well as with LJ-PNB (para nitro benzoic acid). The growth was positive in both drug free as well as LJ-PNB media, suggestive for the presence of non tubercular mycobacteria. The MPT 64 Ag test for confirmation of MTBC was found to be negative from the LJ media growth, suggestive of absence of *Mycobacterium tuberculosis*. The patient was advised for repeat sampling and the same findings were put under observation in August 2013. Finally, it was concluded that the present case was suffering from non tubercular mycobacterial (NTM) pulmonary infection. In the mean time this patient was confirmed as a case of NTM from NABL accredited commercial laboratory based in New Delhi, India.

Discussion

NTM were not widely recognised as human pathogens until the 1950s, when several large series of patients with NTM lung disease were reported[6-8]. The clinical presentation of the pulmonary disease due to NTM is just like tuberculosis. Infection due to NTM should be suspected specially in cases

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in whom initial complete adequate course of antitubercular treatment (ATT) has not produced the desired response. This should be corroborated by repeated isolation of the same NTM from sputum or broncho-alveolar lavage (BAL).

Isolation of these mycobacteria from representative specimens and their rapid identification is very important as the treatment strategy for tuberculosis and NTM is different. Several biochemical, chemical (lipid) and molecular techniques have been developed for rapid identification of these species. Along with suggestive clinical features, poor response to antitubercular treatment and repeated isolation of the organisms from the clinical specimens, these molecular techniques can help in establishing a correct diagnosis.

Medical treatment for NTM infections should be based on background information about sensitivity profiles[2,9], which is very limited for NTM in India[2]. In the United States, trends about the type of NTM isolates and their sensitivity profile have been studied over a long period of time and some broad principles of management have already been suggested by the American Thoracic Society[2] which may be followed. Treatment depends on the site and severity of the infection, the presence of predisposing conditions, such as congenital or acquired immunodeficiencies, and the species of mycobacterium.

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"It is easy to get a thousand prescriptions, but hard to get one single remedy."

– CHINESE PROVERB.

CASE REPORT

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Carbamazepine-induced cardiac arrhythmia

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Carbamazepine (CBZ) is a very common drug used in clinical practice. Cardiac rhythm disturbances are not a commonly reported adverse event with this drug. A 52-year-old male presented to our Emergency Department with intermittent tingling sensation over the left arm for 3 days. There was no chest pain, breathlessness, fatiguability, palpitations, sweating, or similar sensation over any other part of the body. Nothing was suggestive of presyncope or syncope and abnormal body movements. The patient was a known case of neurocysticercosis (MRI proved) since 2 years and was taking carbamazepine 1,000 mg per day. There was no history of any other drug intake.

On examination, his pulse rate was 30/min and irregular. Otherwise, his physical and systemic examination was normal. Electrocardiography showed a rate of 30 per minute, irregular, with normal contours of P, QRS complex, and T waves. The irregularity was due to pauses which were not exact multiples of P-P intervals and was suggestive of sinus pause or arrest. Longest duration of pause was 2.76 secs, and troponin-T was negative. His serum biochemistry, chest radiography was normal. Therefore he was implanted with a temporary pacemaker. In view of reports in literature of cardiac rhythm disturbances due to carbamazepine, it was discontinued and levetiracetam was started. During the course of hospitalisation, the patient attained spontaneous sinus rhythm on the third day and the temporary pacemaker was removed after five days. On follow-up visits after one month and three months, he was found to be asymptomatic.

The main mechanisms of CBZ are inhibition of voltage-gated Na^+ channels and activation of voltage gated K^+ channels. As inhibitors of voltage-gated Na^+ channels have similar effects on the nerves and heart, CBZ has both neuronal and cardiac effects. CBZ has the property of reducing the rate of phase 4 depolarisation (automaticity) of the pacemaker cells of the heart and thus can suppress the idioventricular pacemaker causing bradycardia.

The acute intoxication with carbamazepine can result in stupor or coma, hyperirritability, convulsions, and respiratory depression. However, during long-term therapy, the more frequent untoward effects of the drug include drowsiness, vertigo, ataxia, diplopia, and blurred vision[1]. CBZ-induced sinus node, AV node, and His-Purkinje conduction disturbances have been reported in literature[2].

The analysis of CBZ-induced arrhythmia reveals two distinct forms: sinus tachycardia in the setting of massive carbamazepine doses, and bradyarrhythmia or atrioventricular conduction delay in the setting of therapeutic CBZ concentration. The latter has several characteristics. First, it almost exclusively develops in elderly women, while the former predominantly occurs in younger adults. Secondly, it sometimes occurs after long periods of therapy. Therefore the relationship between the arrhythmia and the drug use may be overlooked. Third, it is associated with either therapeutic or modestly elevated serum concentrations of the drug. Fourth, it rapidly resolves after discontinuing the drug[3].

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CASE REPORT

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Pyknodysostosis: Report of A rare disorder

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Abstract

Pyknodysostosis is a rare form of short-limb dwarfism that presents with frequent fractures but usually a normal life span. Clinical features include short stature, frequent fractures, kyphoscoliosis and deformities of the chest, high-arched palate, proptosis, supernumerary teeth, dysmorphic features including small face and chin, fronto-occipital prominence, pointed beaked nose, large cranium, and obtuse mandibular angle; and small, square hands with hypoplastic nails, with acro-osteolysis of terminal phalanges.

Keywords: Pyknodysostosis, craniofacial abnormalities, dysostoses, acro-osteolysis.

Introduction

Pyknodysostosis, which was first described in 1962 by Maroteaux and Lamy, is a rare autosomal recessive disorder of osteoclast dysfunction causing osteosclerosis. The name derives from the Greek "pyknos" meaning "dens". These authors speculated that the famous French painter, Toulouse-Lautrec (1864-1901), may have suffered from this disease[1]. The disease shows equal sex distribution with high parental consanguinity, having an incidence of 1.7 per 1 million births[2]. A common finding in this disorder is a greater tendency for fractures, especially of the long bones. Spontaneous fractures of the mandible during mastication are uncommon and are usually due to trauma, exodontias, and post-osteomyelitis.

General features of pyknodysostosis include short stature under 150 cm, generalised diffuse osteosclerosis with a tendency for fracture after minimal trauma, hypoplastic clavicles, as well as acro-osteolysis with sclerosis of the terminal phalanges which is an essential pathognomonic feature. Other features include wrinkled skin, finger and nail abnormalities, kyphosis and scoliosis, history of repeated chest infections, and sleep apnoea. The intellectual and sexual development is usually normal in the patients[3]. Cranial and maxillofacial features include fronto-parietal bossing, thick calvaria, open fontanelles and sutures, hypoplastic para-nasal sinuses, wormian bones in the lambdoidal region, relative proptosis, beaked nose, hypoplastic mid-face, and obtuse mandibular gonial angle, often with relative prognathism.

Case report

A 22-year-old boy reported to the Department of Endocrinology with a chief complaint of recurrent fractures and short stature. He had history of fractures of his left femur with trivial trauma 2 years back which healed with malunion; for that he underwent internal fixation. He also

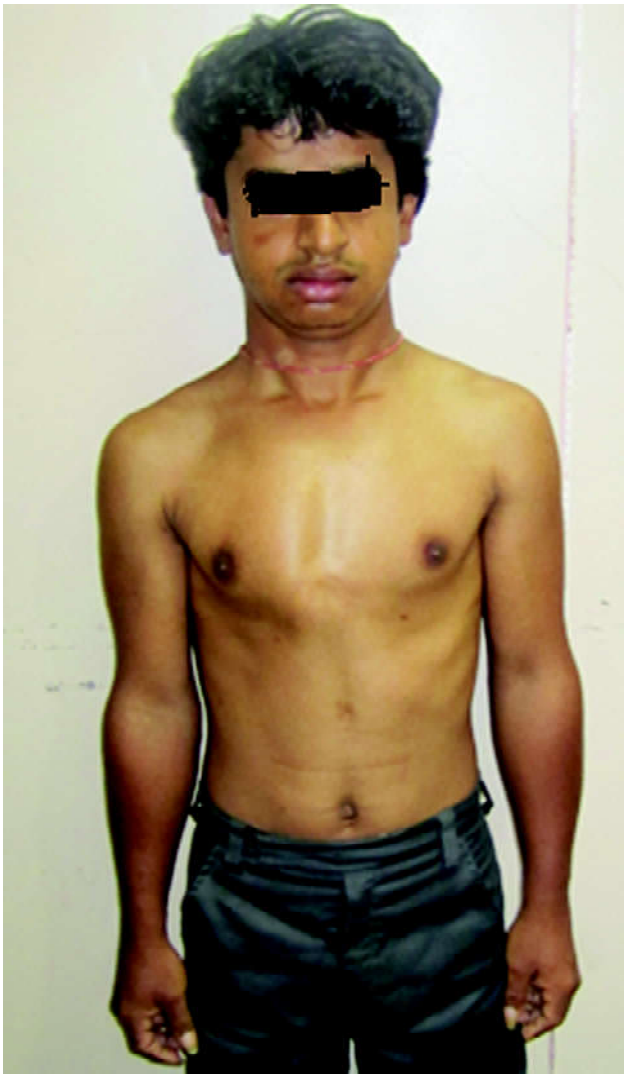

Fig. 1: *Patient showing short stature.*

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had history of fractures of both tibia on trivial trauma 3 months back. On general physical examination (Fig.1, 2), he demonstrated short stature, frontal and parietal bossing, depressed nasal bridge, beaked nose, hypoplastic mid-face, mandibular hypoplasia, obtuse mandibular gonial angle with relative prognathism, and wrinkled skin over the finger tips. Intra-oral examination revealed deep midline antero-posterior ridge of the palate, high-arched palate, multiple retained deciduous carious teeth, crowding, and enamel hypoplasia. Based on the above findings, the differential diagnoses include osteopetrosis, pyknodysostosis, cleidocranial dysplasia, and idiopathic acro-osteolysis.

Radiographs showed (Fig. 3) multiple impacted permanent and supernumerary teeth with narrow left ramus, condyle, and condylar notch. Lateral cephalogram showed hypoplastic para-nasal sinuses with relative mandibular prognathism. Hand-wrist radiograph showed acro-osteolysis of terminal phalanges. Radiographs of lower limbs showed fractured bilateral tibia and internally fixed left femur. His blood biochemistry was within normal limits. Bone marrow examination of the patient was done and revealed partial fibrotic changes. Based on the above investigative reports, the final diagnosis of pyknodysostosis was made.

Discussion

Pyknodysostosis is an autosomal recessive disorder of bone, causing osteoclast dysfunction resulting in osteosclerosis. The sclerosing activity of pyknodysostosis is due to a genetic defect located on chromosome 1q21. This anomaly consists of mutations that produce mutational changes in a lysosomal cystine protease, cathepsin K (CTSK), the

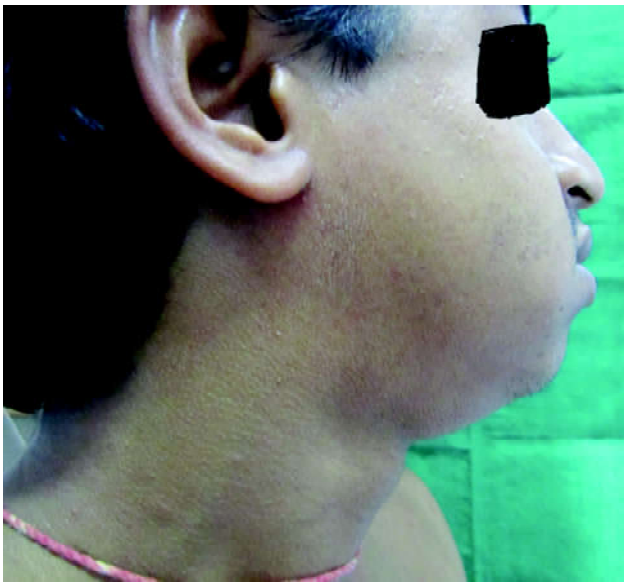

Fig. 2: *Hypoplasia of mandible and obtuse mandibular angle.*

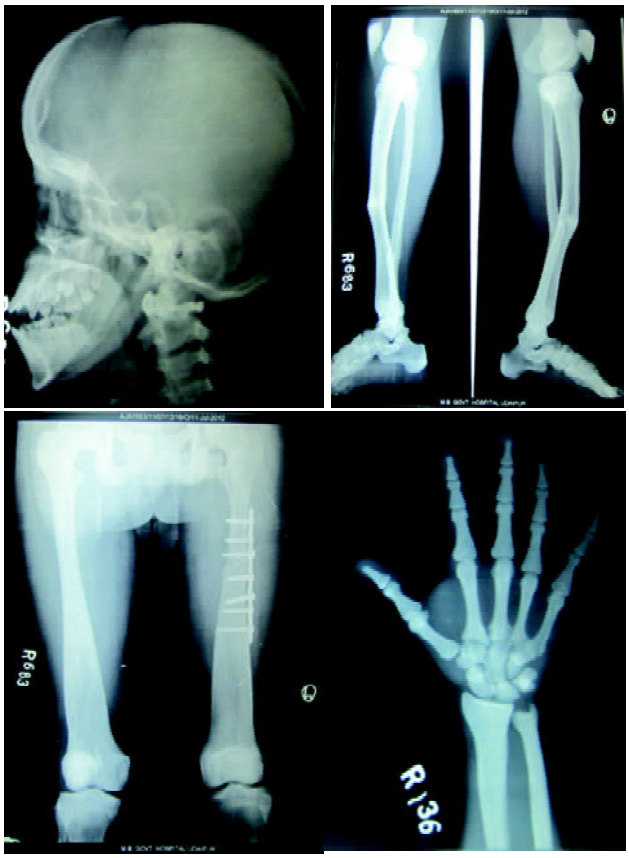

Fig. 3: *Radiographs showing various abnormalities. Clockwise from upper left: hypoplasia of mandible with supernumerary teeth, fracture of tibia bilaterally, acro-osteolysis of terminal phalanges, internally fixed left femur.*

expression of which is reduced in the osteoclasts. This protease is responsible for degrading type 1 collagen that constitutes 95% of the organic bone matrix. The affected bones are abnormally dense and brittle as a result of insufficient resorption[4].

In our case, the findings were short stature, recurrent fractures on trivial trauma, acro-osteolysis with sclerosis of the terminal phalanges which is an essential pathognomonic feature. These findings have been reported in a few case studies previously as well[5]. Cranial and maxillofacial features reported in our case included fronto-parietal bossing, open fontanelles and sutures, hypoplastic para-nasal sinuses, beaked nose, hypoplastic mid-face, and obtuse mandibular gonial angle, often with relative prognathism.

The radiological findings may show some degree of widening of the distal femur. The skull shows open anterior fontanelle and sutures with small facial bones, nonpneumatised para-nasal sinuses, and flattened mandibular angle. Terminal phalanges of the hands are partially or totally aplastic with loss of ungual tufts. The

acromial ends of the clavicles may be aplastic. Other abnormalities include failure of complete segmentation of the atlas, axis, and the lower lumbar spine, coxavalga, and abnormal radio-ulnar articulation[4].

The radiological findings observed were hypoplastic paranasal sinuses with relative mandibular hypoplasia with prognathism, acro-osteolysis of terminal phalanges, multiple impacted permanent and supernumerary teeth, fractured bilateral tibia, and internally fixed femur. The same features were present in the study by Maroteaux *et al* and Fleming *et al*[1].

The histological appearance of bone is identical in osteopetrosis and pyknodysostosis. However, in the latter disease, there is a small and imperfect medullary canal along with attenuated Haversian canal system and microscopical evidence of haemopoiesis[6]. Trabeculae themselves are disorderly in arrangement and the marrow tissue present is usually fibrous.

The differential diagnosis of pyknodysostosis is established with osteopetrosis, cleidocranial dysplasia and idiopathic acro-osteolysis. In osteopetrosis, the bone marrow may be absent; it is therefore frequent for haematopoietic alterations to appear. Signs of compression of the cranial nerves exist such as facial paralysis, deafness, or pain. Cleidocranial dysplasia may seem like pyknodysostosis for presentation of agenesis or clavicular aplasia, as well as alterations of the skeletal bone membranes. However, bone density is not increased. In idiopathic acro-osteolysis, the appearance of the patients is typical, with hypotelorism, exophthalmos, and an upturned nose. The angle of the mandible is acute, and increased bone density is not present.

The diagnosis of pyknodysostosis is primarily based on clinical features and radiographs.

There is no specific treatment as of date for this disorder, and treatment is supportive. Since bone fractures are a primary threat, it is important that care is taken to prevent or minimise tendencies for a fracture to occur. Tooth extraction demands special care, such as carrying out the surgery as atraumatically as possible and with proper asepsis, due to the risk of fracture, especially in the mandible. However, bone healing is normal despite the fragility of bones. The prognosis of the disease is good and no more serious systemic alteration has been noted. Also, life expectancy for a pyknodysostosis patient is normal[3].

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"Always laugh when you can. It is cheap medicine."

– Lord Byron.

CASE REPORT

JIACM 2015; 16(3-4): 261-4

Clinical and electrophysiological profile of Isaac's syndrome: A report of six cases

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Introduction

Isaac's syndrome is an autoimmune disease caused by hyperexcitability of the motor nerves and continuous activation of muscle fibres due to auto-antibodies directed against the voltage-gated potassium channels (VGKCs) on peripheral nerves[1].

Though Denny Brown and Foley (1948) were the first to describe this disorder as undulating myokymia, it was Isaac who emphasised the neurogenic nature of this syndrome and established it as a clinical and electrophysiological entity in 1961[2,3].

It has also been referred to as generalised myokymia, Continuous muscle fibre activity (CMFA), Cramp-fasiculation syndrome, Neuromyotonia, Quantal squander, Armadillo syndrome, Mertens' syndrome and Morvan's' fibrillary chorea' or Morvan's syndrome in the literature[4,5].

Clinically it is characterised by continuous, spontaneous, widespread muscle twitching (fasciculations or myokymia), muscle stiffness, cramps, pseudomyotonia (delayed muscle relaxation after contraction), pseudo-tetany (spontaneous or evoked carpal or pedal spasms) and at times muscle hypertrophy, mild muscular weakness, paraesthesias and numbness. Often, patients also complain of excessive sweating and CNS symptoms like confusion, mood change, hallucinations and insomnia[5-7].

We describe the clinical and electrophysiological features and the response to therapy in six cases of Isaac's syndrome.

Methods

Six patients with features suggestive of Isaac's syndrome encountered over a nine-year period, in our clinical practice at GB Pant hospital, Delhi, a large super-speciality centre of north-west India were subjected to detailed clinical analysis, routine haematological and biochemical investigations and electrophysiological (NCS and EMG) study. Response to treatment with antiepileptic drugs and/or steroids was documented in all the patients.

Case profile

Overall, there were six patients of Isaac's syndrome, aged 17 to 45 years (mean 28.83 years) and all were males. The duration of the illness prior to the presentation ranged from 15 days to 2.5 years (mean 9 mths, median 2 mths).

All six of them presented with widespread, spontaneous, continuous, visible muscle twitching with undulations or clinical myokymia. These twitchings were present only in the limbs in 2 (33.33%), limbs and trunk in 3 (50%), and limbs, trunk, face and tongue in 1 (16.66%) case. In 2 (33.33%) of these cases the clinical myokymia persisted during sleep as well.

Four patients (66.67%) also complained of cramps in both the lower limbs, which worsened on walking or exertion, especially in the hot weather. Three patients (50%) had additional complaints of severe calf pain and two patients (33.33%) had generalised body ache. Increased sweating and painful lower limb paraesthesias was present in two (33.33%) cases each, while bilateral calf hypertrophy, muscle stiffness, abnormal posturing of one hand and pseudomyotonia was present in one case each (16.67%).

There was no motor or sensory deficit. The deep tendon reflexes were normal in all the cases except in one patient with diabetes who had hyporeflexia. Plantar response was flexor in all. Routine investigations including haemogram, complete blood counts, blood sugar, liver and renal function tests, serum electrolytes, serum calcium, phosphate, creatine kinase, thyroid profile, vasculitis screen, chest X-ray, ECG, ultrasound abdomen and CSF examination were normal in all the cases. Serum antibodies to voltage gated potassium channels were not done in any of our cases due to financial constraints.

Electromyography revealed continuous muscle fibre activity firing at frequencies of 200-300 Hz characteristic of neuromyotonia in all six patients. Abnormal spontaneous activity in the form of doublets, triplets, and/or quadruplets was seen in all six patients (100%), and fasciculations in three patients (50%). Three (50%) had abnormal MUAPs in the form of high amplitude, polyphasic discharges with

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incomplete recruitment pattern. Motor and sensory nerve conduction studies were normal in all the cases, with no evidence of either a demyelinating or axonal neuropathy. In addition, motor nerve conduction studies showed stimulus-induced repetitive discharges in the common peroneal and posterior tibial nerves in one patient (16.66%).

Three patients had received carbamazepine (400 mg/day), one patient was on combination of pregabalin (150 mg/day) and carbamazepine (600 mg/day), one patient was on combination of gabapentin (900 mg/day) and carbamazepine (600 mg/day), and one patient had received combination of carbamazepine (400 mg/day), pregabalin (150 mg/day) and prednisolone (60 mg/day). All of them responded well to the treatment.

Discussion

Isaac's syndrome or neuromyotonia is a rare and sporadic disorder that can occur at any age and has even been reported in newborn babies[1,5]. It is more common in males, as was the case with our patients. In another study of 20 cases from north-west India (Panagariya *et al*) 19 of the cases were males[8]. It can occur in isolation, or in association with other autoimmune disorders like SLE, systemic sclerosis, coeliac disease, myasthenia gravis, vitiligo, and Hashimoto's thyroiditis[1]. It may follow on treatment with penicillamine or occur as a paraneoplastic syndrome, in association with lung cancer, plasmacytoma, Hodgkin's lymphoma and thymoma[1,5]. It may also occur in association with genetically inherited diseases such as

Table I: Patient characteristics, clinical features, EMG and treatment response in six patients of Isaac's syndrome.

	Case 1 (S J)	Case 2 (M)	Case 3 (PK)	Case 4 (BM)	Case 5 (R)	Case 6 (BK)	Mean or %
Age	46	40	17	45	25	28	28.83
Sex	M	M	M	M	M	M	
Duration	2.5 yrs	1.5 mths	1.5 yrs	2 mths	0.5 mths	2 mths	9 mths
Regions involved (muscle twitchings)	LL and trunk	LL, trunk and face	LL	LL and trunk	LL and trunk	LL	
Clinical features							
Myokymia	+	+	+	+	+	+	100%
Cramps	+	+	+	–	–	+	66.66%
Muscle stiffness	–	–	+	–	–	–	16.66%
Calf hypertrophy	–	–	+	–	–	–	16.66%
Pseudomyotonia	–	–	+	–	–	–	16.66%
Hand posturing	–	+	–	–	–	–	16.66%
Sweating abnormality	–	–	+	–	+	–	33.33%
Generalised bodyache	–	–	–	+	+	–	33.33%
Severe calf pain	–	–	+	+	–	+	50%
Painful LL paraesthesias	+	–	–	+	–	–	33.33%
EMG (spontaneous activity)							
Neuromyotonia	+	+	+	+	+	+	50%
Doublets/triplets/multiplets	+	+	+	+	+	+	50%
Fasciculations	+	+	+	–	–	–	100%
Abnormal MUAPs	+	+	+	–	–	–	100%
Myokymia in sleep	–	+	–	–	–	+	33.33%
Peripheral neuropathy							
Hyporeflexia	+	–	–	–	–	–	16.66%
Abnormal NCS	–	–	–	–	–	–	Nil
Multiple CMAPs	–	+	–	–	–	–	16.66%
Response to drugs	CBZ, PGB	CBZ, PGB	CBZ	Steroid CBZ, PGB	CBZ	CBZ	100%

Abbreviations: CBZ – Carbamezepine; PHT – Phenytoin; PGB – Pregabalin.

episodic ataxia type I, or hereditary motor and sensory neuropathy, and at times occur as a familial disorder with AD inheritance[1]. None of our patients, however, had any demonstrable association with other autoimmune disorders or cancer and were all sporadic in nature.

In neuromyotonia, spontaneous continuous muscle fibre activity or prolonged action potentials are caused by an excessive release of acetylcholine at the neuromuscular junction due to pathogenic auto-antibodies directed against the voltage-gated potassium channels (VGKCs) on the peripheral nerves[9-11].

Clinically, widespread muscle twitching or 'visible myokymia' is the commonest symptom of Isaac's syndrome, seen in over 90% of the patients[1,5]. Myokymia is seen as a continuous, undulating, wave-like rippling of muscles, likened to a bag of worms under the skin[12].

Twitching can be seen in limbs, trunk muscles and the face, including the tongue. All our patients had this symptom. Rarely, the laryngeal muscles may be involved, causing hoarseness and exertional dyspnoea. In suspected cases with no visible muscle twitching, needle EMG may pick-up continuous motor unit activity or myokymic discharges. Neuromyotonic discharges have been described as persistent during sleep[1,5]. This is explained by the peripheral nature of this disorder. However, persistence during sleep may not always be elicited clinically, and only two of our patients had clear persistence during sleep. Muscle weakness due to continuous muscle fibre activity related fatigue can be seen, but is unusual and was not detected in any of our cases.

Pain in the calves and thighs is a common symptom and may be accompanied by a burning sensation, and was the chief presenting complaint in 19 out of 20 patients, in a report from north-west India[8]. We had two patients who complained of severe painful paraesthesias in the lower limbs. Muscle cramps can be seen in over 70% of cases and can be painful at times. Cramps may be the first symptom that is noticed and may be associated with spasms. The cramps are worsened by cold, attempted voluntary muscle contraction or electrical stimulation, and were observed in 66.67% of our cases. The cramps may be associated with muscle stiffness and at times abnormal postures of the limbs which can affect walking and manual dexterity, as was seen in one of our cases with abnormal posturing of one hand. Muscle stiffness was observed in 25% of the cases in another series from India.

Forearm or upper limb hypertrophy is rare but calf hypertrophy may be seen and was observed in one of our cases also. It is usually bilateral and considered secondary to increased muscle activity by some, and as a part of the disease by others[13]. Pseudomyotonia or slow muscle relaxation following contraction, may be seen in 1/3rd of the patients and can be demonstrated on eye and jaw closure as well as on hand grip. It is differentiated from true myotonia by absence of percussion myotonia. We had only one patient with pseudomyotonia, with abnormally slow release of hand grip. This phenomenon was seen in 5 out of 20 patients reported by Panagariya *et al*[8]. Pseudotetany and Trousseau sign may be seen with Isaac syndrome and can be differentiated from true tetany in which it is precipitatated by hyperventilation.

Increased sweating is a poorly explained phenomenon and can be seen in 50% of the cases. Sixteen cases out of 20 had sweating disturbances or other features of increased metabolic rate in a series from India. In our series, 33.3% cases had sweating abnormalities.

There are occasional reports of hallucinations, delusional episodes and insomnia, sometimes referred to as Morvan's fibrillary chorea. In a report from India (Panagariya *et al*), irritability, sleep disorders, restlessness, and a peculiar worried and pinched face were noticed in 12 of the 20 cases[8]. Of these two had more severe symptoms, including hallucinations. VGKC antibodies have not been demonstrated in the CSF of patients with central symptoms and there is no correlation with the occurrence of CSF oligoclonal bands. The validity of the central correlation remains questionable. None of our patients had central features.

EMG in Isaac syndrome[1,5] reveals continuous motor unit activity or myokymic discharges in the form of spontaneous, irregularly occurring doublet, triplet, or multiplet single or partial motor unit discharges firing at a high intraburst frequency of 30 to 300 Hz, as was the case with our patients. Fibrillation potentials (single spontaneous muscle fibre discharges) and fasciculations (single spontaneous motor unit discharges) may also be seen. Characteristically, electrical stimulation of the nerve results in increased spontaneous activity seen as after-discharges and voluntary muscle contraction can provoke spontaneous motor unit activity lasting several minutes[1,5]. Neuromyotonic discharges are characteristically present during sleep[1,5]. Most spontaneous discharges occur in distal muscles and usually no more than 10 different motor unit (or partial motor unit) discharges are seen[14].

Regional curarisation abolishes the discharges, whereas general anaesthesia does not. This suggests that they arise from peripheral nerve. It is most probable that the generator sites lie anywhere along the whole length of the nerve, from the root to the terminal arborisations[15-17].

As was the case with our patients, motor and sensory nerve conduction studies are usually normal, except in cases with associated peripheral neuropathy.

Using immunoprecipitation assays, anti-VGKC antibodies can be detected in about 40% of patients with acquired neuromyotonia[1,5]. This percentage rises to 80% if there is an associated thymoma. Other autoantibodies due to other associated autoimmune disorders can be detected in approximately 50% of neuromyotonia patients. Anti-acetylcholine receptor antibodies (AChR antibodies), suggesting the coexistent myasthenia gravis is seen in about 20% of the cases with neuromyotonia. Assessment of serum or CSF antibodies directed against the VGKCs was not done in any of our cases however, due to financial constraints.

Isaac syndrome must be distinguished from the stiff-person syndrome, another autoimmune disorder caused by autoantibodies to glutamic acid decarboxylase (40% to 80% cases)[18].

It is characterised by a progressive, involuntary stiffness of axial and proximal limb muscles, hyper-lordosis and deformity of the spine and episodic painful muscle spasms precipitated by active or passive movement due to abnomal excitability of spinal interneuronal networks and descending control over the anterior horn cells in the spinal cord. Unlike neuromyotonia, this is a central disorder with disappearance of the discharges during sleep, general anaesthesia, and peripheral nerve block[1,5]. The treatment of Isaac syndrome and stiff person syndrome is largely different and clinical distinction is mandatory.

Symptomatic treatment with antiepileptic medication (e.g., phenytoin, carbamazepine, sodium valproate, lamotrigine and gabapentin) helps by decreasing neuronal excitability, primarily by blocking the sodium channels[1,5]. Five of our patients showed good response to carbamazepine and one to phenytoin. Immunomodulation with plasmapheresis, IVIG, corticosteroids and azathioprine may partially benefit some patients but was not prescribed to any of our patients[8,19,20,21].

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"Medicine sometimes snatches away health, sometimes gives it."

– Ovid.

CASE REPORT

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Cerebellar tuberculoma presenting as acute reversible hemiplegia: A rare presentation

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Abstract

CNS tuberculosis is one of the most dangerous forms of tuberculosis. Any part of the CNS can be involved, from intracranial to spinal lesions. Intracranial lesions can present as an abscess or tuberculoma. Tuberculomas in the cerebellum usually present with raised intracranial pressure and ipsilateral cerebellar signs. Our patient presented with the chief complaint of hemiplegia and was later diagnosed to be having an ipsilateral cerebellar tuberculoma which is a rare presentation which strengthens the diverse presentations of CNS tuberculosis and the need to work-up the patient in detail.

Key words: CNS tuberculosis, Mycobacterium tuberculosis, cerebellar tuberculoma, hemiparesis.

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* which affects the lungs – causing pulmonary TB, and other sites as well extrapulmonary TB. Extrapulmonary tuberculosis is found more commonly in immunocompromised persons. Central nervous system (CNS) involvement is one of the most devastating and dangerous clinical manifestations of tuberculosis and is noted in 5 to 10% of extrapulmonary TB cases, and accounts for approximately 1% of all TB cases.

In the central nervous system, tuberculosis is usually a meningeal infection but can also present as tuberculoma which is more frequently supratentorial in adults, and infratentorial in children[1].

Tuberculomas are commonly found in the frontal and the parietal regions and much less commonly found in the cerebellum in the cases of adults; whereas in children, cerebellum and brain stem involvement is common[2,3].

Case history

A 35-year-old nondiabetic, normotensive male presented in our casualty with the chief complaints of headache for 8 days along with weakness of the left side of body and difficulty in speech for 1 day. There was no history of fever, convulsions, or head injury. The patient had no history of similar episodes in the past and had not taken any medications in the past. He was a non alcoholic and a non smoker.

General physical examination revealed no significant abnormality with blood pressure 130/100 mmHg. The respiratory examination was normal. Abdomen was soft with no signs of organomegaly. Cardiac examination was normal.

However, there were significant findings on examination of the central nervous system. Higher mental functions were normal and the patient was oriented to time, place and person. The pupils were normal in size and normally reacting to light. There was no neck rigidity and Kernig's sign was absent. The power was 0/5 in left upper limb and lower limb in all the muscle groups, whereas it was 5/5 in right upper and lower limb. The right plantar was flexor while the left side plantar could not be elicited. The sensory examination was normal. Reflexes on the left side were exaggerated. These findings prompted us towards a provisional diagnosis of a lesion in the right side of the cerebral hemisphere thus producing left-sided hemiparesis. Fundus examination revealed no significant abnormality. However, an urgent NCCT head showed a hypodensity in the left cerebellar hemisphere involving both grey and white matter with mass effect on fourth ventricle and prominence of supratentorial ventricles. A radiological diagnosis of infarct was made, and we therefore started the patient on tablet aspirin 325 mg OD and tablet atorvastatin 40 mg HS. Injectible osmotic diuretic in the form of mannitol was added to reduce the mass effect. Routine blood parameters were done and the patient was transferred to the internal medicine ward for further work-up.

Haemogram, kidney function tests, liver function tests, serum electrolytes were all within normal limits. Lipid profile showed a normal result. HIV test was negative. Since it was a case of young stroke, we carried out further investigations to ascertain the cause of the stroke. Blood coagulation profile was normal with prothrombin time (PT) 13.4 seconds,

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activated partial prothrombin time (APPT) of 31.2 seconds and an international normalised ratio (INR) of 1.12. Meanwhile, a neurosurgical consultation was also taken and no active intervention was planned from their side.

The next day the patient had improved and he was beginning to regain the power in his left side which became 2/5. His blood pressure recordings were constantly on the higher side with a mean of 150/100 mmHg. The patient was now on aspirin, statins, and mannitol. A 2D echo was done which was normal and no cardiac lesions were noted.

On the third day of admission, we ordered a carotid Doppler with the radiology department. The Doppler also came out to be normal. However, the patient was clinically improving and by the fourth day of admission the power in the left half was 4/5. Now since the power on the left half of the body improved, cerebellar examination was carried out. The examination was particularly significant with cerebellar signs positive in the left side. The finger-nose test and knee-heel test were positive on the left side. Tandem walk was not possible and the patient was swaying towards the left. Scanning speech was noted in the patient. There was nystagmus with fast component towards left. There was dyssynergia and dysdiadochokinesia. Also there was no titubation and intention tremor. All the cranial nerves were normal on examination.

By the fifth day of admission, we had stopped the intravenous mannitol and had started the patient on tablet acetazolamide 250 mg thrice a day along with a calcium channel blocker, i.e., amlodipine 5 mg once a day. His blood pressure recordings were constantly on the higher side.

MRI brain with gadolinium contrast was done which showed conclusive results, i.e., a cluster of rounded lesions of varying sizes appearing hypointense on T2 weighted and Flair sequences in the left cerebellar hemisphere with perilesional oedema. Mass effect was also seen on the 4th ventricle and the mid brain with mild prominence of the ventricular system. Following IV contrast administration, there was a conglomerate lesion comprising of multiple irregular peripherally enhancing lesions in the left cerebellar hemisphere. Patchy and leptomeningeal enhancement was also noted in the right frontal lobe. This all suggested a tuberculoma in the left cerebellar hemisphere. A Mantoux test was done with the result of a 25 x 20 mm induration suggestive of a positive finding. There was no previous history of tuberculosis or any history of contact with the same. Thus, a final diagnosis was reached which was left-sided cerebellar tuberculoma presenting as left-sided hemiparesis.

The patient was immediately started on anti tubercular therapy with four drugs, viz., isoniazid, rifampicin, pyrazinamide, and ethambutol. Prednisolone was also started according to weight, and supplemental pyridoxine was also given.

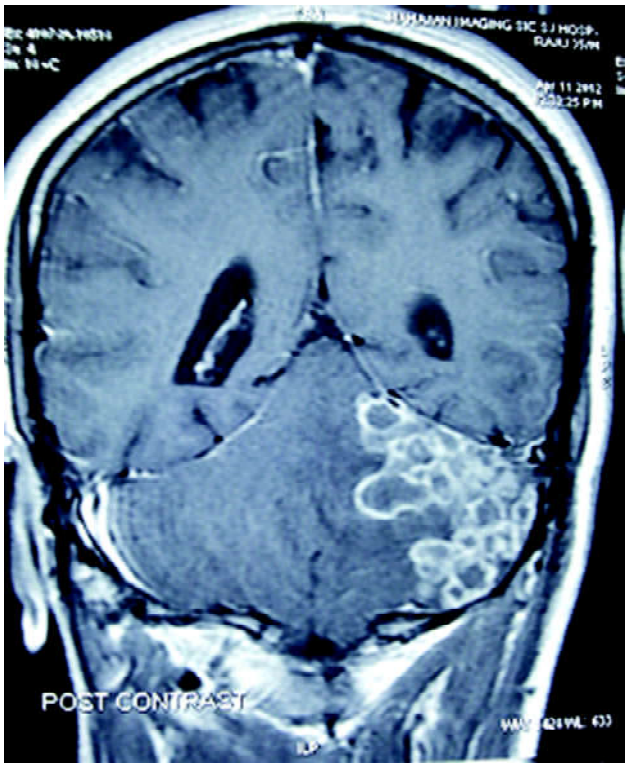

Fig 1: *Post-contrast image of MRI brain showing a conglomerate lesion comprising of multiple irregular peripherally enhancing lesions in the left cerebellar hemisphere.*

Discussion

Tuberculosis is a major global health problem and the second leading cause of death from an infectious disease worldwide.

According to the WHO, worldwide there were almost 9 million new cases of TB in 2011 and 1.4 million TB deaths out of which India accounted for 26% of the global incidence, with about 2 - 2.5 million TB cases occurring every year with a prevalence of 249 cases per 100,000 and an incidence of 181 per 100,000[4,5].

In a large-scale epidemiological study of extrapulmonary tuberculosis in the United States, CNS involvement was found in 5 to 10% of cases[6], and latest data from CDC indicate that 6.3% of extrapulmonary cases (1.3% of total tuberculosis cases) involve the CNS[7].

Bacilli reach the CNS by the haematogenous route. According to Rich and McCordock[8], development of CNS tuberculosis takes place in two stages. Initially, small tuberculous lesions (Rich's foci) develop in the CNS, which

rupture or grow to one or more of small tuberculous lesions producing development of various types of CNS tuberculosis[8,9].

In the absence of an adequate cell-mediated immunity, the parenchymal cerebral tuberculous foci may develop into a tuberculoma or brain abscess[10].

Arsani *et al* studied 113 patients with cerebellar tuberculoma and concluded that intracranial hypertension was present in all the cases, and in 71 % localising signs were also found (a cerebellar syndrome in 62%, and a syndrome of the ponto-cerebellar angle in 9 %)[11].

In our patient, left-sided cerebellum was involved which presented as left-sided cerebellar features as mentioned above. In this case of a young patient, who is from a country like ours with high prevalence rates of tuberculosis and in whom a neurological examination reveals intracranial hypertension with signs of localisation, a diagnosis of tuberculosis can be made. A diagnosis of tuberculoma can sometimes be made without the presence of pulmonary lesions and with a negative history of tuberculosis.

Our patient is unique in that he had localising signs of a cerebellar lesion. However, acute left-sided hemiparesis was also present in our patient which has been described in literature rarely as a presentation of cerebellar tuberculoma. This manifestation could be explained on the basis of compression of contralateral cerebral peduncle to the temporal bone due mass effect from the ipsilateral cerebellum. The hemiparesis gradually improved by the decongestive therapy as the mass effect reduced.

The CNS tuberculosis is treated both surgically and medically. According to the WHO guidelines on treatment of extrapulmonary tuberculosis (4th edition), the standard regimen as for pulmonary tuberculosis must be followed in these cases as well. Treatment must be started with 4 drugs (isoniazid, rifampicin, ethambutol, streptomycin) and continued till 2 months; and should be followed by 4 months of treatment with 2 drugs (isoniazid and rifampicin)[12].

CNS tuberculosis is also treated with concomitant corticosteroids[13]. Clinical response to steroids is usually dramatic with quick improvement of sensorium, normalisation of CSF, and relief of headache[14]. Surgical procedures in patients with tuberculous meningitis are primarily directed to the treatment of hydrocephalus[12] via ventriculo-peritoneal or ventriculoatrial shunting.

In conclusion, our case exemplifies that physicians must maintain a high index of suspicion as CNS tuberculosis can have atypical presentation as in our case, and timely investigations and management can be life saving.

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"When fate arrives, the physician becomes a fool."

– Arabian proverb.

CASE REPORT

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Acute myeloid leukaemia with haemophagocytic lymphohistiocytosis presented as cholestatic Jaundice

Tanvi Sood, AB Mowar**, Sumit Rungta**, Tanu Agarwal***, Pranesh Nigam*****

Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disease of normal but overactive histiocytes and lymphocytes characterised by fever, cytopenias and hepatosplenomegaly with haemophagocytosis. It is traditionally classified as familial/primary HLH which occurs due to genetic abnormalities and secondary HLH which is associated with infections, autoimmune diseases, immune deficiencies, metabolic diseases, drugs or malignancies, without an identifiable genetic abnormality. Haematological malignancyassociated HLH is mostly accompanied by lymphoid neoplasms. The present study reports a rare case of this syndrome in combination with acute myeloid leukaemia with an even rarer presentation of cholestatic jaundice.

Key words: Haemophagocytic lymphohistiocytosis, rare hyperinflammatory condition, secondary HLH, acute myeloid leukaemia, cholestatic jaundice.

Introduction

Haemophagocytic lymphohistiocytosis (HLH), also termed haemophagocytic syndrome, is an aggressive hyperinflammatory condition characterised by prolonged fever, cytopenias and hepatosplenomegaly, along with haemophagocytosis by activated, morphologically benign macrophages. There are two main types of HLH: familial HLH (FHLH) and secondary HLH. FHLH is an autosomal recessive syndrome with an estimated prevalence of 1/ 50,000 live births[1]. Secondary HLH is a wellrecognised entity and is associated with infections, autoimmune diseases, immune deficiencies, metabolic diseases, drugs or malignancies[2].

The incidence of secondary HLH is unknown. Haematological malignancyassociated HLH is mostly accompanied by lymphoid neoplasms. The present study describes a rare case of this syndrome in combination with acute myeloblastic leukaemia (AML) presenting as cholestatic jaundice.

Jaundice as initial presentation in AML is extremely rare and carries a bad prognosis[3]. HLH can also cause hepatomegaly and jaundice with cholestasis.

Case report

A 65-year-old male presented to the emergency department in confused state with history of jaundice, fever and swelling over feet since 30 days and altered sensorium since one day. On examination, he was febrile with pallor, deep icterus in sclera and yellowish discoloration of skin, pitting pedal oedema and moderate hepatosplenomegaly. No lymphadenopathy was found and other systems did not reveal any abnormal findings. There was no significant past history. The patient was managed on lines of hepatic encephalopathy and his sensorium improved within 24 hours of admission.

His initial complete blood counts revealed pancytopenia with haemoglobin Hb 8.9 g/dl (normal range: 13 - 18 g/dl), total leukocyte count TLC 2,100 cells/cumm (normal range: 4,000 - 11,000 cells/cumm) with 68% polymorphs, 27% lymphocytes 5% monocytes and no immature cells, platelet count 50,000/cumm (normal range: 1.5 - 4.5 l/cumm). General blood picture showed predominantly normochromic normocytic RBCs, no immature cells were seen. His parameters further deteriorated to Hb 8 g/dl, TLC 1,080 cells/cumm and platelets 24,000/cumm within 48 hours of admission. His renal profile was within normal range with persistent hyponatraemia (119 mmol/l normal range: 135 - 150 mmol/l). Liver profile showed increased total serum bilirubin 21.3 mg/dl (normal range: 0.2 - 1.2 mg/dl) with more than 50% direct bilirubin (12.2 mg/dl), increased enzymes (SGOT- 139 IU/L SGPT- 74 IU/L), increased serum alkaline phosphatase 637 IU/L (normal range: 30 - 120 IU/L), hypoalbuminaemia 2.2 g/dl (normal range: 3.5 - 5 g/dl) and a normal coagulation profile. Fasting serum triglyceride levels were raised to 479 mg/dl (normal range: 60 - 170 mg/dl) and serum ferritin levels were remarkably increased to 9,070 ng/ml (normal range: 25 - 380 ng /ml). Viral markers were non-reactive including HIV I/II, anti-HCV and HBsAg. Malarial parasite antigen was negative and no hemoparasites were seen on peripheral blood smears. Chest X-ray was within normal limits, ultrasonogram whole abdomen showed an enlarged liver

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with normal echotexture and grossly enlarged spleen with minimal free fluid in the peritoneal cavity. Upper gastrointestinal endoscopy showed a normal study. Bone marrow aspiration was delayed due to deteriorating condition of the patient. A contrast enhanced computed tomography CECT abdomen was done in view of cholestatic jaundice which showed gross splenomegaly with mild hepatomegaly and minimal ascites alongwith enlarged paraaortic and aortocaval lymph nodes, normal common bile duct and portal vein without any intrahepatic biliary radical dilatation. There was no enhancing lesion in the liver parenchyma on triple phase study.

Bone marrow aspiration (BMA) revealed predominant population of blast cells with round to folded nuclei with fine chromatin, conspicuous nucleoli and abundant pale blue cytoplasm. Many mitotic figures were seen. Myeloid and erythroid series of cells were reduced in number. No megakaryocytes were seen and no haemophagocytosis was observed. These findings were suggestive of acute myeloid leukaemia (Fig. 1).

On the basis of both clinical and laboratory findings (fever, icterus, hepatosplenomegaly, pancytopenia, hyperferritinaemia, hypertriglyceridaemia, hypoalbuminaemia and hyponatraemia) a diagnosis of HLH was established. The patient was simultaneously diagnosed with AML. He was advised for flow cytometry for confirmation and typing of AML and also, a liver biopsy to establish whether the jaundice was due to leukaemic liver infiltration by AML or because of HLH itself. He was started on high dose dexamethasone according to the HLH 2004 protocol which showed transient response with improving pancytopenia. However, the patient succumbed to his condition on day 6 of hospital stay before further investigations could be conducted.

Discussion

The term hemophagocytosis describes the pathologic finding of activated macrophages engulfing erythrocytes, leukocytes, platelets and their precursor cells[4].

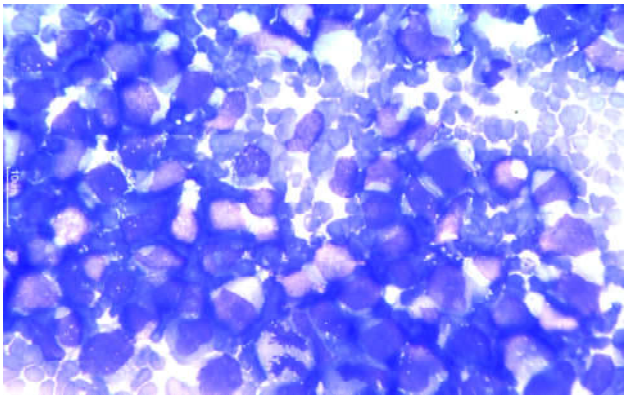

Fig. 1: *Bone marrow aspirate showing blast cells and a mitotic figure.*

HLH is a reactive process resulting from prolonged and excessive activation of antigen presenting cells (macrophages, histiocytes) and CD8+ T-cells. Natural killer (NK) cells are responsible for clearing antigenic stimulus and turning-off the inflammatory response. HLH is characterised by defective NK cells resulting in persistent cytotoxic T-cell activation, macrophage proliferation and haemophagocytosis which cripple the immunologic mechanisms that mediate natural immune contraction[5].

HLH has been traditionally classified as either primary familial HLH with a genetic aetiology, or secondary HLH which is associated with malignancies, autoimmune diseases and infections[6]. It is possible that, in adults with a previously unexpressed HLH genotype, the disease becomes apparent in response to a major immunologic challenge.

The disease is a medical emergency and it is seen in all ages without any predilection for race or sex. HLH should be suspected in cases of an unexplained sudden onset of a systemic inflammatory response syndrome (SIRS), including fever, malaise, hepatosplenomegaly, jaundice, generalised lymphadenopathy and cytopenias[7].

Neurologic symptoms are the consequence of organ infiltration by activated lymphocytes and histiocytes. Central nervous system (CNS) symptoms include seizures, meningitis, encephalopathy, ataxia, hemiplegia, cranial nerve palsies, mental status changes, or simply irritability. In the bone marrow, haemophagocytosis of mature and immature haematopoietic cells is characteristic, in addition to myeloid and erythroid hypoplasia, as well as variable megakaryocytic hyperplasia.

HLH can cause hepatomegaly, jaundice with cholestasis, moderate transaminase elevation, hyperferritinaemia, decreased hepatic synthetic function, and fulminant hepatic failure. Hepatotoxicity is caused by haemophagocytosis in the hepatic sinusoids and portal tracts or by focal hepatocellular necrosis[8].

In accordance with the International Histiocyte Society guidelines (Table I)[9], fever, pancytopenia, hypertriglyceridaemia, hyperferritinaemia (> 500 µg/l) and splenomegaly were present in our patient with supporting evidence of hypoalbuminaemia, conjugated bilirubinaemia and hyponatraemia. Haemophagocytosis was not present in our patient. It has been shown that initial bone marrow biopsies are insensitive for diagnosis of HLH[10]. The microscopic visualisation of haemophagocytosis does not necessarily need to be present to establish a diagnosis of HLH as haemophagocytosis is often cyclical. In addition, morphologic evidence of haemophagocytosis is not a specific finding for HLH.

Table I: Diagnostic criteria of HLH[9].

- HLH-2004 diagnostic criteria
- The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
  - A molecular diagnosis consistent with HLH is made
  - Diagnostic criteria of HLH are fulfilled (5 of 8 criteria below):*
- Fever
- Splenomegaly
- Cytopenias (affecting at least 2 lineages in the peripheral blood):
- Haemoglobin levels < 90 g/l (in infants < 4 weeks old, haemoglobin < 100 g/l)
- Platelets < 100 X 109/l
- Neutrophils < 1.0 X 109/l
- Hypertriglyceridaemia and/or hypofibrinogenaemia:
- Fasting triglycerides ≥ 3.0 mmol/l (i.e., ≤ 265 mg/dl)
- Fibrinogen ≥ 1.5 g/l
- Documented haemophagocytosis in the bone marrow, spleen, or lymph nodes
- Low or absent natural killer cell activity
- Ferritin ≥ 500 µg/l
- Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/ML

**Supportive criteria include neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinaemia and transaminitis, hypoalbuminaemia, hyponatraemia, elevated D-dimers, and lactate dehydrogenase. The absence of haemophagocytosis in the BMA does not exclude a diagnosis of HLH*

Malignant neoplasms are commonly seen in association with HLH in both children and adults. It may be the presenting clinical picture of an underlying malignancy, or it may develop during the treatment for a malignancy. Haematologic malignant neoplasms account for the majority of cases and among these, peripheral NK/T-cell lymphomas, anaplastic large-cell lymphoma and acute lymphocytic leukaemias are often implicated. Hodgkin lymphoma, multiple myeloma, and acute erythroid leukaemia have also been reported. HLH is rarely seen in patients with non-Hodgkin B-cell lymphomas. A possible mechanism of malignancy associated HLH may be the impairment of the cytotoxic pathway by the neoplasm through neoplastic changes in the cytotoxic cell itself or through malignancy-associated immune dysregulation[7].

There have been 2 reported cases of AML and secondary HLH, one of which was associated with infection and another associated AML-M2 with clonal karyotypic abnormalities[6,11]. The incidence of AML increases with age and it is the most common type of adult leukaemia. Palpable organomegaly as a presentation of AML is uncommon as seen in our patient, and significant lymph node enlargement is rare.

HLH is a poor prognostic factor for patients with hematological cancer. It is possible that the development of leukaemia in patients with genetic HLH mutations may trigger overt HLH, particularly when combined with infections[6].

A study was done on 343 AML patients receiving chemotherapy, out of which 32 were identified with HLH during the course of treatment. HLH can be diagnosed in up to 10% of patients with AML undergoing intensive chemotherapy and is associated with early mortality[12].

Cholestasis as the initial manifestation of AML may be due to a stricture of the biliary tree or a granulocytic sarcoma compressing the biliary tree as reported in 2 paediatric cases by Binitha *et al*[13] and in a 29-year-old man reported by Geetha *et al*[14]. Isolated biliary involvement by myeloid sarcoma occurs in 2 - 8% of AML cases[15]. In these reports, radiological investigations of the abdomen showed dilated proximal biliary duct and intrahepatic biliary radicals. Such obstructive radiological features were not present in our case.

Although hepatic involvement in acute leukaemia is usually mild and silent at the time of diagnosis[16], a post-mortem study showed liver infiltration involving both portal tracts and sinusoids in up to 75% of AML cases[17]. Other causes of jaundice in AML can be due to drug induced hepatocellular damage, post-transfusion viral hepatitis, infiltration of the liver by the leukaemic process. A possible explanation for jaundice in our patient could be due to leukaemic infiltration of the liver which can be ascertained after liver biopsy to differentiate it from cholestasis caused by HLH itself.

Conclusion

HLH is an uncommon but likely underdiagnosed disease. It is associated with high mortality hence a timely diagnosis is necessary. It mimics other conditions like severe sepsis, hepatic failure and malignancies which often delay the diagnosis hence a high index of suspicion is required. HLH should be kept in mind as a differential diagnosis for patients with cholestatic jaundice and cytopenias. There are few reports of AML occurring with HLH in the literature and even fewer cases of AML with cholestatic jaundice. Therefore, this finding requires further investigation in a similar setting.

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PICTORIAL CME

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Skin hyperpigmentation: A clinical clue to Addison's disease

Rajnish Singh, MPS Chawla**, Naveen Kumar****

A 32-year-old female patient presented with weakness, fatigue, weight loss, and low grade fever for the last 4 months and abdominal pain, diarrhoea, and dizziness for 2 months. There was past history of pulmonary tuberculosis, for which she was treated 3 years back. On examination, she was thin built with a BMI of 18.2 Kg/m^2. Pulse rate and supine blood pressure were 100/min and 110/70 mm of Hg respectively with the postural drop to 86/60 mmHg on standing. Hyperpigmentation was noticed on oral mucosa, tongue, knuckles of fingers and soles (Fig. 1, 2, 3). Serum cortisol at 8 am, 2.1 mcg/dl, was low (normal range: 4.3 - 22.4). Cosyntropin (ACTH) stimulation test revealed insignificant rise in the serum cortisol, a value of 5.6 mcg/dl at 30 minutes (normal > 20) suggestive of adrenal insufficiency. Basal serum ACTH was raised to 289.51 pg/ml (normal range: 7.2 - 63.3). Contrast-enhanced CT of abdomen showed bilaterally enlarged adrenals. Mantoux test was positive and chest radiograph had bilateral pulmonary infiltrates consistent with tuberculosis. All these investigations confirmed primary adrenal insufficiency (Addison's disease) due to tuberculosis. The patient was put on anti-tubercular treatment (category-II) and steroid replacement therapy.

Skin and mucous membrane hyperpigmentation is present in 95% of patients with primary adrenal insufficiency[1]. It is considered a tell-tale sign of Addison's disease, thus differentiating it from secondary and tertiary hypoadrenalism. This often precedes other manifestations by months to years, and the patient can present with the only complaint of getting darker. Moreover, in combination with other systemic manifestations, it has a very high predictive value for Addison's disease[2]. It results from the stimulatory effect of ACTH on melanocytes. They are prominent in areas subjected to increased pressure (extensor surfaces, knuckles of fingers, skin creases), sun exposed areas of the skin, and scars formed after the disease onset. Other commonly involved areas are nail bed, palmar creases, buccal mucous membrane, perianal and vaginal mucosa. In a country like India, where tuberculosis is endemic, it is a leading cause of Addison's disease, although autoimmune adrenalitis is more common in developed countries[3].

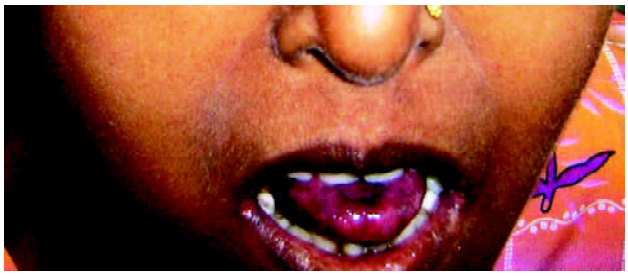
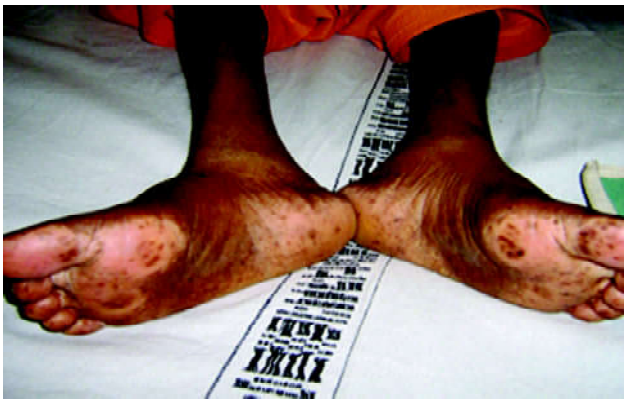


Fig. 1: *Hyperpigmentation of oral mucosa.*



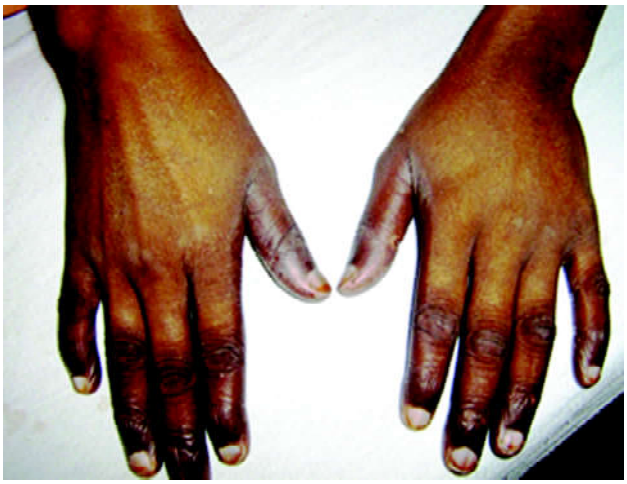


Fig. 2 and 3: *Hyperpigmentation of skin on soles and kunckles.*

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