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Editorial

The field of medicine is in a state of flux. The frontiers of knowledge are expanding in exponential proportion. To make sense out of a profusion of information is as tasking as making a new resolution and sticking to it in letter and spirit. Medical journals are a way of providing distilled knowledge to ever busy and hard pressed physicians, to enable them to grasp a problem in nutshell through reviews and case reports pertaining to topical issues. As I have said earlier, there are no dearth of journals but dearth of readers. Editing yet another one of those ever increasing lineage of publication is a painstaking process, physically as well mentally, since a lot of introspection is necessary to make the journal worthwhile.

After due deliberation topics were selected that would help physicians in daily care of patients. A recent survey showed that the most common problems confronting the population of India at large includes communicable diseases. Other non-communicable diseases like diabetes, hypertension ,coronary artery disease, osteoporosis,osteoarthritis and rheumatoid arthritis have a big contribution as well, but mostly in the urban scenario.

Unfortunately,communicable diseases are not 'glamorous' enough to attract serious attention of most medical fraternity. In the age of instant gratification, pharmaceutical driven hype of certain disorders has attracted more attention and financial support. The skewed research activity in these fields is testimony of this belief.

In a research paper published recently in US it was found that less than 10% of people who buy a book rarely read the first chapter. It is not known if they ever complete it. It is frightening to think what would be the fate of a book or journal provided free of cost. The success of our effort can be evaluated if physicians take the journal seriously and the articles help them in understanding some of the problems. Till then we shall keep our fingers crossed.

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Dr Jayanta Kumar Panda

ASSOCIATION OF PHYSICIANS OF INDIA

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Original Article

OBSERVATIONS ON ACUTE ACCIDENTAL INHALATIONAL EXPOSURE TO CHLORINE GAS IN ADULTS

P. K. Mohanty[*], D. K. Patel[**]

ABSTRACT

Accidental release of chlorine gas from a water treatment system leading acute inhalational exposure in 30 adult victims were studied. Fatality was noted in one case. The rest manifest with respiratory symptoms and sign like dyspnea (79%), Cough (48%), wheezes (86%), apprehension (83%). Other symptoms were headache, dizziness, abdominal bloating, tingling and pain in limb, irritation and watering from eyes. The victims who made it to the hospital recovered following treatment with intravenous theophyline, glucocorticoid and oxygen inhalation. In view of ongoing industrialization in Orissa state, employee training, preventive equipment maintenance and upgrading of emergency departments with trainings of staffs is the need of the hour for meeting the challenges of toxic gas exposures.

Key words: Chlorine gas, acute exposure

INTRODUCTION

Exposure to toxic gases resulting from mechanical failure or human error endangers life of large number of people in a very short period of time. Of these Chlorine gas is one of the most common single, irritant, inhalation exposures, occupationally and environmentally[1]. It is a greenish yellow gas with pungent odour[1]. Various toxic manifestation in exposed person include irritation, burning and watering of eyes; sneezing, itching of nose and rhinorrhea; choking in throat and chest, burning sensation in throat and substernal area, coughing, dyspnoea and pulmonary oedema; abdominal fullness, nausea and vomiting; dizziness, headache, muscle weakness and limb pain.[1,2,3,4,5,6,7] In the most severe form it leads to respiratory failure and death. The tissue injury and inflammation produced by chlorine may be due to formation of hydrochloric acid or hypochlorous acid when it combines with water or due to release of free oxygen radical.[1,7,8] The sources of exposure include industrial bleaching, treatment of sewage and water, swimming pool chlorination, and leakage during storage or transportation.[1,2,6,9] The exposed persons are treated by removal and decontamination, β_2 agonist inhalation, O2 inhalation and at times nebulized sodium bicarbonate.[1,6,9] The role of steroids although debated is often used in practice.[1,10] In September 2005 we came across an instance of acute exposure to chlorine gas as discussed below.

PATIENTS AND METHODS

Following exposure to chlorine gas leak from water purification system in Railway Department in Sambalpur fifty one cases attended casualty of V.S.S. Medical College and Hospital, Burla after initial treatment at Sambalpur. One of the victims was found dead on arrival. Of the rest, twenty one children were sent to pediatric department. The adult victims treated in casualty department and later in medicine department as inpatients were included in the study. On arrival the patients were examined for symptoms and signs of toxicity particularly signs related to eye, respiratory system, GI system and nervous system. Continuous monitoring of the patients were done until they are free from the risk. The cases were treated with theophyline and aminophyline injection, injection of dexamethasone or hydrocortisone, and O_2 inhalation. Prophylactic antibiotic were administered and associated illness are also taken care .

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OBSERVATIONS

There were 30 adult victims brought to the casualty of whom one male person had died. The rest twenty nine exposed victims came to emergency department in different phases. Of them eleven were male and nineteen were male. The age varied from sixteen to seventy years (children victims were sent to pediatric department and managed there). The various symptoms and signs noted are mentioned in table below. Difficulty in breathing (79%) was the most common symptom with apprehension. Tachypnoea (97%) and wheezes (86%) were the most common signs. Repeated cough was noted in 48% of the cases. Noncardiogenic pulmonary oedema was found in one case.

Table – 1

Symptoms and signs observed in adults exposed to chlorine gas (n=29)

Symptoms & sign	No of cases	Percentage
1) Burning of eye	5	17
2) Lacrimation	2	7
3) Redness of eyes	3	10
4) Burning in mouth throal	2	7
5) Choking in throat	5	17
6) Cough	14	48
7) Dyspnoea	23	79
8) Tachypnoea	28	97
9) Cyanosis	1	3
10) Wheezes	25	86
11) Crepitation	12	41
12) Pulmonary oedema (ARDS)	1	3
13) Abdominal bloating	4	14
14) Abdominal pain	2	7
15) Apprehension	24	83
16) Dizziness	2	7
17) Headache	7	24
18) Tingling in limbs	7	24
19) Pain in limbs	4	14
20) Tachy cardia	11	38

The cases were treated with injectable theophylline (24 cases) or aminophylline (5 cases); glucocorticoid injections (28 cases); O_2 inhalation (28 cases) and intravenous fluids. β_2-agonist nebulization was given to 2 cases. Some cases also received ceftriaxone injection, diclofenac injection for limb pain and H_2 blocker, for fever, limb pain and dyspepsia respectively.

DISCUSSION

The most of the adult victims sought medical care for having anxiety, dyspnoea, cough and suffocation. The predominant signs were tachypnea and wheezing. Similar symptoms and signs were noted by other observers.[3,4,5,6,7,8] In the present study only one of the patient had cyanosis and none developed hypotension. The respiratory symptoms are thought to result from irritation and inflammation giving rising to mucosal oedema and exudation in brochial tree and alveoli (Das R et al).[8] This leads to narrowing of the airways and pulmonary oedema. One of the victims who was most seriously ill had pulmonary oedema and severe airway obstruction. This patient had a history of chronic obstructive airway disease. Abdominal bloating and tingling in limbs were noted in few patents, as described by others also.[1,2] Other symptom noted were anxiety and apprehension, irritation & burning of the eyes, choking sensation, headache and dizziness etc.

Because of resource limited setting the standard treatment of β_2 agonist inhalation by nebulizer could be given to only selected patients who had the severest form of respiratory distress. Instead theophylline given parenterally served the purpose. Humidified oxygen was administered to all patients. Guloglu C et al in a study of 106 cases found. Humidified O_2 and β_2 agonist inhalation to be most useful in acute chlorine intoxication.[9] Although Bosse GM has found Nebulized sodium bicarbonate to be safe and effective in a study of 86 cases from 49 medical facilities others have not found such results.[1,6] Nebulized sodium biocarbonate was not given to our cases. Most of our patients received intravenous glucocorticoids; however there role has been controversial and has been used in chlorine gas exposure with severe respiration tract obstruction.[10] In our study the patient became free of symptoms by 48 hours after exposure with a range from 8 hours to 48 hours. Bosse GM found a mean hospital stay of

1.4 days (1-3 days) similar to ours.[6] Only one patient died before reaching hospital probably due to ARDS. Rest of the patient recovered without sequalae.

CONCLUSION

The problem often faced by health care professional when such mass exposure occurs is lack of adequate infrastructure to handle these cases. Such instances often overwhelm the medical facilities. Although most patient could be saved in the present mishap probably because of low level of exposure, preparedness for such events in future must be made in emergency departments of district and medical college hospitals with provision for adequate number nebulizers, oxygen cylinders, ventilators and other life saving systems keeping in view the increasing industrialization in Orissa state.

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Review Articles

DIABETES, LIPIDS AND CORONARY ARTERY DISEASE IN INDIANS

Sidhartha Das

ABSTRACT

Diabetes mellitus (DM) is a protean metabolic disorder that adversely affects the vascular channels of the body leading to occlusive vascular events like coronary artery disease (CAD) and peripheral vascular disease (PVD).Besides the diabetic state, higher levels of Triglycerides , lower HDLcholesterol and more of glycated Apo B100 contributes to the excess of atherogenesis in these subjects. In Indian subjects with DM the lipid profile and pattern is greatly influenced by the ethenic origin, food habit , nutritional status and lifestyle influences. There has been a quantum increase in the incidence of CAD amongst urbanites while the picture in rural India has changed very little, suggesting the major impact of lifestyle modifications on lipid profiles and the deleterious effect of the latter in causing accelerated and more extensive CAD as evident angiographically.These alterations in lipid profiles precede the events much in advance and also prevalent in the adolescent siblings of patients with CAD. In our social setup, it is the nurture which has been the main determining factor than the nature per se.Conventional dyslipidmias of hypercholesterolaemia with high LDLc may not be the commonly found abnormalities in our subjects and due attention should be given to Type IV and Type IIb hyperlipidemias as cause of excessive CAD in our population groups besides tight glycemic control to avert increased glycation of functional proteins and Apoproteins.Raised triglyceride levels can be used as surrogate lipid markers for CAD in the susceptible population and families .

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Key Words : Non-LDL Dyslipidemia, Hypertriglyceridemia, Coronary Artery Disease, .

DIABETES, LIPIDS AND CORONARY ARTERY DISEASE IN INDIANS

Insulin is an anabolic hormone having widespread influence on various processes which are growth enhancing and beneficial to the organism. Insulin exerts profound influence on expression and activity of genes regulating various key enzymes involved in lipid metabolism as well as synthesis and expression of apolipoproteins both in the liver and peripheral tissues. (adipocytes, skeletal muscle, endothelial cell, fibrocyte etc). In the peripheral bed at the endothelial tissue interphase, it primes the lipolytic enzymes (lipoprotein lipase = LPL) and enhances the clearance of very low density lipoprotein (VLDL) and chylomicrons.These triglyceride (Tg) rich lipoproteins break down to liberate free fatty acids (FFA) and glycerol.While FFA is used as the main source of energy in the postabsorptive state,glycerol recycles back to the liver.In the process of hydrolysis of fat,mono and diglycerides are also liberated at these sites.[1]

Levels, composition, size and metabolism of plasma lipoproteins in subjects with diabetes mellitus (DM) are influenced by factors such as:

1) Type of diabetes mellitus
2) Habitus i.e lean, standard weight and obese.
3) Nutritional status: under nourished or well nourished.
4) Insulin sensitive or resistant stage
5) Glycaemic status and type of treatment

6) FFA influx to the liver vis a vis insulin level in portohepatic bed.

7) Presence of complications like nephropathy. Broadly the lipid abnormalities (dyslipidaemia) seen in Type 1 and Type 2 diabetes are presented in Table-1. Hypertriglyceridaemia is the common dyslipidemia seen in uncontrolled diabetic state, insulin resistant stage and presence of nephropathy in Type 2 diabetics.[2] Figure-1 and Table-2 depict the influence of nutritional status and glycaemic control in patients with Type 2 diabetes. Again, in Indian diabetics hypertriglyceridemia with increased VLDL is more common dyslipidaemia than low high density lipoprotein (HDL) cholesterol levels.[3] This is very likely due to over production of VLDL by the liver.

VLDL Tg is endogenous in origin and thus the dyslipidemia is Type IV hyperlipoproteinemia. The hypertriglyceridemia is consequent to both over production by liver and poor clearance of VLDL in the peripheral tissues. due to inappropriate action of LPL.The suppressed activity of LPL is because of the insulin resistant or insensitive state in metabolically uncontrolled diabetics. With adequate glycemic control and maintenance of euglycemia it reverts to near normal levels. Therefore presence of hypertriglyceridemia is a good indicator of the state of poor metabolic control in patients with DM. Alterations in cholesterol levels are not uniform in patients with DM. In the diabetics of the West as well as affluent populations of our country, a rise in cholesterol levels along with Tg is seen, so the type of hyperlipoproteinemia is Type IIb.[4] However diet, nutritional status and anthropometry play a vital role and the picture is different in most of our diabetics.[5] Even in an uncontrolled state, only about one fourth of diabetics revealed hyperchlesterolemia.[2]

Lipid Profile in Indian Population :

Interpretation of dyslipidaemia in diabetics has to be done keeping in view the lipid normogram of the inherent population. The National Lipid Normogram is presented in Table – 3.[1]

Population based studies on lipid profiles, done at our center are depicted in Figures - 2 and 3.[3] The Tg levels revealed U shaped distribution in upper, middle and lower socio economic groups (S.E. Groups) respectively. While higher Tg levels in the upper SE group is very likely to be due to higher fat intake compounded with slower VLDL clearance, relatively higher levels in the lower SE group is mostly due to very high carbohydrate diet. Interestingly, analysis of lipid profile done in persons living in a geographical area of 10 kilometers radius but belonging to different ethnic groups as well as having different lifestyle and food habits revealed significant differences in the lipid profiles, as shown in Table-4,[6] The fishermen (Naulia) had the most ideal lipid profile to be followed by tribals where the cholesterol profile was ideal but Tg levels were similar to urban elite population.The fishermen were physically most active,consumed on an average 500Gms of fish per day while the Tribals were nutritionally deprived with poor protein intake.Both these communities were on high carbohydrate diets while the Urbanites had more refined carbohydrate food, richer in both fat and proteins This further confirms that high carbohydrate diet had a great influence in modulating Tg levels vis a vis physical activity in our populations. The National lipid normogram again reflects the influence of inherent dietary pecularities on the lipid profile of people from east, west, north and south zones of India.[1]

Lipid Levels and their Interpretations in Different Type of DM :

Type-1 DM : This is a typical situation where insulin production is minimal to nil and therefore its concentration is low both in the porto-hepatic circulation and peripheral blood. The lipoprotein composition is accordingly affected with low high density lipoprotein-cholesterol (HDLc), poor esterification of cholesterol, more of Tg with less VLDL clearance. This is more so in inadequately treated patients with poor glycemic control. The activity of enzymes like lecithin cholesterol acyl transferase (L-CAT) and lipases are suppressed due to low circulating

insulin levels. This adversely affects HDL metabolism. Besides, higher concentration of free cholesterol in low density lipoprotein (LDL) and intermediate density lipoprotein (IDL) makes them more atherogenic. However, institution of insulin treatment and maintenance of euglycemia rapidly reverses lipid metabolism to normal.

Type-2 DM : In patients with Type-2 DM there is global dysfunction of lipoprotein metabolism. The degree of dyslipidemia is more widespread (Table-1). There is increases in small dense LDL (LDL3) which is highly atherogenic. In patients with poor glycemic control, levels of Tg rich lipoproteins are higher. This rise is not only due to over production of VLDL but also poor peripheral clearance consequent to lesser expression of ApoB100 receptors on endothelial cell surface. In uncontrolled patients with Type-2 DM the recycling of receptors is also slow. Glycated ApoB100 have longer interaction with its receptors and so prolongs the half life of both LDL and VLDL molecules. The HDL levels may not be low in these type of diabetic subjects, more so with fair glycemic control. Unlike Type-1 DM, patients with Type-2 DM have good insulin reserve and so much higher porto-hepatic insulin concentration which keeps the HDL cycle and hepatic enzyme system at an optimum. Patients with poor peripheral insulin levels may therefore have near normal HDLc levels while values of VLDLc, LDLc, IDLc and Tg may be higher. Such discordance is peculiar to Type 2 DM. Type IV type IIb and Type III dyslipoproteinemias commonly met with in Type 2 DM often reverses with diet and hypoglycemic drug therapy. (Fig.-4)[4,7]

Low body weight Type 2 DM (Lean Type-2 DM)[2,3,8] : The diabetic state differentiates Lean Type-2 DM from PEM in many respects including lipid profile. Cholesterol content in LDL and VLDL are higher as is Tg content, although the absolute values of these lipid levels are much lower than in well nourished diabetics (WND). Levels of mean HDLc is visibly higher in Lean Type-2 DM irrespective of glycemic status. The Tg levels in Indian subjects with DM is higher both in Lean Type-2 DM as well as in WND when compared with data from the west. This profile is likely to be the true reflection of the influence of nutritional status lipid profile in developing societies rather than a consequence of any specific biological alterations.

Studies done by Seshiah et al from Chennai had also revealed similar alterations in the lipid profile in obese, non-obese and lean diabetics in their population.[9] While in the WND there was a positive correlation suggesting slower removal of Tg in the obese, there was no correlation in the Lean Type-2 DM. Studies on Lean Type-2 DM have shown that pre-existing dyslipidemia found in an uncontrolled state improves with establishment of glycemic control. Hypercholesterolemia is very unusual in such Lean patients with DM.

It is a well established fact that hypertriglyceridaemia and Tg content of muscle bears a negative relationship to whole body insulin sensitivity. The patients with Type-2 DM invariably have serious breakdown in lipid dynamics often reflected as elevated levels of FFA and Tg together with excessive deposition of fat in various tissues including muscle bed. The high FFA levels adversely effects insulin mediated glucose disposal in peripheral blood. Such FFA arises from hydrolysis of Tg. In peripheral circulation. Therefore Tg is considered to be a surrogate marker for fatty acids in general. Levels of long chain fatty acids and their derivatives increase in states of insulin resistance (obesity, IGT, Type-2 DM) which involves in disrupting the insulin signaling cascade and interferes with movement of glucose transporter –4 (GLUT-4) from an intracellular compartment to muscle cell surface.[10]

Coronary Artery Disease (CAD) :

Over the decades,there has ben a phenomenal rise in the incidence of CAD in India.The prevalence of CAD in urban and rural population of India as observed by various investigators since 1960 are presented in Table-5.[11] The diagnosis of CAD was done in these studies on clinical basis with the help of

ECG...In the urban population there has been a steady increase in the prevalence of CAD from 1.05% to 7.3% on an average while it was as high as 11% in New Delhi and 12.6% in Trivandrum respectively, suggesting an epidemic like situation in these places. However the change in profile of CAD in rural areas has not been that significant (Table-5).The quantum rise in the prevalence of CAD in urban-India is very likely due to changes in lifestyle, neo-affluence and changes in food habits.Besides stress and strain of urban life,the changes in the content of food viz.high lipid,salt with less of fibre and green vegetable intake could be one of the major determinants The biochemical marker is the ensuing dyslipidemia in them.

Study on mortality profile in patients with CAD from different Asian countries had revealed that the prevalence was highest amongst Indians as compared to people of Chinese origin, Indonesians and Malaysians (Table-6).[12] Premier study done by us had shown HDLc was lower and LDLc higher in non-diabetics with CAD while such dyslipidaemia was not obvious in diabetics with CAD.[13] As reported by us, more than decades ago, Tg levels were much higher in diabetics with CAD. Recent studies from Chennai "CUPS NO.5" revealed no difference in HDL values amongst subjects with or without CAD (Fig.5).[14] Hospital based studies from Patna also did not reveal any statistical difference in mean lipid levels in patients with CAD and controls (Fig.6).[15] The conventional dyslipidemia of low HDL and high LDL is probably not the significant cause behind higher prevalence of CAD in Indians.

Further data from studies using coronary angiography as a tool to diagnose CAD done at different centres revealed that higher triglycerides with marginally raised LDLc where associated dyslipidemia in patient with South India, whereas increase in total cholesterol and LDLc was common in those from North India (Table-7).[16,17] This again reflects the influence of dietary habits on lipid parameters as there is visible difference in dietary practices in these populations.

CAD amongst patients with DM :

Now focusing on prevalence of CAD amongst diabetics in India, starting with the data of the multicentric study conducted by ICMR (1984-87) to recent publication from Ahmedabad, there has been substantial rise in the prevalence of CAD from 5.8% to 20-30% amongst diabetics over the period of time (Table-8).[11] This is an alarming situation and needs introspection with reference to the quantum increase in prevalence as well as risk factors.

Studies done by us in patients with established acute myocardial infarction (AMI) with or without diabetes and publication from Bangalore on diabetics with CAD showed serum Tg levels to be higher in the diabetic group whereas other lipid fractions were nearly similar and not significantly elevated as would have been expected Table-9.[18,19] The diabetic state per se is the major determinant for developing CAD amongst diabetics and thus the American Heart Association has correctly conferred that DM is coronary equivalent and should be treated as aggressively as non-diabetics with atherogenic dyslipidemias.

Further more,studies done on siblings of patients with CAD showed existing dyslipidemia in the siblings as compared to healthy controls (Fig-7).[20] From the latter study it was observed that risk factors for CAD were more frequently met in the siblings of patients with CAD from a very early age. Both in age groups of 0 – 19 and 20 – 59 years the levels of serum Tg, LDL cholesterol and VLDL cholesterol were higher as compared to young controls of the corresponding age group. The study pointed to the fact that even at the age of 19 years a person from the family of CAD should be screened for lipid profile and primary prevention instituted at this stage.

Such dyslipidaemia casts its shadow much before the event manifests and so can be used as a marker for both detection and prevention of CAD in vulnerable population.

Coronary angiography is one of the most reliable procedures adopted to diagnose CAD. Angiographic

data on Indian patients with suspected CAD had revealed that triple vessel disease (TVD) was much higher in diabetics as compared to non-diabetics, to be followed by double vessel disease (DVD) while single vessel disease (SVD) was more common in non-diabetics (Fig.8).[21] This is corroborative of western observations that diabetics have more extensive involvement of coronary artery (CA) as compared to non-diabetics.[22] To further elucidate the extensiveness of atherosclerotic involvement of coronar arteries , in diabetics and non-diabetics, in the same cohort and to analyse the existing dyslipidaemia in such patients , a prospective study was undertaken at our centre. The coronary angiogram was analysed as per the criteria laid down by American Heart Association with regards to segments (fifteen in toto) and severity of occlusion (Grade 0-4). The gross angiographic profile is given in Table-10 where it is obvious that occlusion of left main coronary artery DVD and TVD were more in diabetics whereas SVD was higher in non-diabetics respectively. The extensiveness of involvement and degree of occlusion was categorized as per Ledru et al as described below.[23]

Coronary score : No. of coronary arteries exhibiting stenoses > 75%.

Extent score : No. of segments exhibiting lesions ≥ Grade – 1

(adjusted to 15 coronary segments)

Severity score : Average grade of stenosed coronary segments

Atherosclerotic score : Calculated as average severity of all analyzable segments.

The degree of atherosclerosis of coronary arteries and corresponding mean lipid levels are presented in Table-11. The diabetics had statistically significant higher values for all the above four scores suggesting both extensive and higher grade of occlusive CAD. The associated dyslipidemia was lower HDL cholesterol with higher levels of serum triglycerides.

The crux of the issue is now well known that majority of diabetics have dyslipidaemias. Central characteristics of such dyslipidaemias are increase in triglyceride levels, more of triglyceride rich VLDL and lower HDL levels in those with overt CAD.. LDL cholesterol levels may not be raised as compared to non-diabetics but could have more of small dense LDL with glycated ApoB100 which is highly atherogenic. This lipid triad confers a risk for cardiovascular disease that equals or exceeds the risk conferred by LDLc levels of 150 – 220mg/dl. Therefore diabetic dyslipidaemia even without established CAD should be treated as aggressively as non-diabetics with CAD. Hypertriglyceridaemia and lower HDLc levels may preceed development of overt Type2DM/Insulin resistant state and so can be used as markers.

Diabetes Mellitus ,Type 2 in particular, is a progressive macro vascular disease with universally established excessive predilection for coronary arteries irrespective of race, ethnicity, gender or geography . Salient biochemical markers for this vasculopathy are chronic hyperglycaemia and non-HDL dyslipidemia.

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Table - 1

TYPES OF LIPID ABNORMALITIES IN DM

Type 1 DM :

Usual level of glycemia (Euglycemia)	:	Similar to non-diabetics
Poor glycemic control	:	↑Tg level and ↑LDLc oxidation
Diabetic Nephropathy	:	↑LDLc & Lp(a), ↓HDLc

Type 2 DM :

Usual levels of glycemia (Euglycemic)	:	↑Tg, ↓HDLc, prevalence of small dense LDL, ↑LDL susceptibility to oxidation
Poor glycemic control	:	Worsening of Hypertriglyceridemia
Diabetic Nephropathy	:	↑Tg, ↑Lp(a) , ↓HDL

Table - 2

Lipid profile in Controls, Untreated and Treated Undernourished (UND) and Well nourished (WND). Type 2 diabetics (mg%).

Sub	Tg	Tc	HDLc	LDLc	VLDLc
Untr. UND	157.1	283.4	63.6	158.8	64
Trt.UND	107.8	199	70.4	104.6	24
Cont.	95.3	216.4	68.7	131.2	16.5
Untr.WND	168.4	300.2	52.8	182.2	65.2
Trt.WND	123.2	230.2	67.3	136.2	26.7

Das, Tripathy, Samal & Panda, DIABETES CARE, 1984

Table - 3

Lipids and Lipoprotein Cholesterol Normograms in Indians (mg%)

Zone		Triglycerides	Total Cholesterol	HDLc	LDLc
East		115	185	42	115
South	(a)	155	180	38	107
	(b)	119	172	40	108
West		107	188	38	129
North		132	150	43	101

Based on population studies as reported from different parts of India

Sidhartha Das & V.Mohan,Chapter on Lipids,A.P.I. Text Book of Medicine, 7th Edn.,2003

Table - 4

Lipid profile in Tribals, Fishermen and Urban elite population in mg/dl.

Sub	HDLs	LDLs	VLDLs	Tc	Tg
Urban	41.8	114.8	28.8	185.4	144.4
Fishermen	43.5	71.4	24.8	139.8	124.2
Tribals	33.6	70.9	28.9	133.5	144.9

Mondal, Das, Mohanty et al, Jr. Nutr. Med. 1994

Table – 5

Prevalence of CAD in Urban and Rural India

Author	Year	Place	CAD(%±SD)
		URBAN POPULATION	
Mathur KS	1960	Agra	1.05 ± 0.3
Padmavathi	1962	Delhi	1.04 ± 0.3
Sarvotham SG	1968	Chandigarh	6.60 ± 0.6
Gupta SP	1975	Rohtak	3.63 ± 0.5
Chaddha SL	1990	Delhi	9.67 ± 0.3
Shety KS	1994	New Delhi	10.9
Gupta R	1995	Jaipur	7.59 ± 0.6
Singh RB	1995	Morababad	8.55 ± 2.3
Begom TR	1995	Trivandrum	12.65 ± 1.5
Ramchandran	2001	Chennai	3.9
Mohan V	2001	Chennai	11
Gupta R	2002	Jaipur	7.30
		RURAL POPULATION	
Dewan BD	1974	Haryana	2.06 ± 0.4
Jajoo UN	1988	Vidarbha	1.69 ± 0.3
Kutty VR	1993	Kerala	7.43 ± 0.8
Wander GS	1994	Punjab	3.09 ± 0.5
Gupta R	1994	Rajasthan	3.53 ± 0.3
Singh RB	1995	U.P	3.09 ± 1.4

Gupta OP,Phatak S. Int.J.Diab.Dev.Count.,2003

Table – 6

CAD mortality in Asian countries (/100,000 population)

Country	1992
China	
Urban (M, F)	90.61
Rural (M, F)	45.31
Hong Kong (M, F)	55.33
India (Bombay)	158
Indonesia	60
Malaysia(West)	60
Philippines	32
Singapore (M, F)	154, 84
Taiwan (M, F)	35
Thailand	56

Chandalia HB,Lipid India,1996.

Table - 7
Lipid and Lipoprotein levels in angiographically proved CAD and controls, Delhi and Vellore

Sub	Tc		LDLc		HDLc		LDL/HDLc		VLDLc		Tg	
	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.	Del.	Vell.
Patients	211	206.72	117	124.14	43.5	36.43	2.6	X	49.7	X	155	193.3
Controls	186	180.47	88	107.5	42.1	37.98	2.2	X	56.1	X	167	155.19

Del.-Delhi, Chopra, LIPID INDIA,'99
Vell.-Vellore, Krishnaswami S, LIPID INDIA,'96

Table – 8

Prevalence of CAD amongst Diabetics, In India

Author	Year	Place	Prevalence of CAD (%)	
ICMR*	1984-87	Multicentric	8.1%	Males
			4.7%	Female
A. Ramchandram	1998	Chennai	14.2% (3.9+10.3%)	
V. Mohan	2001	Chennai	21.4%	
PODIS**	2001	Multicentric	4.5%	
Gupta PB	2001	Surat	19%	
Gupta S	2001	Nagpur	33.5%	Males
			21.5%	Females
Phatak SR	2002	Ahmedabad	20.2%	Males
			26.1%	Females

**** ICMR – Indian Council of Medical Research***
***** PODIS – Prevalence of Diabetes in India Study***

Table – 9

Lipid profile in patients with CAD –Diabetics and Non-Diabetics, Cuttack and Banglore (mg%)

Sub	Tc		HDLc		LDLc		VLDLc		Tg	
	Ctc.	Bang.	Ctc.	Bang.	Ctc.	Bang.	Ctc.	Bang	Ctc.	Bang.
CAD - Diabetics	192.2	194.1	39.2	40.2	118.3	105.9	34.7	48.4	150.6	209.4
CAD-Non-Diabetics	197.1	200.4	41.5	44.9	116.2	128	39.3	27.5	120.3	137.6

Ctc.-Cuttack : Das S. and Panda R. , Jr. Diab. Asso.India, 1998
Bang.-Bangalore : Pitchumani, Dharmalingam, Deva & Prasanna Kumar, LIPID INDIA,'98

Table – 10

Coronary Angiographic Profile in Diabetics a nd Non Diabetics (n=147 in each group) in %.

Sub	Left main	SVD	DVD	TVD
Diabetics	6.1	11.6	42.9	39.4
Non-Diabetics	1.3	33.4	34.6	30.7

Mishra, Routray, Das, Behera, Satpathy & Pattnaik, Cuttack,2003

Table – 11

Degree of Atherosclerotic Involvement of CA and corresponding Lipid levels (Mean & S.D.)

		Diabetics	Non-Diabetics	P Value
Coronary Score	:	0.91 (0.63)	0.43 (0.39)	<0.001
Extent Score	:	4.91 (3.1)	2.3 (1.81)	<0.001
Severity Score	:	1.85 (0.41)	1.2 (0.32)	<0.001
Atherosclerotic Score	:	0.52 (0.31)	0.21 (0.26)	<0.001
Lipid Values in mMol/L				
Total Cholesterol	:	4.81 (0.31)	4.70 (0.29)	N.S.
HDLcholesterol	:	0.84 (0.13)	1.12 (0.15)	<0.001
LDLcholesterol	:	3.29 (0.19)	3.23 (0.22)	N.S.
Triglycerides	:	2.98 (0.07)	2.41 (0.06)	<0.001

Mishra, Routray, Das, Behera, Satpathy & Patnaik , Cuttack, 2003

ORGANOPHOSPHOROUS & CARBAMATE POISONING: A REVIEW

C.B.K Mohanty*, B.N.Mohapatra, N.Mohapatra**, P.K.Thatoi*****

An organophosphate (op) is the general name for esters of phosphoric acid or phosphinic acid. Many of the biochemicals are organophosphates; including DNAand RNA as well as many cofactors that are essential for life. These diverse group of chemicals are also widely used as insecticides(malathion, parathion, diazinon, fenthion,dichlorous, chlorpyrifos), herbicides{tribufos(DEF)}, G' nerve war weapons[tabun(GA), sarin(GB), soman(GB) and venom x(VX), solvents, plasticizers and antihelmintics(trichlorfon)(2)

However in health, agriculture and government the word 'organophosphates' refer to a group of insecticides or nerve agents acting on the enzyme acetylcholine esterase(Ache).

Carbamates are another group of insecticides which are the ester of carbamic acid and these compounds also act on choline esterases;but through different mechanisms. Examples of carbamates are Aldicarb, carbofuran, furadan, fenoxycarb,carbaryl and ethienocarb. In addition some carbamates are used in human pharmacotherapy; for example the cholinesterase inhibitors neostigmine and pyridostigmine. Since there are no rule to regulate the sales and purchases of these products and because of their 'over the counter' easy availability, they have emerged as a common cause of poisoning all over the world, may it be suicidal or accidental and even rarely be the homicidal poisoning. Estimates from the WHO indicate that each year 1 million accidental poisoning and 2 million suicide attempts involving pesticides occur worldwide.

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CLASSIFICATION OF OP COMPOUNDS

1. Highly toxic OP (parathion, tetraethyl pyrophosphate).These are used as agricultural insecticides.
2. Intermediate toxic OP (coumaphos, chlorpyrifos,trichlorfos).These are used as animal insecticides.
3. Low toxic OP (diazinon, malathion, dichlorvos).These are used for house hold applications and field sprays.

MECHANISM OF ACTION OF OP COMPOUNDS & CARB AMATES

Acetylcholine (Ach) is the neurotransmitter released at all postganglionic parasympathetic nerve endings, synapses of both sympathetic and parasympathetic ganglia,myoneural junction and also in central nervous system. Ach is hydrolyzed by the enzyme cholinesterase.

Acetyl cholinesterase is present in two forms :

a. True cholinestaerase: found in tissue and erythrocytes
b. Pseudo choline esterase: found in the serum and liver

OP compounds firmly (and sometimes irreversibly) phosphorylate the active site on the red cell acetyl choline esterase and pseudo choline esterase in the serum, and locally at the site of Ach release causing inhibition. The cleavage of carbon enzyme bond from Ach that normally occurs is complete within few microseconds whereas the breaking of the phosphorous enzyme bond requires a period varying

from 60 min to several weeks depending on the OP compounds.

There are two types of OP intoxications:

a. direct action by the parent compounds(i.e. tetraethyle pyrophosphate) or

b. indirect action by the toxic metabolite(parathoxone or malathoxone)

Carbamates cause temporary or reversible carbamylation of the active sites of enzymes for approximately six hours with no permanent damage. Carbametes have poor CNS penetration and cause minimal CNS symptoms.

Once an OP compound binds to AchE, the enzyme can undergo 1 of the 3 processes

1. Endogenous hydrolysis by esterase or paroxonases

2. Reactivation of enzymes may occur spontaneously. The rate of reactivation will depend upon species, tissue and the chemical groups attached to the enzymes. The reactivation may be enhanced by hydrolysis of the acid radical enzyme through the use of a strong nucleophile such as pralidoxime(PAM)

3. Complete binding and inactivation (aging).If the OP–AchE bond is not broken by pharmacological; intervention within 24 hrs, Large amount of cholinesterase are destroyed causing long term morbidity or death.

When a critical amount ;greater than 50% choline esterase is inhibited, Ach accumulates and causes transient stimulation at cholinergic synapses and sympathetic terminals(muscarinic effect),the somatic nerves, the autonomic ganglion(nicotinic effect) and CNS synapses followed by eventual exhaustion and disruption of neural transmission in peripheral as well as in CNS.(PNS AND CNS)

KINETICS

Absorption is by all routes; intact skin, mucus membrane, conjunctiva, gastrointestinal and respiratory tracts. Following ingestion toxicity occurs as early as 3 hrs, usually by 12 hrs and always before 24 hrs.Lipid soluble compounds (fenthion) absorbed through skin may have delayed onset of toxicity even beyond 24 hrs.Inhalation toxicity occurs immediately. Massive ingestion can lead to toxicity within minutes.

Following absorption OP compounds are rapidly redistributed to all body tissues. The highest concentration is found in liver and kidneys. High lipid solubility help them to cross blood- brain barrier; thus causing potent CNS effects.

Metabolism occurs primarily by oxidation in liver with conjugation and esterase hydrolysis producing a half life of minutes or hours.

The metabolite of malathion and parathion (malaoxon & paraoxon) are active forms and are subsequently hydrolyzed.Elimination of OP compounds and their metabolites occurs chiefly via urine, bile and faeces.

CLINICAL FEATURES

The clinical symptoms and signs in OP & carbamate poisoning are non-specific and will depend on the specific agent , the quantity and the route of entry.

The clinical features can be broadly divided into—

A) Muscarinic effect, B) nicotinic effect and C) central receptor stimulation.

Early case may be present with parasympathetic over activity and often with characteristic gastric smell. End result may be a multisystem manifestation involving GI, CVS and Nervous system as well as involvement of skeletal muscles other organs and metabolic effects such as hypo or hyperglycemia.

Mnemonic devices used to remember the muscarinic effect of OP's are SLUDGE (salivation,lacrimation,urination,diarrhea,gi upset, emesis) and DUMBELS(diaphoresis and

diarhea,urination,miosis,bradycardia,bronchospasm,bronchorrhoea,emesis,excess lacrimation and salivation).Other muscarinic symptoms and /or signs include hypotension,rhinorrhoea,severe respiratory distress, abdominal pain and blurring of visions.

Later sympathetic and nicotinic effect occurs consisting of MATCH; muscle weakness and fasciculation (often with eyelid twitching and diaphragmatic failure), adrenal stimulation, tachycardia, cramps in muscles and hypertension. Besides pallor and mydriasis may be noted at this stage.Finally, paralysis of skeletal muscles ensures.

The CNS effects include anxiety, emotional lability, restlessness, confusion, ataxia, tremors, seizures, delirium, toxic psychosis, coma and respiratory paralysis, cranial nerve palsies and delayed hallucination have also been described.

Besides acute paralysis secondary to continued depolarization at the neuromuscular junction (type 1 paralysis), two other form of paralysis are seen with OP poisoning.

Type 2 paralysis (intermediate syndromes)is paralysis of proximal muscles,neck,trunk with relative sparing of distal muscle group and also respiratory distress developing 24 hr to 96 hr after resolution of acute OP poisoning symptoms. It persists for 4 to 18days often requiring mechanical ventilation and may be complicated by infections and cardiac arrythmias.Type 3 paralysis ; OP– induced delayed polyneuropathy(OPID) occurs 2 – 3 weeks after exposure to certain OPs.(triethyle cresyl phosphate,bromoleptophos,methomidophos) and is due to inhibition of neuropathy target esterase. Distal muscle weakness, with relative sparing of the neck muscles, cranial nerves and proximal muscle group characterizes OPIDP. Recovery can take up to 12 months.

Other features described in OP poisoning ,though rare include ototoxicity,optic neuropathy,retinal degeneration,defective vertical smooth pursuit,myopia,laryngeal spasm, and cardiac rhythm disturbances(extrasystoles,atrial and ventricular tachycardia and fibrillation, prolonged Q-T interval ,AV block)acute flu like syndrome in agricultural workers chronically exposed to OP has also been frequently described.

Complication includes-aspiration, pulmonary edema, and acute respiratory distress.

Carbamates do produce almost similarly toxicity like OP compounds but lack CNS toxicity due to poor penetration, their inhibition of AchE is reversible and transient. PAM- the enzyme regenerator may not be required in the management of carbamate poisoning.

OTHER PROBLEMS TO BE CONSIDERED.

a. Poisoning due to nicotine, carbachol, arecolin, bethanecol, neostigmine, mushroom poisoning, (elitocybe, inocybe) poisonous hemlock.

b. Myasthenia gravis, Eaton Lambert syndrome, guillain-barre syndrome, Botulism.

LABORATORY STUDIES.

OP toxicity is a clinical diagnosis. Confirmation of OP poisoning is based on choline esterase activity.

If possible, draw blood for measurement of RBC and plasma choline esterase prior to treatment with pralidoxime.Monitoring serial levels can be used to determine a response to treatment.

Note:

1. RBC choline esterase represents AchE in RBC membrane similar to that found in neuronal tissue .Therefore measurement more acuratly reflects CNS OP AchE inhibition.

2. Plasma choline esterase is found in CNS white matter, the pancreas and the heart. It can be affected by pregnancies, infection and medical illness.

3. Falsely depressed RBC choline esterase is noted in pernicious anaemia, haemoglobino pathies, use of antimalarial drugs and oxalate tubes.

4. Falsely depressed choline esterase are observed in liver dysfunction, low protein condition, use of certain drugs (codeine, morphine, succinyl choline) pregnancy.

RBC choline esterase roughly correlates with clinical severity. Mild poisoning is 20-50% of normal, moderate is 10-20% of normal and severe poisoning is 10% of normal (>90% depressed)

Monitoring should also include—

Chest radiograph, blood glucose, oxymetry, ECG,blood coagulation status, liver function test, serum amylase and urine analysis for metabolite alkyl phosphate paranitrophenol.

MANAGEMENT:

The treatment must be initiated immediately on clinical suspicion without waiting for blood investigations.

SPEED IS IMPERATIVE

1. Prehospital care: paramount to the management of OP & carbamate poisoned patient is decontamination which should begin as soon as possible.

Care is required to prevent secondary casualty as compounds are well absorbed through the skin and lungs.Appropiate barrier protection(use of gloves,gowns,goggles,masks) should be maintained. General decontamination consists of isolation, bagging and disposal of contaminated clothings and other articles. Vital function should be established. Cardiac and oxygen saturation monitoring rare needed. Secretion should be suctioned until and full atropinisation drying is achieved. Intubation and assisted ventilation may be needed (monitor respiratory rate, tidal volume/vital capacity) neck muscle weakness, ocular muscle involvement and arterial blood gas analysis at the onset and during the subsequent stages.)

N.B:-AVOID SUCCINYL CHOLINE SINCE IT MAY LEAD TO PROLONGED PARALYSIS.

Atropine to control secretion and bronchospasm may be more helpful than intubation.

DERMAL DECONTAMINATION involves removal of clothings and cleansing of the affected areas of skin, hair with soap and water or shower. Also watch the eyes with normal saline or water. Gastrointestinal decontamination is done if the ingestion is recent i.e. d”1 hr.with gastric lavage.The patient should receive activated charcoal 0.5 -1 gm/ kg every 4 hrs to promote adsorption of OP compounds in the GI tract.

NOTE: Enforced emesis usually precipitates seizure.

MEDICATION

The main study of medical therapy in OP poisoning includes atropine, pralidoxime (2-PAM) and benzodiazepines (diazepam).

The initial management must focus in the use of atropine.(Note: optimization of oxygenation is necessary prior to atropine therapy to prevent dysarythmias)

In 1991 De Silva in two consecutive studies noted that atropine alone was as effective as atropine plus 2-PAM in the treatment of acute OP poisoning.

The controversy continued when other authors observed higher mortality rates and respiratory rates with use of high dose of 2-PAM. Low dose 2 – PAM (1-2 gm slow IV) is still the commonly used practice in OP poisoning.

Intravenous glycopyrolate and diphen hydramine may provide alternative anticholinergic agent used to treat muscarinic toxicity.Glycopyrolate has been claimed to have less CNS side effect; but with better antisecretory action.

Intravenous diazepam is used to control seizures, and arrhythmias are treated as usually.

ATROPNE SULPHATE is both a diagnostic and therapeutic agent in OP poisoning. It counteracts the muscarinic effects; but partially effective for CNS

effect (seizure and coma). Preservative free atropine (no benzyl alcohol) is to be used.

ADULT DOSE-1mg IV (initial and diagnostic)

2-4mg IV every 15 min (therapeutic) until drying of pulmonary secretion

Note : benefitial effects are seen within 1-4 min and max effect in 8 min. avg dose in 24 hr is 40mg; but 1000mg or more has been required in severe cases. An alternative is a continuous infusion of atropine 8 mg in 100ml of 0.9% saline @ of 0.02-0.08mg/kg/hour(0.25-1ml/kg/hour)with additional 1-5 mg boluses to dry secretion. There are reports of poisoning requiring 2mg/kg/hr.iv drip for several weeks to control secretions. Poisoning with lipophilic OP compounds such as fenthion, chlorfenthion, may require weeks of atropine therapy.

PEDIATRIC DOSE-0.015mg/kg/hr (diagnostic or initial) 0.015-0.05mg/kg every 15 min (therapeutic)

NOTE: the signs of atropinisatiojn includes an increased heart rate (>100 beat/min), moderately dilated pupil, reduction of bowel sounds, dry mouths and a decrease in bronchial secretion contrary to earlier belief that atropinisation (fully dilated pupil, absent bowel sounds, heartrate>150beats/min) is no longer necessary since these involves risk of hyperexitability and cardiac complications. The dose of atropine requirement is maximal on day 1 and tends to decrease over next few days.

Oximes are nucleophilic agents that reactivate the phosphorylated acetyl choline esterase by binding to OP molecule.

The commonly used oxime i.e. 2-PAM (pralidoxime) has three main actions—

- A direct reaction converting the OP to harmless compounds
- A transient reaction protecting the enzyme from further inhibition
- Reactivation of inhibited alkyl phosphorylated enzyme to free the active unit (if given early enough)

Pralidoxime chloride has both antinicotinic and antimuscarinic effects and possibly also CNS effect. It reduces the requirement of atropine. Its use may prevent intermediate syndrome and delayed neuromuscular complications. It should be started as early as possible to prevent permanent binding of OP to AchE.i.e ageing of phosphate bond. However recent reports indicate that 2-PAM is beneficial even several days after poisoning. Improvement is seen within 10-40min. the initial dose of 2-PAM is 1-2 gm in 250ml of normal saline over 5-10 min(max200mg/min)in adults. or 25-50mg/kg(max4mg/kg/min) in children <12 years of age. An alternative is a continuous infusion of 1gm in 100 ml normal saline at 5-20mg/kg/hr up to 500 mg /hr. max adult dose is 12gm/24 hrs. Cardiac and BP monitoring is mandatory during and after 2-PAM infusion. Where obidoxime is available, loading dose of 250mg is followed by an infusion of 750mg every 24 hrs.

OTHER NEWER MEDICATION-[5,6]

High dose sodium bicarbonate (5meq/kg iv over 5 min)has been reported effective although mechanism is not known

In a single centered randomized study by Paloumand etal 2004 found a benefit to magnesium therapy in addition to standard oxime and atropine therapy. The mechanism appears to be inhibition of acetyl choline and OP antagonism.

DRUGS CONTRAINDICATED[2]

Morphin, aminophyline, opioids, phenothiazine, reserpine, parasympathomimetics and succinyl choline.

DISPOSITION

1. Hospitalise all symptomatic patients, preferably in ICU setup.

2. The patient who is asymptomatic 12 hrs after exposure can generally be discharged. Symptoms usually occurs within this time frame.

3. Incase of intestinal poisoning the patient requires psychiatric clearances for discharge.

4. Observation of milder case of carbamate poisoning for 6-8 hrs may be sufficient.

5. Following occupational exposure the workers should not return to workplace unless the AchE level rises to 75% of the normal value.

MORTALITY

Worldwide mortality studies report mortality from 3-25% mortality rates depend on the type of compound used ,amount ingested, general health of the patient, delay in discovery and transport, insufficient respiratory management, delay in intubation and ventilator dependency.

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SICKLE CELL DISEASE - REVIEW AND EXPERIENCE AT V.S.S. MEDICAL COLLEGE, BURLA

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ABSTRACT:

Sickle cell disease (SCD) is a common inheritable disease in Western part of Orissa with total frequency of 15% which includes both carrier and disease state. A single nucleotide mutation of beta-globin gene (GAG ®GTG) on chromosome 11 results in production of sickle hemoglobin(HbS) with substitution of valine for glutamic acid in 6th position. HbS on deoxygenation polymerizes to give an abnormal sickle shape to erythrocyte which is rigid and non pliable. Membrane abnormality and anti-gel coating leads to accelerated hemolysis of sickle erythrocytes resulting in anemia and jaundice. Microvascular occlusion whether acute (vaso-occlusive crisis) or chronic leads to life threatening complications and organ damage. Clinical course and severity depends on b-globin haplotype, intra-erythrocytic HbF concentration and presence of a-thalassemia. In comparison to African haplotypes (Benin, Senegal, Bantu, Cameroon) the Asian haplotype of SCD found in Saudi-Arabian and Indian patients runs a benign course due to raised fetal hemoglobin concentration (HbF). Recent advances in treatment includes drugs like hydroxyurea to raise HbF, bone marrow transplantation and gene therapy. In view of serious nature of SCD prenatal diagnosis by polymerase chain reaction (PCR) offers a definite diagnosis and option for medical termination of pregnancy.

KEYWORDS:

Sickle cell disease, Haplotype, Vasoocclusion, Anemia, Prenatal diagnosis.

INTRODUCTION

Sickle cell disease (SCD), one of the common heritable diseases affecting man [1] is characterized for the production of abnormal sickle hemoglobin (HbS). The abnormality is due to the substitution of valine for glutamic acid normally present at sixth position from the amino terminus of the -chain of the haemoglobin [2] The abnormal HbS tends to polymerise on deoxygenation and the red blood cells containing HbS become less pliable and consequently deform into the characteristic sickle shape, for which the disease is named so. The disease is acquired by inheriting abnormal sickle genes from both the parents[2]and thus a genetic disease. The first report of SCD came from a Chicago cardiologist Dr. Herrick in 1910 while examining a medical student from Jamaica who had hemolytic anemia in conjunction with elongated red blood cells [3].

GENETICS AND NOMENCLATURE

The globin protein, of adult hemoglobin is made up of two alpha and two beta polypeptide chains. The gene for a-chain is located in the a-globin gene cluster present in chromosome 16. Similarly, the b-globin gene cluster on chromosome 11 codes for

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synthesis of b-chain of the adult hemoglobin [21]. The b-globin gene cluster spans over 60 Kb of DNA and has three coding blocks (exons) separated by two intervening sequences (introns). In SCD a single mutation substitutes adenine for thymine nucleotide in the sixth codon of the b-globin gene (GAG ®GTG) thereby encoding valine instead of glutamic acid in the sixth position of b-chain resulting in sickle hemoglobin (HbS) formation.

In a normal cell of an adult the 11th chromosome pair contains two normal b-globin genes one inherited from each parent. A person who inherits an abnormal HbS gene from one parent and a normal beta globin gene from the other becomes the harmless carrier state of sickle cell trait or sickle cell heterozygote (AS). Inheritance of abnormal sickle HbS genes from both the parents results in the homozygous state of sickle cell disease(SS) [2], which causes serious health problems leading to early death. A person inheriting one HbS gene and another abnormal b globin gene HbC or thalassaemia represents a double heterozygote and tend to have either HbSC or sickle cell b-thalassaemia. Sickle cell disease means a person is either having sickle cell anemia (the homozygous state, SS) or sickle cell b-thalassaemia (the double heterozygous states of SC) [4]. But many a times the terms sickle cell disease and sickle cell anemia are used interchangeably.

EPIDEMIOLOGY AND HAPLOTYPES

The highest prevalence of HbS gene has been, recorded in tropical Africa. It occurs in lower frequency in Mediterranean basin, Saudi Arabia, USA, India, Latin America and Caribbean Islands[1]. Lehman and Cutbush [5] reported HbS gene in the veddoids residing in the Nilgiris of South India. The prevalence of HbS gene in India and specifically in Orissa has also been reported by Kar 1990. The high incidence has been reported from Indian states like Orissa, Madhya Pradesh and Maharastra and in lesser degrees in states like Andhra Pradesh, Gujarat, Bihar and Kerala.

In Orissa, Nanda [6] reported SCD for the first time in Agharia community. Subsequently, Kar et al. (1987) gave a detailed report on SCD and its distribution in different castes of Western Orissa[7]. The frequency of HbS gene in people of Western Orissa is 15.1%. In a study of 622 patients in our centre the prevalence of sickle cell hemoglobinopathy in various castes were Agharia (29.23%), Kulita (26.41%), Gouda (10.56%) and Scheduled castes (9.86%) (Table 1). The selective distribution of HbS gene in certain geographic areas is thought to be due to resistance of sickle cell traits to falciparum malaria infection giving them advantage of survival [2].

Although SCD is caused by point mutation of beta globin gene in 11th chromosome in the adjacent

Table.1 : Caste wise distribution of sickle cell disease patients at sickle cell clinic, V.S.S. Medical College, Burla

Cast	Number	%	Cast	Number	%
Agaria	166	29.23	Brahmin	6	1.06
Kulita	150	26.41	Sundhi	4	0.70
Harijan	56	9.86	Dhoba	14	2.46
Teli	30	5.28	Mali	2	0.35
Gouda	60	10.56	Sahara	6	1.06
Dumal	24	4.23	ST	6	1.06
Bhulia	08	1.41	Other	88	15.49
Khandayat	02	0.35	**Total**	**622**	**100**

part of the sickle mutation is not identical in all SCD patients. Accordingly five genetic types (haplotype) has been found throughout the world. They are Benin, Bantu, Senegal, Cameroon & Asian. The most common HbS haplotype is the Benin haplotype which is found in Benin and Central West Africa and migrated to North Africa, Greece and Western Saudi Arabia via. slave trade. The second Senegal haplotype is prevalent in Senegal and African West coast. The third haplotype i.e Bantu haplotype is found In Central African Republic. The Asian haplotype probably represents an independent HbS mutation and is found in eastern Saudi Arabia and India [2]. Persons with Asian haplotypes in India and Saudi Arabia have milder course of disease in comparison to that of the African haplotype due to presence of excess fetal hemoglobin in their red blood cells [8].

Haplotype pattern of the SCD patients of Western Orissa has been analysed in our laboratory.

Table 2

Haplotype analysis of 100 patients of SCD by PCR in our centre

Haplotype	Percentage
Asian Indian	85
Asian / Senegal	3
Atypical	12

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Presence of valine instead of glutamic acid in 6th position of b-chain in HbS makes it sticky. Under mild hypoxic condition deoxygenation of HbS leads to polymerisation resulting in HbS polymer formation making the red blood cells less pliable, deformed and sickle shaped. These stiff red cells cannot easily negotiate the capillary beds resulting in blockage of blood flow (Vaso-occlusion) to organs. In addition, abnormality in the shape of red cells and certain immunological factors lead to excess and premature destruction (hemolysis) resulting in anemia and jaundice.

Oxygen deficiency is the most important physiologic determinant of HbS polymerisation, gelation and sickle cell formation. Polymerisation occurs only on deoxygenation. Reoxygenation leads to solubilization of HbS and normalisation of the sickled red cells to normal bioconcave shape. However in the course of sickling and desickling the red cell losses membrane and in course may become an irreversible sickle cell (ISC).

There is positive correlation between the amount of HbS and polymerisation. In sickle cell disease there is virtually no normal adult Hb and almost all is HbS. So there is extensive sickle cell formation. In sickle cell trait on the other hand the amount of HbS is 40% and HbA 60%; therefore, under severe hypoxic condition there is sickling.

Presence of HbA (Adult Hb) and HbF (Fetal Hb) inhibits polymerisation and sickling. However HbC, HbD, HbO Arab readily co-polymerize with HbS leading to sickling. Because HbF decreases sickling, drugs are now being used in sickle cell disease to increase HbF production.

CLINICAL PROBLEMS IN STEADY STATE OF SCD

Anaemia

The lifespan of red blood cell in SCD is decreased from a normal 120 days to 10-12 days. The usual hemoglobin level in the patient is 6-9 gm/dl and reticulocyte count 5-15%. But even with this anemia tissue oxygen delivery is near normal because of hyperdynamic circulation and much lower oxygen affinity of HbS within the red cell. However, due to increased bone marrow activity folic acid demand increases and the metabolic demand of the expanded bone marrow may compete with demand of growth phases leading to impaired growth. Excess hemolysis leads to increased bilirubin synthesis, jaundice and pigment gall stone formation.

The mechanism of hemolysis in SCD is intravascular red cell destruction due to shedding of microfilaments during the process of unsickling. ISC are also subjected to hemolysis because of exposure to high shear rates that occur during exercise. Damage of sickled red cell membrane by macrophage secreted proteases and oxidative damage leads to exposure of i.e., senescent antigens and formation of anti -galactosyl IgG (anti-Gal) antibody which binds upon these sickled blood cell (9). Antibody coating makes these red cells susceptible for excess phagocytosis and immune

mediated hemolysis by macrophages. In a study of 50 cases of sickle cell disorder the titers of anti-Gal IgG was found to be significantly high in SS and AS groups in steady state. The level sharply diminished during crisis probably due mopping up of the antibody on sickle erythrocyte and speedy removal [10].

Vaso occlusion

Vascular occlusion is a major pathologic phenomenon in SCD contributing to different morbidity and mortality in these patients. There are multiple mechanism of vascular occlusion in SCD. These include microvascular occlusion by sickle erythrocytes, vascular intimal hyperplasia, thrombosis or thrombo-embolism, bone marrow or fat embolism and vasospasm [11].

Oxygenated non reversible sickled erythrocytes are generally pliable and readily pass through microvasculature. But deoxygenated irreversible sickle cells which are least dense adhere to the post venular capillary endothelium leading to significant obstruction and ischaemia to the concerned organ. This micro vascular occlusion is dependent on excess gelation of HbS in the capillary due to delay in transit time and red cell dehydration. Reduced blood flow due to increased capillary resistance caused by raised blood viscosity is an important rheological abnormality in these patients. In an investigation conducted by the authors the plasma viscosity in 18 patients of SCD was found to be significantly higher, compared to the control. Higher viscosity is due to increased levels of acute phase reactants like SAA, CRP, and fibrinogen[12]. Leucocytes may also play a role in vaso occlusion of SCD due to increased adhesiveness of sickle cell neutrophils to fibronectin.

Recently, it has been demonstrated that endothelium of the blood vessels is activated in patients of SCD in steady state and during vaso-occlusive crisis. Increased number of activated endothelial cells and endothelial cell adhesion molecules like ICAM-1, VCAM-1 and E- selection have been found in blood of SCD patients. Infection with agents such as Herpes virus and Sendai virus is thought to upregulate the endothelial adhesion molecules and precipitate sickle red cell occlusion of microvasculature and precipitate vaso-occlusive complications [13]. Both microvascular endothelial cells and a subpopulation of sickle reticulocytes have CD36, which binds to thrombospondin secreted by activated platelets. In addition to thrombospondin, high molecular weight Von Willibrand factor makes an important contribution to adhesion [14].

Current evidence indicates that complications related to vascular occlusion like acute painful vaso-occlusive crisis, acute chest syndrome and stroke are leading causes of death in adult patients of SCD. Vascular occlusion is also a major cause of morbidity in SCD via a variety of generally nonfatal complications like aseptic necrosis of bone, chronic renal failure, priapism, leg ulcer and proliferative retinopathy.

Vascular occlusions in cerebral blood vessels lead to stroke and hemiplegia in SCD. This can be recurrent and treatment now focuses on chronic blood transfusion or bone marrow transplantation. Repeated microocclusion of the splenic vasculature by sickled erythrocytes leads to splenic dysfunction at early life. Because of nonfunctioning spleen the incidence of infection with pneumococcus is high which may be life threatening for which early diagnosis and prophylactic pneumococcal vaccination and penicillin prophylactic is helpful in children with SCD. In addition to this, neutrophil dysfunction and defective interleukin-1 production with impaired immunity make these SCD patients more prone to other infections. In a study of 50 cases of SCD presenting with fever, [15] found that various infections were more in these patients compared to control and enteric fever was the leading cause. Due to repeated splenic occlusion splenic infraction and nonpalpable spleen is common in western patients of SCD. But in SCD patients of Western Orissa the spleen is frequently enlarged which may be due to sickle (beta-thalassaemia, chronic malaria, alpha-thalassemia or some unknown factor)[16].

Growth and Development

The growth is usually affected in SCD patients leading to lowered height and weight with delayed sexual development. In a study conducted by the authors on fifty male patients, gonadal function was found to be normal. In addition to physical parameters like height, weight, testicular size, seminal analysis and testicular biopsy, hormonal assay was also done

which revealed that though there was growth retardation in SCD patients the male gonadal function and fertility was near normal [22].

Pregnancy

Pregnancy in sickle cell disease carries increased risk of painful crises and acute chest syndrome in mother. The fetal wastage from abortion, still birth and fetal growth retardation is high in SS women. Various factors that contribute to this adverse outcome are anemia, urinary tract infection, toxaemia of pregnancy and severe vaso-occlusive crisis as found in a study of pregnant mothers with SCD [23].

Infection:

Chronic anemia and acute hemolytic episodes necessitates repeated blood transfusion making these patients susceptible to hepatitis B virus (HBV) infection. In a study on immunological markers of HBV infection in 43 cases of SCD it was found that 28% of SCD patients were infected with HBV whereas only 4% controls were positive for HBV infection[24]. In addition to the above problems, chronic renal failure, genitourinary problem, proliferate retinopathy, chronic leg ulcers are also additional morbidities found in sickle cell disease

Chronic organ damage:

CNS: Patients of SCD are prone for cerebral vaso-occlusion and ischemic infarction leading to stroke. Some of them are prone for intra-cerebral hemorrhage.

Renal: Glomerulosclerosis and chronic renal failure is an important complication in SCD . Chronic renal failure is the cause of death in 10% of SCD patients.

Hepatobiliary disease: Patients with SCD are usually liable for hepato-biliary disease especially viral hepatitis. Chronic hepatic fibrosis and portal hypertension are late complications. Cholelithiasis due to pigment stones is a common problem in these patients. Majority of the gallstones are asymptomatic.

Pulmonary: Acute chest syndrome is an acute complication as a part of systemic vaso-occlusion and can be fatal. Chronic pulmonary hypertension is an important complication and develops in the later part of the clinical course.

Osteonecrosis: Osteonecrosis of femoral and humeral head due to chronic ischemia is found in around 6% of our patients. It is an important cause of limping and pain in hip joints. Besides, osteomyelitis is an important complication of SCD.

Crisis:

These are acute life threatening complications which develop in the clinical course of SCD. The various types are:

1. Painful (Vaso occlusive) crisis
2. Sequestration crisis.
3. Aplastic crisis
4. Megaloblastic crisis
5. Hemolytic crisis

Painful (Vaso occlusive) crisis

In adolescence and early adult life the most severe problem is pain crisis or vaso-occlusive crisis characterized by severe pain around the knee, elbow, shoulder joints, rib, spine and pelvis. The pediatric counterpart of painful crisis is hand-foot syndrome (dactylitis) which affects the small bones of hand and feet. It usually resolves completely although superimposed infection and may cause premature epiphyseal fusion and deformity [2].

Acute chest syndrome is caused by a spectrum of pathology including infection, infarction, pulmonary sequestration and fat embolism. The SCD patient develops acute pain in chest associated with breathlessness, cough, fever and pulmonary infiltrate on radiology and is a major cause of morbidity and mortality. Recurrent episodes of acute chest syndrome may result in pulmonary fibrosis and chronic sickle lung disease.

Sequestration crisis

In children of SCD acute splenic sequestration may result in pooling of blood in spleen with life threatening fall in hemoglobin requiring transfusion. Prophylactic splenectomy is recommended after two such attacks [2]. It is called as sequestration crisis

Aplastic Crisis:

SCD patients may develop anemia rapidly following parvovirus infection and destruction of erythrocyte precursor. There is rapid fait of hemoglobin (1 gm / dl /day) with reticulocytopenia

and this condition is called aplastic crisis. Supportive treatment with blood transfusion leads to complete recovery of bone marrow unction in 7-10 days [2].

CLINICAL SEVERITY AND NATURAL HISTORY:

The clinical severity of SCD depends on various factors like the type of sickle cell disease (SS, SC, S Thai), intracellular fetal hemoglobin concentration, beta-globin haplotype and presence of alpha-thalassemia. Patients of SCD in our region in general have a milder clinical course similar to the Saudi Arabian form which may be attributed to the milder nature of this Asian haplotype, raised levels of fetal hemoglobin and frequent a-thalassemia interaction. However, the clinical manifestations of the disease are extremely variable ranging from completely asymptomatic cases to life threatening complications and sudden death [16].

The highest mortality of SCD occurs in the first year of life especially in later half. The major cause of mortality in this age group includes splenic sequestration, pneumococcal septicemia, aplastic crisis and acute chest syndrome. In adult life, painful vaso-occlusive crisis increase the morbidity and patients may die of acute chest syndrome. Though the frequency of painful crisis decreases over time, after 40 years SCD patients may die due to chronic renal failure and progressive pulmonary fibrosis. In reproductive years female patients may die due to pregnancy related complications [2].

DIAGNOSIS:

1. **Sickling slide Test :** It is a simple laboratory test which can be done by taking a drop of blood and sealing with paraffin, and examining the slide under light microscope after 24 hours for sickled red cells. Sickling test is a useful screening procedure and will be positive in sickle cell carrier (AS), sickle cell anemia (SS) and the double heterozygote states like SC, SE and S-Thal. So further differentiation of different genotypes can be done by Hb electrophoresis.
2. **Solubility Test:** Basing upon on the relative solubility property of sickle and normal hemoglobin [17] in solutions of high molarity phosphate buffers, lysing and reducing agents. This test is very simple and can be even done at field for large scale on the spot screening

Table 3. Clinical severity and Diagnostic Testing of different sickle Syndromes (Lane, 1996)

Syndrome	*Clinical Feature*	*Hemoglobin type and percentage*				
		HbA	*HbA_2*	*HbS*	*HbF*	*HbC*
Normal (AA)	Nil	95-98	<3.5	0	2	0
Sickle Cell Trait (AS)	Nil Except special situation	50-60	<3.5	35-45	2	0
Sickle Cell Anaemia (SS)	Sever symptoms	0	<3.5	80-95	2-20	0
Sickle cell beta$^+$ thalalssemia (S – thal)	Mild	5-30	3.5-6.0	65-90	2-10	0
Sickle HbC diseases (SC)	Mild	0	-	45-50	15	45-50

without the help of trained technician and microscope. Results can be obtained in 5 minutes.

3. **Hb Electrophoresis:** Because of different electrical charge and mobility the different hemoglobin can be separated by Agarose gel electrophoresis in acidic/ alkaline medium. Since the establishment of Sickle Cell clinic at this institute this is routinely being done in our centre.

High Performance Liquid Chromatography (HPLC): This method is recommended for simultaneous detection & quantification of hemoglobin fractions. Since the systems are automated, operation of the analyzer is simple, but interpretation of chromatogram requires expertise. This is useful for large scale screening programs. The exact nature and concentration of common abnormal & normal hemoglobin HbA, F, E, D, and S can be quantified by this method (Table 3).

MANAGEMENT

The clinical course of sickle cell disease runs into two phases that of steady slale and crisis. The management of this disease can therefore be divided into three strategies namely

1. Management of steady state,
2. Management of crisis
3. Newer frontiers.

1. MANAGEMENT OF STEADY STATE

➢ **Anaemia:** Patients of sickle cell anemia are chronically anemic. However due to extreme physiological adjustment they have adequate oxygen delivery to tissues and hemoglobin level of 5g or more is adequate in these patients. It has been a common mistake for unnecessary transfusion in these patients. After ruling out other possible cause like iron deficiency and worm infection they can be supplemented with folic acid 5mg daily.

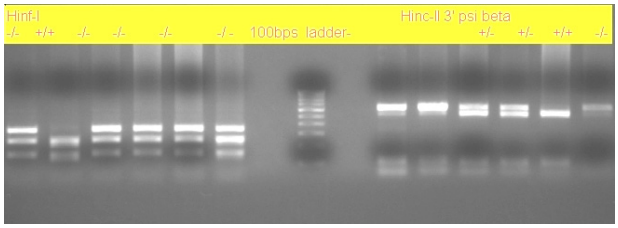
➢ **Infection:**

Pneumococcal: These patients are prone for a number of infections due to various reasons. Because of nonfunctioning spleen the incidence of infection with pneumococcus is high which may be life threatening for which early diagnosis and prophylactive pneumococcal vaccination and penicillin prophylactic is helpful in children with SCD.

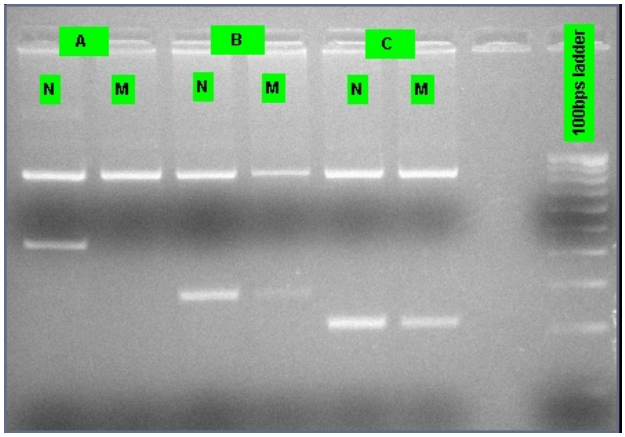
***Salmonella*:** In addition to this, neutrophil dysfunction and defective inlerleuktn 1 production with impaired

Patients diagnosed by PCR technique at VSS Medical College, Burla

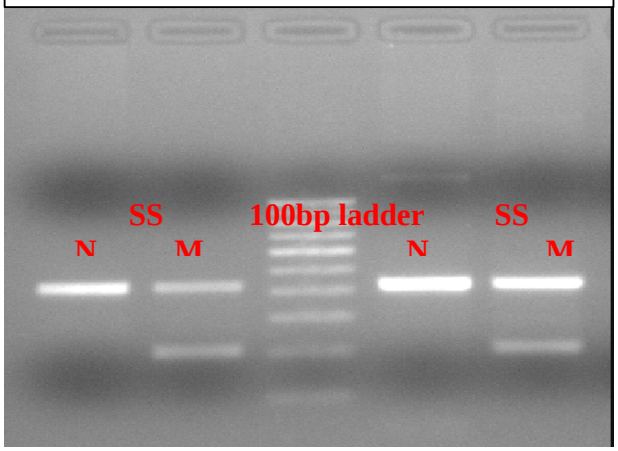
Hinf I 3'B (-/-, +/+, -/-) and HincII 3' ψB (+/-, +/+, -/-) digestion bands run with 100bp ladder



Thalassemia detection by ARMS PCR: Sample A: Homozygous (normal) IVS 1-1nt G-T , sample B: Heterozygous IVS1-5nt G-C, Sample C: Hetetrozygous cd 8/9 +G

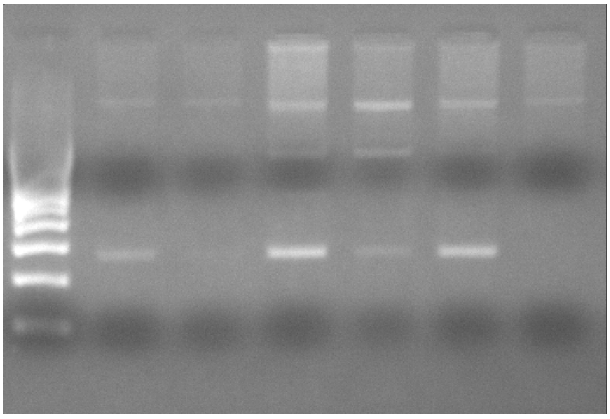


ARMS PCR electrophoresis for sickle cell diagnosis control band ~400bp ; Normal/ Mutated band ~200bp



Source: Sickle Cell Research Project

HbE detection by ARMS PCR: Sample A & C: HbA Homozygous Normal, Sample B: HbE heterozygous.



immunity make these SCD patients more prone to other infections. In a study of 50 cases of SCD presenting with fever, we found that various infections were more in these patients compared to control and enteric fever was the leading cause (Patel et al 1994).

***Hepatitis*:** Patients with SCA are usually liable to viral hepatitis. Chronic anemia and acute hemolylic episodes necessitates repeated blood transfusion making these patients susceptible to hepatitis B virus (HBV) infection. In a study on immunological markers of HBV infection in 43 cases of SCA, we found that 28% of SCA patients were infected wilh HBV whereas only 4% controls were positive for HBV infection (Panda et al l997). So patients of sickle cell disease should be vaccinated early wilh hepatitis li vaccine.

***Malaria*:** Contrary to earlier belief we found that persons of sickle cell trait and sickle cell disease are prone to falciparum malaria and the mortality is high compared to patients without sickle cell anemia. So in endemic areas these patients may be considered for chloroquine prophylaxis (Patel et al, 2000).

2. MANAGEMENT OF CRISIS:

➢ **Vaso occlusive crisis (VOC):** Patients of sickle cell anemia suffer from acute life threatening condition called crisis. The different form of crisis are vaso-occlusive (painful) crisis, sequestration crisis, acute chest syndrome and aplastic crisis. In mild form acute painful crisis the patient can be managed by oral analgesics and rest. Severe form of crisis needs hospitalization followed by injectable analgesics and intravenous fluids. Recently US FDA has approved the use of hydroxyurea in patients of sickle cell anemia with repeated episodes of painful crisis. We are undertaking an clinical trial of hydroxyurea in our center and the result is awaited.

Acute chest syndrome is a form of painful crisis characterized by chest pain, breathlessness and mild fever. This is caused mostly by pulmonary vascular micro-occlusion and infarction which needs immediate hospitalization and treatment with ceftrioxane and O_2 inhalation.

➢ **Sequestration crisis:** Sequestration crisis is a medical emergency found in younger patients of sickle cell anemia and characterized by rapidly enlarging spleen and hypovolumia clue to splenic pooling of blood. Patient should be treated immediately with blood transfusion and fluid replacement. Parents of these patients can be educated for splenic palpation at home and report to the doctor on suspicion of splenic enlargement.

➢ **Aplastic crisis:** Aplastic crisis is caused by acute bone marrow dysfunction caused by parvovirus infection leading to development of anemia and thrombocytopenia. If patient is severely anemic than blood transfusion may be necessary. Currently a vaccine is available in western countries for prophylaxis.

Above all patients of sickle cell anemia should be encouraged to take a lot of water and avoid unaccustomed exercise.

3. NEWER FRONTIERS IN TREATMENT:

➢ **Induction of HbF:** The observation that Intra-cellular fetal Hb decreases the sickling process and the benign course of SCD patient of Saudi Arabia- Indian genotype associated with high fetal Hb concentration prompted scientists to search for drugs which could stimulate increased HbF production. 5-azacytidine, an anticancer drug was the first one to be trialed, was used initially but due to its myelotoxicity was abandoned. Subsequently hydroxyurea was found to be suitable for clinical use and is the only drug approved by USFDA for ameliorating the severity of Sickle Cell Disease. The mechanism of hydroxyurea is to increase the level of fetal hemoglobin which is beneficial in sickle cell disease patients.

In a double-blind, placebo-controlled trial of hydroxyurea conducted in USA in 299 adults with sickle cell anemia presenting with at least three episodes of pain in the year preceding the study it was found that hydroxyurea reduced the frequency of episodes of pain, the acute chest syndrome, and hospitalization and the need for blood transfusion(18)

Hydroxyurea has been found to be safe in children and infants undergoing treatment for 1 – 2 years. However the patients should be monitored closely. The most commonly observed toxicities were those related to its myelosuppressive effects. These toxicities were transient and resolved quickly once HU was discontinued (19). A recent update of the Multicenter Study of Hydroxyurea (MSH) showed that at 9 years' follow-up, the mortality rate among patients who take HU is reduced 40% compared with the rate among patients who do not take the drug (18). There was no toxicity even with nine years of continuous treatment with hydroxyurea.

At present we are undertaking a clinical trial of Hydroxyurea in patients of Sickle Cell Disease in our centre. Fifty patients have already been enrolled. The preliminary results are encouraging.

➢ **Bone Marrow transplantation :** In selected patients of SCD with severe systemic

symptoms and unfavorable genotype bone marrow transplantation can be curative for SCD. Recently Walter et al (20) have successfully undertaken allogenic bone marrow transplantation in SCD children with 4 year survival of 73%. However this procedure is costly, prone to failures and is not yet been tried in India.

- **Gene Therapy:** The most suitable treatment of sickle cell disease would be the correction of the genetic defect by gene therapy. Here the abnormal gene of the red cell precursor in patients is deleted followed by insertion of normal b-globin gene by retroviral particles. Gene therapy is still in its infancy with respect to sickle cell disease and the scientific community is eagerly waiting for it to be a reality in future.

PREVENTION:

Sickle cell disease is a disease with multi systemic problem with shortened life span. So it would be pertinent to take preventive measures for it. At selected centres in India this disease can be diagnosed in unborn fetus during pregnancy (prenatal diagnosis). However this has not been possible to apply this technique in mass scale. So the society in general and the high risk castes in particular should be made aware of the problem and appropriate genetic and marriage counseling should be done. This can be done by:

A) Mass education

B) Screening - Population

Neonatal

C) Supportive genetic counseling

In this regard we are conducting mass awareness camps in remote areas of Western Orissa. In the health camps we collect blood samples from patients for sickle cell screening, providing necessary medical consultation and generate awareness through counselling, lectures & mass communication media.

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ACUTE RENAL FAILURE: AN OVERVIEW

K N Padhiary*, Sriprasad Mohanty**

Definition: Acute renal failure (ARF) is the deterioration of renal function within hours to days characterized by retention of nitrogenous waste products and disturbance of water, electrolyte and acid base homeostasis.

Though the hallmark of ARF is reduced Glomerular filtration rate (GFR) manifesting as oliguria but it can exist with adequate urine output, the so called high output ARF/ non-oliguric ARF. At times renal failure may be suspected from signs and symptoms of uraemia; but in majority of the cases it is asymptomatic at least in the early stages. If urine output is not measured correctly or if it is a high output renal failure it can only be diagnosed by measuring the blood level of nitrogenous waste products (urea and creatinine).

Acute renal failure is a potentially fatal condition, but if treated properly it is a curable state without any residual damage to the structure or function of the kidney.

Aetiology:

There is a long list of causes of ARF in most of the text books. In stead of quoting them in that way we have tried to group them as commonly observed and relatively uncommon causes. Readers are requested not to interpret that the list given below is scientifically complete.

(A) Common Causes

(i) Hypovolemic conditions
- Diarrhoea and vomiting
- Acute blood loss
- Burn(plasma loss)

(ii) Severe Falciparum malaria

(iii) Snake bite(Haemotoxic)

(iv) Acute glomerulonephritis

(v) Crush injury

(vi) Septicemic states(irrespective of the cause)

(vii) Toxemia of Pregnancy and abruptio placentae

(viii) Intravascular haemolysis of various causes

(ix) Hepatorenal syndrome

(x) DIC

(B) Uncommon Causes
- Obstructive uropathies
- Consumption of nephrotoxic drugs and toxins
- Anaphylaxis
- Collagen diseases like SLE, rheumatoid arthritis, scleroderma
- Haemolytic uraemic syndrome
- Urate nephropathy following cancer chemotherapy
- Use of radio contrast dyes
- Multiple myeloma
- Fish gall bladder
- Bilateral renal vein thrombosis

Pathophysiology :

Prerenal form ARF :

Fall in the systemic pressure leads to fall in GFR. In any state of profound hypotension body homeostasis tries to maintain circulation to vital organs like brain, heart and lungs. Though blood flow to kidney is also maintained for certain time, but ultimately renal blood flow suffers, thereby initiating

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the process of ARF. If perfusion pressure is quickly established renal failure is prevented. When the RBF falls there are several compensatory mechanisms try to prevent ARF. AngiotensinII, arginine vasopressin, norepinephrine act in a coordinated manner. They together cause selective vaso-constriction of non-essential parts and selective constriction of efferent arteriole. This tries to main intraglomerular pressure and GFR. Prostaglandins and prostacyclines are also synthesized. They cause selective dilatation of afferent arteriole. This also increases intraglomerular pressure. When all these prove inadequate ARF sets in. One should be careful in using cyclooxygenase inhibitors(NSAIDs) and ACE inhibitors at this point of time as they are likely to hasten the process of ARF. This form of ARF is the most commonly encountered in our set up.

Renal form of ARF:

This can be divided into 4 groups. These ares-

(a) Diseases of large renal vessels
(b) Diseases of renal microcirculation and glomerulus
(c) Ischaemic and nephrotoxic ARF
(d) Tubulointerstitial diseases

Prerenal ARF and ischaemic ARF are part of the same process. The later arsing out of the former. Most of the acute renal failure is due to ischaemia. This ischaemic insult usually results in acute tubular necrosis (ATN). So ATN and ARF are often used interchanged. Transition of ischaemia to ischaemic intrinsic ARF is an important step. Maintenance of fluid balance can avert the progression. But the contrary is also important. At this stage patients should not be infused overzealously. Fluid administration should be stopped once hydration is corrected. We encounter many such overhydrated cases due to continuation of fluid(oral/ parenteral) beyond this point. At times patients present with acute pulmonary oedema.

The couse of ischaemic ARF is typically charactersised by three phases. The phase of initiation, the phase of maintenance and the phase of recovery.

Phase of Initiation: This phase lasts for hours to days. During this phase GFR is reduced, the renal tubules are blocked by the denuded epithelium, there is back leak of tubular fluid into the interstitium which increases the interstitial pressure and further compromises the renal function.

Phase of maintenance: this phase typically lasts for one to two weeks. The urine output is lowest during this period. Urination does not improve despite correction of systemic haemodynamics.

Phase of recovery: This is characterized by regeneration of tubular epithelial cells. Often total recovery occurs following a phase of diuresis. This is due to elimination of retained salt and water, improper function of regenerating epithelial cells, continued use of diuretics. Maintenance of water and electrolyte, Acid base balance is very important in this period. The patient should not be declared cured simply from adequate urine output. The patient might be still in a state of high output renal failure.

Post renal form of ARF:

This is relatively uncommon; amounts to 5% of the total causes of ARF. Bladder neck obstruction (prostatic neoplasm, stricture, use of anticholinergic drugs, neurogenic bladder etc) is the main cause. Other causes include accidental ligation of bilateral ureter. Though the palpation of a full bladder is a common bed side method to know these causes, but at times an ultrasonographic examination may be required in some cases.

If the mechanism of ARF is due to ATN; recovery is usual with fluid, electrolyte balance and diuretics. But the situation is not so simple or favourable. Aetilological agents affect the kidney variably. ATN may be associated with acute cortical necrosis (ACN) or acute glumerulonephritis (AGN). In such cases the outcome need not be satisfactory.

These are the gross pathogenesis of ARF. However few other factors operate in specific situations as described below.

(a) In diarrhoea- There is mostly acute tubular necrosis; rarely there can be acute cortical necrosis. Fibrin thrombi in the glomerulus is seen in if there is a component of haemolytic uraemic syndrome.

(b) In Malaria- Renal failure in malaria results from a combination of intravascular haemolysis, heavy parasitemia causing hyperviscousity and alteration in renal microcirculation.

(c) In intravascular haemolysis- Vasoconstrictors released by he damaged erythrocytes during the episode of haemolysis, intra-tubular obstruction by the tubular casts, concomitant dehydration and acidosis lead to development of ATN.

(d) In Snake bite- Pathogenetic features leading to ARF following snake bite include DIC, intravascular haemolysis, haemorrhage, hypotension, and direct nephrotoxic effect of the venom.

(e) In leptospirosis- The organisms get entry into the blood stream, traverse the glomerular circulation and enter the renal tubular cells. Bacterial enzymes metabolites, endotoxins, compliment medicated damage or vasculopathy could be responsible for renal failure.

(f) In obstetrical situations- ARF in pregnancy shows a bimodal distribution. One peak is seen around 7-8 weeks of gestation and the other peak is at 32-36 weeks of gestation. ARF in early pregnancy is associated with septic abortion. In late pregnancy the common causes of ARF are abruptio placentae, paeripartum and post partum haemorrhage and eclampsia and puerperal sepsis. Renal histology usually shows acute tubular necrosis. However a significantly high incidence of bilateral diffuse and patchy acute cortical necrosis is also seen. Prognosis is not favourable in the later conditions.

(g) In renal cortical necrosis- Bilateral renal cortical necrosis is the most catastrophic form of ARF. The striking features of the condition are- a prolonged period of oliguria and failure of renal function to recover completely. It has been reported to occur following a variety of conditions including haemolytic uraemic syndrome, graft rejection, septicemia, intravascular haemolysis, acute pancreatitis etc. However it most commonly occurs as a complication of pregnancy and snake bite.

Clinical Features:

The hallmark of ARF is of course oliguria. If required it must be established by indwelling catheterization. However a normal urine output does not exclude ARF. Hence it must be substantiated by biochemical parameters. The symptoms and the signs of the underlying condition will be there. Features of acidosis might be observed as well as features of overhydration could be noticed. A neglected case might present in a state of uraemic encephalopathy and with other complications of uraemia.

Diagnosis: Diagnosis of ARF is not difficult. Documentation of reduced urinary output, detail urine analysis, measurement of serum urea and

creatinine are enough to establish the diagnosis. But other parameters are also to be recorded for proper management, particularly serum sodium and potassium. ECG may be more easily accessible investigation to know the serum potassium status. It should always be kept in mind that some cases might be truly acute over chronic renal failure. These cases are also to be evaluated and treated like ARF. So the detail clinical set up which led to the present state will help. An abdominal ultrasound may help to settle the issue. This test will also help to know if there is any obstructive element or not. Tests to know the underlying condition should always be made as the outcome of treatment invariably depends on the cause.

Management:

Management of ARF can be discussed under three broad headings; conservative, dialysis and treatment of the underlying condition.

Conservative: This means without dialysis. Treatment will be different in oliguric phase and polyuric phase.

In oliguric phase attempt should be made to increase the urine output. If the patient is still volume depleted he should be rehydrated with suitable fluid/blood/plasma as per requirement. Without correction of intravascular volume no diuretic should be administered. If the patient is already hydrated or overhydrated no time should be wasted and parenteral potent diuretics like frusemide/torsemide should be given. It should be given in high dose. In the mean time patient's water and electrolyte status should be observed. Amount of water to be consumed should be output+ the insensible water loss. If there is vomiting or loose stool more amount of water can be given proportionate to the loss. The insensible loss in our country may be quite high (may be more than 1liter) particularly in summer season. This practical point is to be remembered for administering fluid. It may be difficult to give enough calories with limited water. If enough calories are not given it will encourage lypolysis and ketone body production; adding to the existing acidosis. In such situation enteral feeding can give more calories than parenteral. So whenever possible oral/nasogastric feeding should be maintained. Sodium and potassium intake, particularly the latter should be restricted.

In the polyuric phase intake and output should be measured correctly otherwise the patient may get dehydrated. The patient carries the risk of hypokalemia and hyponatremia. So no restriction on intake of water, sodium and potassium is required. Sodium and potassium can either be given in the form of sodium chloride and potassium chloride solution or simply the ORS can be given. However all the time the corresponding parameter is required to be measured to encourage or restrict intake. At times patient goes to a state of non-oliguric renal failure. Urine output is more than 500ml, but not enough to wash out the nitrogenous wastes. These patients should be taken to a polyuric stage (urine output>3liters) either by giving more fluid or by giving more diuretics or addition of another diuretic. These patients usually do not go to a fluid overload state. At times it may be required to increase urine output to 5liters or more. Accordingly intake must be maintained. As long as the urea and creatinine has not come to normal, patients must be on a protein restricted diet, whether he is in oliguric or polyuric phase. Just seeing improved urinary output should not be declared as cured; must have documentary evidence of normalization of urea and creatinine. Once urea and creatinine comes to normal, the patient should be slightly kept on negative fluid balance. By this time most of the patients are

polyuric, requiring a lot of water. By restricting water (usually75-80% of out put) the renal concentrating power is regained. .

Some patients may require correction of acidosis by administration of sodium bicarbonate injection. Attempt should be made to maintain pH above 7.2.

Dialysis: The indication of dialysis is known to all. High potassium level and pulmonary oedema require emergency dialysis. Besides them a creatinine level more than 8mg%, uraemic encephalopathy, uraemic pericarditis are some other indications of dialysis. If there is a need for dialysis it should be given without delay. Haemodialysis or peritoneal dialysis can be done as per suitability. Once patient goes to ployuric phase rarely dialysis is needed. It is to be remembered that after dialysis the urine output may drop in the first 24 hours.

Treatment of underlying cause : While the patient is being treated for ARF active management for the underlying condition should be continued as that decides the final outcome. While treating attempt should be made to avoid nephrotoxic drugs, avoid fluid overload, and proper dose adjustment of the drugs used

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CHIKUNGUNYA – REVIEW

L.K. Meher

INTRODUCTION :

Chikungunya is a viral disease transmitted by Aedes mosquito. It is characterized by abrupt onset of high fever, myalgia, headache, skin rash and incapacitating arthralgia. The disease was first described in 1955 by Marion Robinson and WHR Lumsden following an outbreak in 1952 on the Makonde Plateau, along the border between Tanganyika and Mozambique[1,2]. The term "Chikungunya" is derived from the Makonde root verb Kungunyala, meaning "to become contorted" or more specifically as "that which bends up". This refers to the stooped posture adopted by the patient as a result of arthritis. It is a self limiting disease and rarely fatal. The virus is endemic in Africa, India and South East Asia.

AETIOLOGY :

Virus :

Chikungunya virus (CHIKV) is an arbovirus belonging to the genus Alphavirus, in the family Togaviridae. It has a single stranded RNA genome, a 60-70nm diameter capsid and a phospholipid envelope. Genetic analysis of Chikungunya virus have revealed three distinct lineages: Southern and East African strain, West African strain and Asian strain.

Vector :

In Southeast Asia the main vector for this disease is Aedes aegypti which breeds mainly in stored fresh water. Recently the Pasteur Institute of Paris has claimed that the virus has suffered a mutation that enables it to be transmitted by Aedes albopictus (Tiger mosquito). A large range of Aedes species (A furcifer, A vittatus, A fulgens, A luteocephalus, A dalzieli, A vigilax) also transmit the virus in Africa.

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Reservoirs :

Human beings serve as the Chikungunya virus reservoir during epidemic periods. Outside these periods the main reservoirs are monkeys, rodents, birds and other unidentified vertebrates.

EPIDEMIOLOGY :

As with all arboviruses, Chikungunya virus outbreaks begin during the rainy season when vector density peaks. This disease can occur in both epidemic and endemic form. The endemic form appears to affect the rural African, but the epidemic form of virus tends to affect the urban Asian population.

Since the first recorded Chikungunya epidemic which occurred in Tanzania in 1952, human Chikungunya virus infection has been documented in Burma, Thailand, Cambodia, Vietnam, India, SriLanka and Philippines. Asia reported its first outbreak of Chikungunya virus in Thailand in 1958. In 2001-2003, CHIKV re-emerged in Java, Indonesia, after a gap of 20 years.

The first reported outbreak of Chikungunya in India was in Calcutta in 1963[3]. It was followed by epidemics in Chennai, Pondichery and Vellore in 1964. From February 2006 to October 10th, 2006, the WHO regional office for South East Asia and National Vector Borne Disease Control Programme of India reported 151 districts located in ten states/ provinces of India had been hit by Chikungunya fever. About 1.36 million suspected cases have been reported in South India. Andhra Pradesh was the first Indian province to report a suspected case in December 2005, and is also one of the worst affected state[4]. Other states like Tamil Nadu, Karnataka, Gujrat, Madhya Pradesh, Orissa are also under the onslaught of infection since 2006. The recent outbreak in India are caused by Central/East African genotype of Chikungunya virus[5].

CLINICAL FEATURES :

The incubation period is 1-12 days with an average of 2-4 days. Clinical onset is abrupt with high fever, headache, back pain, myalgia, conjunctival suffusion, mild photophobia, nausea, severe joint pain (arthralgia or arthritis) and skin rash. Fever typically lasts a few days to couple of weeks, though it usually lasts for 2 to 3 days. However extreme degree of prostration may last for 7-10 days.

Arthralgia/ arthritis:

Arthralgia / arthritis appears to affect 73-80% of patients with seorologically confirmed chikungunya virus infection and rarely occurs in children. Joints of the extremities like knee, ankle, wrist, interphalangeal joints are affected. The underlying mechanism is unknown. Joint pain may last for weeks to months. It persists for 4 months in about 33%, 20 months in 15% and 3-5 years in 10% of cases[6,7]. Radiological findings are normal and biological markers of inflammation are normal or moderately elevated. Persistent joint pain for several months or years appear to be more common in patient with HLA-B-27.

Dermatological Manifestation :

Skin involvement occurs in about 40-50% of cases. The dermatological manifestation observed in a recent outbreak in Karnataka were maculopopular rash on the thorax, blotchy nasal erythema, freckle like pigmentation over centrofacial area, lichenoid erruption and hyperpigmentation in photodistributed areas, multiple aphthous like ulcers over scrotum, crural areas and axilla, multiple ecchymotic spots in children, vesicobullous lesions in infants and subungual haemorrhage.

Ocular Involvement :

Ocular manifestations are rare, but various manifestations reported are photophobia, retrobulbar orbital pain and conjunctivitis. The various types of ocular involvement reported in an epidemic outbreak from Tamil Nadu were granulomatous and non-granulomatous anterior uveitis, optic neuritis, retrobulbar neuritis, keratitis, bilateral neuroretinitis and multifocal choroiditis with cystoid macular oedema[8]. Conjunctivitis was not noted in that series and ocular symptoms occurred after a mean of 33.2 days.

Other Rare Manifestations :

Neurological complications such as meningoencephalitis were reported in a few patients both during the first Indian outbreak in 1973 and during the recent Indian outbreak[4]. One case of acute myocarditis has also been reported recently from France[9]. Four cases with haematuria and proteinuria have been reported from Delhi[10]. It is not a life threatening disease, but Stephen Higgs have reported about 155 deaths in the Reunion outbreak which might have been directly or indirectly caused by the disease[11].

Chikungunya infection in pregnancy and newborn babies.

There have been cases of materno-fetal transmission of Chikungunya virus. There is a 48 percent risk of infection at birth if the virus is present in the mother's blood. Such an infection in the newborn is rarely serious and they recover quickly. The possible risk of embryopathy, and late sequelae are unknown and prospective follow up of these Chikungunya virus babies is therefore warranted.

INVESTIGATIONS :

1. **Hematological :** Few patients develop leukopenia and mild thrombocytopenia.
2. **Biological Diagnosis :** There are three main laboratory tests for diagnosis.
   - *i)* ***Virus Isolation :*** It is a definite test, but rarely performed, as it is difficult. Two to five ml of blood is collected in the first week of illness in commercial heparinised tube and transmitted on ice to the lab. The CHIKV produce cytopathic effect in a variety of cell lines including BHK-21, HeLa and Vero cells. The result takes 1-2 weeks.
   - *ii)* ***RT-PCR :*** It is useful during the initial viraemic phase (day 0 to 7). Recently RT-PCR technique for diagnosis of CHIKV has been developed using nested primer pairs amplifying specific amount of 3 structural gene regions

capsid (C), Envelop E-2 and part of Envelop E1. PCR result can be available within 1-2 days.

iii) ***Serological diagnosis :*** It can be done by demonstration of 4 fold increase in antibody titre in acute and convalescent sera or demonstration of IgM antibody specific CHIKV. A commonly used test is IgM antibody by capture enzyme linked immunosorbent assay (MAC-ELISA). Result of MAC-ELISA can be available within 2-3 days. Cross reaction with other viruses such as O'nyong-nyong and Semliki Forest virus can occur. However infection by the latter viruses are rare, but if further confirmation is required, it can be done by neutralization test and haemagglutination inhibition assay (HIA). The IgM antibody is detectable after an average of 2 days and persists for several weeks to 3 months. IgG is detected in convalescent samples and persists for years.

TREATMENT :

There is currently no effective antiviral treatment for Chikungunya. Synergistic antiviral effect was reported between interferon alfa and ribavirin on CHIKV in vitro. Treatment is symptomatic in the form of rest , nosteroidal anti-inflammatory drugs and paracetamol for relief of fever and arthralgia. Aspirin should be avoided. Chloroquin phosphate (250 mg/ day) has been tried in the treatment of unresolved arthralgia with promising result[12], but further reports of double blind controlled clinical trials are necessary to prove its efficacy.

Pending vaccine development, the only effective preventive measures consist of individual protection against mosquito bites and vector control. Surveillance is also important for early identification of outbreaks. Strengthening public health system in India is the need of the hour.

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VIRAL ENCEPHALITIS

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ABSTRACT

Virus encephalitis is a clinicopathological syndrome with world wide prevalence. The common viruses causing encephalitis in India are Japanese Encephalitis and HSV encephalitis. The diagnosis of Japanese encephalitis made on the site of neurological affection detected by clinical, imaging and EEG studies. Treatment is mostly supportive but effect of interferon-á is still under clinical trial. The diagnosis of HSV encephalitis can be made from CSF-PCR, MRI and EEG studies and specific therapy with acyclovir is effective in a good number of cases if started early. In a patient of suspected encephalitis acyclovir should be started empirically pending confirmation of diagnosis.

INTRODUCTION

It is a clinico-pathological syndrome with world wide prevalence, but specific virus infections are more common in different geographical regions. Although they may present with diverse clinical picture, prognosis and sequelae, the basic clinical presentation is essentially unified. The infectious process and associated inflammatory response involves the brain parenchyma. There may be associated inflammation of meninges (meningo-encephalitis), spinal cord (encephalomyelitis) and nerve roots (encephalo-myeloradiculitis).

AETIOLOGY : - In the United States, there are 20,000 reported cases per year. Hundreds of viruses are capable of causing encephalitis, although a limited subset is responsible for most cases, in which specific cause is identified. The common viruses causing encephalitis are Arbovirus, Enterovirus and HSV-1 virus. The less common are CMV, EBV,HIV and Mumps and the rare viruses causing encephalitis are Adenovirus, influenza , hepatitis C, LCMV, rubella, rabies and rota- virus. The common acute viral encephalitis in Southeast Asia and Indian sub-continent comprises – Japanese B encephalitis, Herpes Simplex virus, Rabies, Mumps, measles, Dengue, KFD and Enterovirus encephalitis.

CLINICAL FEATURES : - Most of the patients present with acute febrile illness with myalgia, headache, vomiting and bodiache. They have confusion, behavioral abnormality, and altered level of consciousness starting from mild lethargy to deep coma. Patient may have hallucinations, agitation, personality change, behavioral disorder and at times psychotic state. Meningeal involvement may lead to signs of meningitis. Focal or generalized seizures occur frequently in severe encephalitis. Focal neurological signs may be seen in some cases in the form of aphasia, ataxia, hemiparesis, involuntary movements, cranial nerve deficits (III, IV, VI & VII), hypothalamic involvement may lead to hyperglycemia, hyponatremia and poikilothermia. It is very difficult to identify the virus from clinical grounds.

LABORATORY DIAGNOSIS :-

CSF examination – should be done in all patients. The findings are lymphocytic pleocytosis (> 5cells /μ l), a mildly elevated protein concentration and normal glucose. RBC (>500/μ l) may be found in hemorrhagic encephalitis seen in HSV.

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CSF PCR – It is the primary diagnostic test for HSV, CMV, EBV, VZV and enterovirus infection. In HSV encephalitis, this test has 98% sensitivity and 94% specificity. It becomes positive after 72 hours of onset of illness and continues up to one week of antiviral therapy. For enteroviruses, the specificity and sensitivity is > 95%. For EBV and VZV viruses CSF PCR has not been established. CSF PCR has no role in Japanese B encephalitis.

Serological Studies – It remains a crucial tool for diagnosis of Arbovirus infection. Particularly in patients of Japanese Encephalitis, a four fold rise of IgM antibody between acute phase and convalescence phase helps the diagnosis. But this will be of no value for treatment of acutely ill patients.

Radiology and EEG -

HSV encephalitis – (1) T_2 weighted MRI images show areas of increased signal intensity in the fronto-temporal, cingulate or insular region of the brain in 90% of cases.

(2) Contrast enhanced CT scan shows temporo-parietal areas of low absorption with mass effect. It is less sensitive than MRI.

(3) EEG shows periodic focal temporal lobe spikes in a background of slow or low amplitude activity in >90% cases.

Japanese Encephalitis – (1) MRI typically demonstrates more extensive lesions (high signal density on T_2 weighted images) of the thalamus, cerebral hemispheres and cerebellum. Thalamic lesions of mixed density may also be seen on the T_1 & T_2 weighted images suggesting hemorrhage.

(2) In about 50% of patients, CT scan shows bilateral non-enhancing low density areas in the one or more of the thalamus, basal ganglia, midbrain, pons and medulla.

(3) EEG shows theta and delta coma burst suppression, epileptiform activity and occasionally alpha coma. Diffuse slowline may be seen in a number of cases.

VZV encephalitis – MRI shows hemorrhagic infarction reflecting the tendency of this virus to produce CNS vasculopathy.

Brain Biopsy – After the development of CSF PCR, the brain biopsy is rarely required. If brain biopsy is done then the tissue can be cultured for virus isolation.

DIFFERENTIAL DIAGNOSIS

Viral encephalitis should be differentiated from

a) Cerebral malaria

b) Pyogenic and tubercular meningitis

c) Cerebrovascular accidents

d) Metabolic encephalopathy

e) Acute disseminated encephalomyelitis

Meticulous history, clinical examination and laboratory investigations will be able to differentiate these conditions. Once the diagnosis of viral meningitis is done, it is prudent to identify the virus responsible because therapeutic modality depends upon that. Now we can consider the salient features of specific types of viral encephalitis.

JAPANESE ENCEPHALITIS

It is the leading cause of viral encephalitis in South-East Asia, including Indian subcontinent, mainly effecting children under 15 years of age. It has high mortality of 20- 50 % and high morbidity rate of 1.5 per 10,000 populations. It is the only virus causing epidemic in India . It is a zoonotic disease among mosquitoes and vertebrates. Pigs and wading birds are the amplifying hosts. The common mosquito vectors are *Culex tritaeniohrunchus* and *Culex vishnui*. Humans are dead end hosts. It usually takes place in July to September as paddy fields are ideal for breeding of those mosquitoes. It is essentially a rural disease.

Besides the common feature of encephalitis, the classic manifestations are dull flat mask-like facies with wide unblinking eyes, tremor, generalized hypertonia and cog-wheel rigidity. Opisthotonus and rigidity spasms occur in about 15 % cases. Other extra-pyramidal features like pill rolling movements, opsoclonus-myoclonus, chorio- athetosis and bizarre facial grimacing and lip smacking. Brainstem involvement leads to respiratory irregularities, flexor and extensor posturing, abnormal pupillary and occulo-cephalic reflexes and are poor prognostic signs. The salient features of diagnosis are a rapidly progressive encephalitis, with clinical and neuro-imaging features of brainstem, basal ganglia and thalamic involvement.

HERPES SIMPLEX ENCEPHALITIS

In tropical countries, it is the second common form of encephalitis, usually sporadic and effects all ages and both sex. In this encephalitis there may be focal or diffuse neurological signs and imaging studies show fronto-temporal involvement. CSF PCR is a very important diagnostic test with high degree of specificity and sensitivity. One should try to diagnose HSV encephalitis, as soon as possible as there is specific therapy.

RABIES

A history of bite by a dog or other cause is usually available. Incubation period is variable, starting from 4 days to many years. There is a prodromal phase of 3-4 days with no specific symptoms followed by neurological features of wide spread excitation of all parts of nervous system. There is hydrophobia, aerophobia, light intolerance, dilated pupils, salivation, lacrimation, apprehension, irritability and depression. No specific therapy is available and the cases are invariable fatal.

MUMPS & MEASLES ENCEPHALITIS

They occur either due to direct invasion of the brain or due to post infectious demylating process. Neurological features of diffuse brain involvement occur. They have a variable course and mortality very low.

DENGUE

Usually present with fever with rash. There may be neurological features like myelitis and encephalitis which is usually self limited. Diagnosis is done by clinical features and serology.

ENTEROVIRUS ENCEPHALITIS

Many of the serotypes cause viral meningitis but rarely they cause encephalitis. In addition to the non specific features they have skin rash. Diagnosis is done by RT-PCR in CSF or rising titer of specific antibody in convalescent serum.

TREATMENT

General measures

Careful monitoring of ICP

Fluid restriction

Suppression of fever

Seizure treatment with anticonvulsants

Skin, bladder and bowel care

Acyclovir

It is used for the treatment of HSV encephalitis and should be started empirically with suspicion of viral encephalitis while awaiting viral diagnostic studies. The other viruses who also respond to acyclovir are VZV and EBV. All the three viruses encode an enzyme, deoxypyrimidine kinase that phosphorylate acyclovir to acyclovir-5' monophosphate, then again it is phosphorylated to triphosphate derivative which acts as antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains.

Dose is 10mg/kg I.V. 8 hourly for 14 days. Dose adjustment is required in patients with renal failure.

Gancyclovir & foscarnet

They are used in combination in CMV related CNS infections. Cidofovir is the alternative drug for CMV encephalitis.

Interferon-á-

Currently it is the most promising potential treatment for Japanese Encephalitis. It is produced naturally in the CSF in response to infection with Japanese Encephalitis virus and in vitro it has activity against the virus. Recombinant interferon-á has been given in open trials to a few patients with encouraging results and is being currently assessed in a placebo controlled double blind trial. Live attenuated vaccine for Japanese Encephalitis has been developed in China and is found to be successful in more than 90% cases in preventing Japanese encephalitis.

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SEPSIS : PATHOGENESIS AND MANAGEMENT

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ABSTRACT

The human body responds to infection in various ways. At the cellular level, the microbial signal induce the inflammatory response by the activation of innate immune system through Toll like receptors and MyD88 protein. It activates transcription factor NF Kappa B, which stimulates immuno-regulatory gene for synthesis and release of cytokines .The imbalance between pro-inflammatory and anti-inflammatory cytokines results in the clinical syndromes like sepsis, septic shock and lastly multi organ failure. These clinical syndromes are the result of tissue dysoxia and cellular dysfunction, caused by the inflammatory response. The inflammatory cascade may have a direct effect on cellular mitochondria. The diagnosis of septic shock is mainly clinical. The treatment constitutes control of infection, organ support and adjuvant therapy by antimediator and anti-endotoxin agents. In spite of intensive care management the death is 30-50%. Therefore prevention of infection is important.

INTRODUCTION:

Septicaemia has been defined in the past as the presence of micro-organisms or their toxins in the blood causing symptoms. However, this definition has been used clinically in a variety of ways causing confusion. It neither describes the entire spectrum of pathogenic organisms that may infect the blood nor the clinical events. Therefore, in 1991, American College of Chest Physicians / Society of Critical Care Medicine consensus conference agreed on a set of definitions on infection and infection related clinical conditions as described below [1].

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a) Infection: Microbial phenomenon characterized by inflammatory response to presence of micro organisms or invasion of normally sterile host tissue by those organisms.

b) Bacteraemia : Presence of viable bacteria in blood (presence of other organisms in blood should be described in similar manner – viraemia, fungaemia etc).

c) Systemic inflammatory response syndrome (SIRS): Systemic inflammatory response to variety of insults including infection, pancreatitis, ischaemia, multiple trauma and tissue injury, haemorrhagic shock, immune-mediated organ injury and exogenous administration of inflammatory mediators, such as tumour necrosis factor or other cytokines; SIRS is manifested by (but not limited to) two or more of the following conditions. (1)Temperature > 38^0C or < 36^0C (2) Heart rate > 90 beats/min (3) Respiratory rate > 20/min or P_aCO^2<32 mm Hg, (4) White blood cell count > $12.0x10^9$/1, <$4.0x10^9$/1 or >0.10 immature (band) forms. These changes should represent acute alteration from baseline in absence of another known cause(s) of abnormalities.

d) ***Sepsis:*** Systemic response to infection; this response is identical to SIRS except that it must result from infection.

e) ***Severe sepsis:*** Sepsis associated with organ dysfunction, perfusion abnormalities or hypotension.Perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria and acute alteration in mental status; hypotension is defined as systolic blood pressure <90 mmHg or reduction of >40 mm Hg from base line in absence of another known cause of hypotension

f) ***Septic shock:*** Sepsis with hypotension (as defined above,) despite adequate fluid resuscitation, in

conjunction with perfusion abnormalities (as defined above); patients receiving inotropic or vasopressor agents may not be hypotensive when perfusion abnormalities are measured, yet may still be considered to have septic shock.

g) ***Multiple organ dysfunction syndrome (MODS) :*** Presence of altered organ function in acutely ill patient, such that homeostasis cannot be maintained without intervention; primary MODS is direct result of well defined insult in which organ dysfunction occurs early and can be directly attributable to insult itself, secondary MODS develops as consequence of host response and is identified within context of SIRS.

Epidemiology :- Septic shock is a frequent and grave medical problem. It is the leading cause of death in critically ill patients in USA. The incidence of sepsis is 7/1000 admissions to hospital. Of these 20% develop septic shock, and 70% of them die[2]. Recently, incidence of Gram positive septic shock are increasing. In India epidemiological data on sepsis is lacking. However F. malaria, meningococcus, filariasis, diabetic patients with infection, tuberculosis, AIDS are common causes of sepsis in India.

Risk factors for development of infection and sepsis:-

Risk factors for development of infection and sepsis are patients of extremes of age (old age & infants), obesity, immuno-compromised patients, malnutrition in severely ill patients, smoking, COPD, diabetes mellitus, prolonged hospital stay. The procedures associated with increased risk are use of catheters and other invasive equipments, prolonged intubation, chemotherapy, immuno-supressive agents, use of antacids & H_2 blockers.[3]

Clinical presentations :-In a setting of infection, tachypnoea, tachycardia and changes in mental state are early manifestations of severe sepsis. It frequently precedes fever and hypotension. Apart from these features of shock, when shock progresses that gives rise to different organ dysfunction and we get the clinical pictures accordingly.

Isolated thrombocytopenia without evidence of DIC, is seen in more than 50% patients of septic shock. Other common complications include ARDS, which develop in 30-50% of patients. Intrahepatic cholestasis and renal failure may be present. A fall in urine output is often an early sign of systemic problem in critically ill patients. Restoration of good renal function, as reflected by normalisation of acid base balance, urine flow, plasma potassium & creatinine can be useful indicators of successful resuscitation. Neutropenia, hypothermia, encephalopathy are associated with poor out come.

Pathogenesis :-

The pathogenesis of sepsis is far more complex than it was initially anticipated. It can be received as clinical manifestations of failing innate immune response that ultimately results in an over- stimulation of the physiological host response [4]. For a better description, we discuss this complex pathogenesis in different stages:(Fig-1)

(1) Microbial signals.

(2) Transfer of signal to host cell.

(3) Host responses.

(4) Pathophysiology of cellular dysfunction causing symptoms.

1. Microbial signals :- The immune system recognizes certain microbial molecules as signals which differ according to the type of organisms.

(a) In Gram negative organisms, *lipopolysaccharide* (LPS), also called *endotoxin* is the most potent signal causing sepsis. It is a component of bacterial cell wall with toxic moity lipid-A. LPS is the most widely studied bacterial signal causing sepsis[4].

(b) In Gram positive organisms, components of bacterial cell wall like *peptidoglycan* (PGN), *lipoteichoic acid* (LTA) act as signals inducing sepsis[5].

(c) Exotoxins of some Gram positive organisms act as *super-antigens* which directly stimulates the T cells without processing[2].

(d) Modulins, a new class of recently identified bacterial virulent factors which includes '*adhesins*', '*aggressins*', '*impedins*' & ' *invasins'* can induce sepsis.

(e) Antibiotic induced release of biologically active cell wall components derived from Gram positive, negative bacteria or fungi may act signals[6].

(f) Unknown toxins of P.falciparum & associated Gram negative infection induce sepsis in falciparum malaria[7].

(g) Bacterial DNA can bind the receptors causing sepsis[6].

2.Transfer of signals to host cell: The innate immune system is the 1st line defence against invading micro-organisms. The microbial signals (products) activate the innate immune system either by combining with different receptors on the cell walls or directly as in cases of super antigen.

The different receptors, which recognise the signals and transfer it to the cells are:

(a) Toll- like Receptors (TLR): - Toll- like receptors (TLR) are most recently identified receptors on the cell wall of macrophages and other cells of innate immune system[8,9]. These receptors and their signaling pathways are conserved through out the evolution and found in plants, fruit flies & mammals. Ten members of the TLR family have been identified in humans & several of them appear to recognize specific microbial products including LPS, PGN, LTA and bacterial DNA. In other words, macrophages and other defensive cells "see" the endotoxin(TLR-4), peptidoglycan(TLR-2), bacterial DNA(TLR-9), LTA (TLR-4) through Toll-like receptors.

(b) CD_{14} - It is another receptor, which is responsible for signal transfer along with TLR. Endotoxin binds to CD_{14} and recently identified TLR-4 for recognition by cells of myelomonocytic linkage (innate immune system). Cell wall components of Gram positive organism like PGN activate the cells through an interaction with CD_{14}, TLR-2 and probablyTLR-6, whereas LTA acts through CD_{14} and TLR - 4[10].

(c) The exotoxins of Gram positive organism may act as *superantigens*. Unlike common antigens, *superantigens* directly stimulate the T cells without prior processing[2].

3. Host Response: After the signal entered to the cell, a chain of reactions follow in the innate immune system. Patients with septic shock have a *biphasic* immunological host response. There is an initial *overwhelming inflammation* followed by a period of *immunodepression*.[11]

3.1. *Initial overwhelming inflammation* occurs in multiple steps which includes:

a. Activation of the Transcription Factor, Nuclear factor-Kappa B: Recent advances suggest that bacterial signals binds with TLR and subsequently with MyD_{88}, a general adaptor protein activates the transcriptional regulatory complex, Nuclear factor Kappa - B (NF- KB) in a step wise manner[12]. NF-KB binds to the promoter region of immuno regulatory (IR) gene leading to its expression and synthesis of cytokines. Cytokines are soluble proteins and are pleiotropic in their action. Four main groups of those substances are released.

b. Release of cytokines : Cytokines are soluble proteins and are pleiotropic in their action. Four main groups of those substances are released[13].

i). Pro-Inflammatory cytokines: The primary pro-inflammatory cytokines are TNFα, IL-1, IL-6, Monocyte chemotactic protein (MCP) 1,2, & 3. These cytokines can directly affect the organ function and may act indirectly through secondary mediators. Of all TNFα has been considered as the central mediator of the whole process. It stimulates leukocytes and vascular endothelial cells to express cell surface adhesion molecules and also increases arachidonic acid turn over.

ii). Production of Inducible Enzymes: It produces various inducible enzymes. (1) *Inducible Phospholipase and Cyclo-oxygenase:* These enzymes produce arachidonic acid, prostaglandins and thromboxanes. PGE_2 and prostacyclins cause vasodilatation whereas thromboxane is a vasoconstrictor and promotes platelet aggregation. (2) *Inducible NO synthase (iNOS).* Recently NO produced by iNOS has been considered as a mediator of shock, causing hypotension and myocardial depression. *Peroxynitrate* formed from the reaction between

superoxide radical and NO may cause direct cellular injury.

iii) Cell adhesion molecules and different growth factors: Adhesion molecules like P-selectin, E. selectin, ICAM-1, ICAM-2, and VCAM-1 are produced. The endothelial adherence of activated neutrophils and their trans- migration into the extra-vascular space result in microvascular and tissue injury. Platelet derived growth factors (PDGF) also help in platelet aggregation. All these increase tissue factor expression on endothelial cell. They also activate extrinsic pathway leading to fibrin deposition, platelet aggregation and development of DIC. Complement activation also occurs. All these lead to endothelial dysfunction.

iv) Anti-inflammatory cytokines : In addition to the substances promoting inflammation , the immune system also liberates anti-inflammatory cytokines e.g. IL-10 and IL-4. Their function is to control the adverse effect of excessive inflammatory response.

3.2. ***Period of Immuno depression and Control Mechanism:*** As there is an elaborate mechanism of inflammatory response, there is also an anti-inflammatory mechanism for control [11]. The role of anti-inflammatory response seems to be more complex, overlapping and poorly understood.

i). Anti-inflammatory substances - Endogenous corticosteroids and catecholamines are raised and have anti-inflammatory activity. Glucocorticoides inhibit cytokine synthesis by monocytes *in vitro*. The rise in blood cortisol level early in septic response presumably plays a similar inhibitory role.

ii). Anti-inflammatory cytokines- IL10, IL4, PGE-2, soluble TNF receptors and IL-1 receptor antagonist are the anti-inflammatory mediators released in septic shock. These substances alter immune function which leads to a period of immune depression after the initial shock episode. It is meant to reduce the release of inflammatory cytokines. The immune depression is indicated by a decrease in monocyte expression of Type II HLA, which is important in antigen presentation. Similarly monocyte responsiveness to inflammatory stimuli is also decreased. Persistence of the hyporesponsiveness has been associated with increased risk of nosocomial infection and death.

4. Patho-physiology of cellular dysfunction causing symptoms: All pathologic processes in the cellular function of human body during septic shock are a result of the *disbalance of a number of mediators with inflammatory and anti-inflammatory effects.* It is interesting to note that the overall response is *independent* of the type of invading organisms[4]. Pathophysiologically, septic shock has been considered to be the classic example of *distributive shock.* The clinical findings are a consequence of the combination of **haemodynamic alterations** and **tissue oxygen metabolism** [11].

i). Haemodynamic alterations: Alterations in peripheral vascular tone and cardiac function contribute to the cardiovascular manifestations of septic shock. Heart rate and cardiac out-put commonly increase. Systemic vascular resistance is low because arteriolar tone is decreased, whereas pulmonary vascular resistance is high. Despite the increase in cardiac output, tissue hypo-perfusion is manifested by raised blood lactate concentration, with less oxygen extraction.

Myocardial dysfunction is seen in most patients with septic shock. Substances that depresses myocardium are NO, TNFα. Pulmonary hypertension and down regulation of β adrenergic receptors are other factors that may impair cardiac function in septic shock. Recently the expression of TLR on the myocardium has been detected. Hence the microbial signals may directly affect the myocardium through TLR [14].

ii). Oxygen Metabolism: The mechanisms that alter tissue oxygen metabolism causing *dysoxia* are complex [11].

(a) In most patients, impaired oxidative metabolism seems to relate to the *inability* of systemic tissues to *extract oxygen* from blood.

(b) Some patients have decrease in cardiac output (Hypodynamic circulatory state) leading to limited oxidative metabolism.

(c) Toxin mediated organ injury that occurs independent of tissue hypoperfusion may also impair cellular oxidation.

(d) The inflammatory cascade may also have a direct effect on cellular mitochondria and metabolic activity.

In consequence, impaired oxidative metabolism occurs in septic shock. This metabolic dysfunction coupled with the haemodynamic alterations, cause progressive deterioration of cellular function giving rise to multi organ failure & death.

Diagnosis : The diagnosis of sepsis & septic shock is invariable made on clinical grounds. It is because (1) the overall response of sepsis is independent of the specific type of invading organisms and there is no specific test. (2) negative culture does not exclude associated infection entirely. (3) sepsis is a life threatening condition & effective management with antibiotics can not wait upon positive culture. (4) therapies to manipulate host's inflammatory response must be started early [15].

Investigations and Monitoring : *The investigations* are of limited value in diagnosis of sepsis. In addition to routine investigations, culture of blood, urine, sputum, line–tips, wound swabs, throat swabs should be done. Ultra-sonography & CT scan of abdomen and pelvis may be done for detection of any pus collection. The biochemical tests like bilirubin, AST, ALT, urea, creatinine,blood glucose, electrolytes are done to know the organ functions and biochemical monitoring.

Monitoring in critically ill patients is essential from management point of view. Regular clinical examination can give a lot of information. The monitoring of the circulation is done by ECG monitor, automated sphygmomanometer, CVP monitor by a catheter placed in the internal jugular or subclavian vein, pulmonary artery wedge pressure & pulmonary artery occlusion pressure, cardiac output, urine out flow, fluid balance, peripheral / skin temperature. The monitoring of respiratory function is done by measuring oxygen saturation (SpO2), arterial blood gas analysis, lung function & capnography. Day by day the monitoring system devices are increasing but it should be used when necessary[2].

Scoring systems: Critical care systems are widely used to measure severity of illness by APACHE II (Acute Physiology Assessment & Chronic Health Evaluation) & SAPS-2 (Simplified Acute Physiology Score) system.

Treatment : The treatment of sepsis consists of mainly 3 steps[16].

(A) Control of infection : Control of infection is done either by *surgical removal* of the focus when present or by appropriate *anti-microbial chemotherapy*. Anti-microbial chemotherapy should be initiated pending the culture report. The antibiotics should not be saved for the post-mortem room. The most effective broad spectrum agents at maximum recommended doses should be used with adjustment for impaired renal function. Available information about patterns of anti-microbial susceptibility of the hospital is useful in deciding therapy. The recommended empirical therapy in different clinical conditions are given in Table-1.

(B) Supportive therapy : The principle of supportive therapy is that when sepsis progressed to septic shock, circulatory abnormalities leads to global tissue hypoxia which results in multi-organ failure & death. Hence adequate organ perfusion is essential. The main focus of supportive management is on haemodynamic & ventilatory support.

(1) Haemodynamic support : [16]

(a) Conventional support strategy : It consists of attempting to improve DO2 (oxygen delivery) and VO2 (oxygen consumption) by optimising cardiac output with (I) restoration of intravascular volume with a colloid and/or a crystalloid. (ii) administration of vasopressors and inotropes (e.g. norepineptrine with dobutamine).

(b) Goal directed therapy : Goal directed therapy is to increase the DO2 & VO2 by increasing cardiac index using volume load, dobutamine and/or norepinephrine.

(c) Early goal directed therapy : It is same as goal directed therapy but it should be achieved as early as possible. It has been directed to achieve mean arterial pressure >60 mm Hg or systolic >90mm Hg, cardiac index >4L/mt/m^2, CVP 8-12mm.in a sequential fashion [17].

(a) Fluid resuscitation – normal saline 500 ml in½ Hr. may be increased to 1- 2 L till, CVP is 8-12 mm. (b) Administration of vasopressor or dilator agent. (c) red cell transfusion if Hb is less than 8 – 10 g/dL to increase the oxygen delivery. (d) Inotropic medication to achieve target CVP of 8-12 mm of Hg, mean arterial pressure 60 – 90 mm of Hg or systolic pressure 90 mm of Hg, urine output 0.5 ml / kg / hr, central venous oxygen saturation at least 70 %. If there is no response patient is sedated & put in mechanical ventilation. In a randomised trial, in hospital mortality in early goal directed group was 30.5 % compared to 46.5 % in conventional support therapy.

Drugs used for circulatolry control : In patients with hypotension, *catecholamines* are most commonly used drugs to maintain arterial pressure. Differences exist between catecholamines in their effect on blood pressure, cardiac contraction and visceral perfusion. *Dopamine*, a β_1 and α_1 adrenergic agent, is the first choice in hypotensive patients with low cardiac output at a dose of 20-50ug/kg/mt,at which it exerts its α_1 action. In patients with a mean arterial pressure > 60 mm Hg and evidence of tissue hypoperfusion, *dobutamine* (2.5-15.0ug/kg/mt), a $\beta_{1,2}$ adrenergic agent should be started. *Norepinephrine*(NE), an α_1 & β_1 adrenergic agent, has balanced inotropic & vasopressor activity is administered at a dose of 1-12ug/mt. Its major effect is to increase arterial pressure without significant changes in cardiac output & heart rate. Hence NE should be considered for patients who respond to dopamine with excessive tachycardia or who remain hypotensive despite high doses of dopamine[11,16]. *Dobutamine* increases splanchnic blood flow compare to other catecholamines. In hypotensive septic patients, NE increases splanchnic perfusion, where as dopamine seems to decrease it. *Vasopressin* (20units over 15 mts; then 0.4-1units/min iv) and *enoximone* (90ug/kg/mt over 30 mts. then 5-20ug/ kg/mt.).[18]

(d) Gut directed therapy : The principle of gut directed therapy is to prevent gut ischaemia and maintain normal gut flora. For this the patient receives general measures to increase blood pressure, cardiac output & oxygen delivery and early enteral feeding which increases splanchnic blood flow , maintain normal gut flora & immuno competence. Splanchnic hypoxia can be measured by pH_{im} and may be treated with *dopexamine*, a specific splanchnic vasodilator[19].

(2) Ventilatory support: The indications are progressive hypoxaemia & hypercapnia, neurological deterioration, respiratory muscle failure, sustained tachypnoea (Respiration rate> 30 / mt) and failure of early goal directed therapy.

(3) General support :

(4) Metabolic support: Supplemental hydrocortisone (50 mg I.V. 6 hourly) is given when adrenal insufficiency, complete or partial is detected by cosyntropin test. Clinically adrenal insufficiency has been considered in septic patients with refractory hypotension, fulminant N. meningitides bacteraemia, prior glucocorticoid use, disseminated tuberculosis and AIDS. In these patients low dose of hydrocortisone will be beneficial[20].

(C) Adjuvant therapy : As death is very high in septic shock in spite of antibiotic and supportive therapy, two kinds of agents that may help prevent these deaths are being investigated[21].

(1) Antimediator agents : Drugs that interfere with one or more mediators of inflammatory response & may benefit all patients of sepsis.

(i) Activated protein C (drotrecogin alfa) : A recombinant human form of activated protein C has been recently approved by the FDA, USA for severe sepsis in adults with high risk of death. It possesses anti-inflammatory and anticoagulant activity[22].

(ii) Other anti-inflammatory agents: Soluble receptors of TNFα, monoclonal antibodies to TNFα anti-thrombin tissue factor pathway inhibitor, platelet activating factor acetyl hydrolase, pyri doxylated Hb polyoxyethelene are tried in sepsis.

2. Anti endotoxin agents : Neutralisation of lipid-A toxic moity by monoclonal Ab has been used without any benefit.

3. Nuclear factor Kappa–B inhibitor – IRF1042 is a NF-KB inhibitor that blocks NF-KB. It reduces TNF-m RNA levels and finally reverses endotoxic shock[23]

Outcome: The outcome of sepsis and related syndromes are poor. The mortality of patients with sepsis is 15-20%. It increased to 40-60% in patients with septic shock and 80-90% when complicated with ARDS[2].

In spite of treatment, the mortality is very high in septic shock. Therefore, prevention of infection during the hospital in ICU is more important. The prevention of infection comes into two categories. The *prevention of transmission of organism from external source* includes patient to patient, hospital staff to patient, IV lines, device-associated infections like intubation, ventilator tubes etc. The *prevention of over growth of bacteria in the gut* is done by avoidance of H_2 antagonists and antacids. H_2 antagonists and antacids used for prevention of stress ulcer and gastric bleeding, increase in gastric pH which colonise the bacteria in the gut. This leads to aspiration pnemonia, leaking of the bacteria from the g.i. tract to blood causing sepsis. Selective digestive decontamination and early enteral nutrition help in preventing it.

TABLE – 1

1) Immune competent adult	1. *Ceftriaxone* (1gm q 12 h) **or** *Ticarcillin Clavulanate* (3. 1 g q 4 – 6 h) **or** *Piperacillin-Tazobactam* (3.75 gm q 4 – 6 h *2. Imipenem-Cilastatin* (0.5 g q 6 h) **or** *Meropenem* (1 g q 8 h). Genatmicin or Tobramycin (5 mg / kg 24 h) *may be added* to each regimen. **b lactam allergy** - Ciprofloxacin (400 mg q 12 h) + Clindamycin (600 mg q 8 h). If Methicillin resistant S.aureus(MRSA) in the hospital, add Vancomycin (15 mg 1 kg q 12 h).
2) Neutropenia (< 500 / m)	1. *Ceftazidime* (2 g q 8 h) **or** *Ticarcillin – Clavulanate* (3.1 g q 4 h) **or** *Piperacillin – Tazobactam* (3.75 g 4 h) plus *Tobramycin* 5 mg / kg q 24 h).*2. Imipenem – Cilastatin* (0.5 g q 6 h) **or** *Meropenem* (1 g q 8 h) **or** *ceflazidime* **or** *Cefopime* (2g q 12 h). Vancomycine 15 mg / kg q 12 h & ceftazidime should be used *if the patient had infected catheter*.
3) Splenectomy	Cefotaxime (2 g q 6 – 8 h) **or** *ceftriaxone* (2 g q 12 h).
4) I.V. drug user	*Nafcillin* or *oxacillin* (2 g q 4 h) + Gentamicin (5 mg / kg 24 h **or***Vancomycin* + *Gentamicin* if MRSA is high.
5) AIDS	*Ceftazidime (2 g q 8 h), Ticarcillin- Clavulanate* (3.1 g q 4 h) **or** *Piperacillin -Tazobacteum* (3.75 g q 4 h) + *Tobramycin* (5 mg / kg q 24 h).**b lactam Allergy** – Ciprofloxacin + Vancomycin+ Tobramycin.

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ROLE OF ADJUVANT THERAPY IN CEREBRAL MALARIA

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Severe malaria results in high mortality all over the world mostly in Africa and South-east Asian countries. The estimated death is around 1.5 to 2.5 million every year.[1,2] the therapy in malaria is directed against the blood stages of the parasite. Till date the drug of choice in severe malaria was parenteral quinine. Its use for centuries has established it as a safe and effective drug with few side effects. Recently the use of Artemesine derivatives particularly intravenous artesunate has reduced mortality by 22% in a large multinational trial. [3]. The Artemesin group of drugs is highly effective in clearing parasites with practically little side effects or toxicity. In addition, it is not only the fastest acting anti-malaria drug, but no resistance has been reported till date. In spite of this advancement the mortality due to severe malaria (viz: cerebral malaria, acute renal failure, severe anemia etc.) remains unacceptably high. This clearly shows that the treatment of severe malaria does not end with the clearance of parasite. The organ involvement like cerebral malaria, acute renal failure, acute respiratory distress syndrome, etc. may persist or may become worse even after the parasites are cleared from the blood. The complication like ARDS may set in late in the course of the disease with-out any detectable plasmodia in peripheral blood. [1] There is no definite drug available to combat these complications, hence the supportive therapy constitute modalities like blood transfusion, haemodialysis, mechanical ventilators etc. Hence there is an urgent need to develop alternate therapeutic strategies and /or to identify drugs (new or existing) to combat these problems of organ damage due to falciparum malaria.

In order to understand the role of adjuvant therapy it will be worth while to discuss, in brief, the pathogenesis of cerebral malaria, the most dreaded complication of *Plasmodium falciparum* malaria.

The pathogenesis of cerebral malaria is not yet completely understood. The hypothesis up till now is obstruction to microvascular circulation due to sequestration and clogging. This results from decreased deformability of parasitized red blood cells (pRBC). Cytoadhesion to vascular endothelium, rosette formation and cytokine mediated injury to blood brain barrier (BBB) result in cerebral oedema and raised intracranial pressure (ICP). The most popular and extensively studied mechanism in cerebral malaria is sequestration of pRBC deep inside the vascular bed causing compromised blood supply and hypoxia which results in impaired brain function leading to altered sensorium or even deep coma. The common manifestation is diffuse encephalopathy but occasionally focal neurological deficit [4].

The decrease deformability results from the change in cytoskeleton of pRBC. There is increase in the membrane stiffness and rigidity resulting in the inability of these pRBC to pass through capillary. It has been demonstrated that there is rigidity and lack of deformability of the uninfected RBC and the deformability was less in fatal cases than survivors.[5] If these phenomena are uniform in all cases of CM then drugs like pentoxyphylilline which modifies the morphology of RBC will be good candidate for adjuvant therapy.

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During maturation of the parasites there occur a number of changes in the erythrocyte membrane which could be recognized by spleen leading to splenic entrapment. To evade this process p.falciparum has developed a technique to cytoadhere deep inside the capillaries of different organs known as cytoadherence. Its apposition of infected RBC with the endothelial cells brought about by parasite adhesion molecules and endothelial receptors (ligands) [6]. Knobs appear in the membrane of RBC containing mature parasites which act as an cell to cell contact with specific receptors in vascular endothelium, [7,8]. The role of knobs was further confirmed when Knobless pRBC failed to adhere both in vivo and in vitro[9,10]. Several host molecules such as CD 36, intracellular adhesion molecule (ICAM), vascular adhesion molecules (VCAM), thrombospondin etc. get up-regulated in CM [11,12] facilitating cytoadherence of pRBC in cerebral and other severe malaria. The most important parasite molecule that plays crucial role is *P. falciparum* erythrocyte membrane protein 1 (PFEMP-1) which is coded by a **var** gene12. The other parasite proteins that play important role in cytoadherance are histidine rich proteins (HRP 1, HRP 2) and mature erythrocyte surface antigen protein (MESA). However, the nature and extent of sequestration varies from organ to organ and individual to individual. It's postulated that organs or individuals whose endothelium expresses more adhesion molecules in response parasites or mediated by host cytokines are more prone to organ dysfunction like CM.

Rosette formation is a process in which non parasitized RBC (non pRBC) form a rosette around pRBC to form a tight non-deformable complex, leading to further vascular clogging and hypoxia in severe malaria. This process is thought to be a biological evolution where the pRBC are protected from host immune system. Persons with abnormal haemoglobin like sickle cell or thalassiaemias have an impaired ability to form rosette which thought to be a protective mechanism against severe malaria.[13]. However this phenomenon has been consistently demonstrated in all severe malaria cases. Rosette is also seen in *P .vivax* and *P.ovale* malaria which rarely cause CM.

It has been proposed that inflammatory cytokines secreted by activated macrophages also play a role in severe malaria. The cytokines include tumor *necrosis* factor alpha (TNF alpha), gamma interferon, and interleukin 6, 12 (IL6, 12). These pro inflammatory cytokines up regulate the endothelial receptors like ICAM 1, VCAM which facilitates pRBC adhesion to the capillary surface. TNF alpha also causes parasite killing by activated macrophages and also responsible for the symptoms like pyrexia, hypoglycemia etc. In low levels it is helpful in clearing parasites but high levels are deleterious to different organs. It has been seen in higher concentration in patients of severe malaria than non severe malaria.

Interleukins play both pro-inflammatory and anti-inflammatory in severe malaria. IL12 released by activated macrophages confers immunity by release of INF gamma; it has a protective role against the blood stages of infection. The concentration of IL 12 has been low in the serum of African children with severe malaria... IL 18 which structurally close to IL 12 act synergistically to up regulate the production of INF gamma, T helper cells, cytotoxic T cells and NK cells which in turn acts a protection against severe malaria [14]. However, uncontrolled release of these cytokines results in severe anaemia in African children . Anti-inflammatory cytokines like IL 4, 5 and 10 inhibit TNF alpha and has been found to protect marine models of cerebral malaria. In a study from Vietnam 287 children of severe malaria who died had low levels of IL 10 in comparison to their counterparts who survived. Till date the role of these pro and anti inflammatory cytokines are clearly know, hence there are a host of them implicated in severe malaria causing difficulty in targeting a molecule for therapy.

Reactive oxygen species(ROS) are generated in large quantity by activated neutrophils in the host

and degeneration of haemoglobin in parasite causing lipid peroxidation and damage to vascular endothelium leading to intravascular permeability [15,16]

Increased intracranial pressure and cerebral oedema due to disruption of blood brain barrier (BBB) as a consequence to cytokines, nitric oxide and oxygen free radicals is an area of controversy in cerebral malaria. It has been shown in Kenyan children with CM the opening CSF pressure was high in all the 61 children. [17] In the Gambia raised ICP was seen in 32 out of 40 children with CM[18]. In a study by the authors cerebral oedema was demonstrated in 70% of cases with CM by CT scan and opening pressure of CSF was high in 50% cases. (Unpublished observation) It has been postulated that increased cerebral blood volume and disruption in BBB leading to cerebral oedema causes raised ICP. It has been suggest that apart from clogging of pRBC deep inside the capillaries disruption in the vascular endothelium causing leak of plasma fluid into the brain interstitium does play a crucial role in severe malaria particularly CM and the activated macrophages which release inflammatory cytokines aid the process by up regulating the adhesion molecule in the endothelium and cause tissue damage permitting the leakage of plasma fluid into the brain.

Reviewing the pathogenesis it is quite obvious though the aetiology is same the manifestations of the symptoms varies from person to person depending on the host response to the parasite. The drugs recommended only takes care of the parasite; hence there is a room for additional therapy along with the currently available drugs. Over the years there are reports of different agents being tried in severe malaria with varied results, so it's imperative to have a review of them systematically.

Corticosteroids have been used in CM to reduce intra cranial pressure [19]. It is known that steroids help to reduce ICP in vasogenic cerebral oedema like brain tumor and abscesses; however it's ineffective in cytotoxic oedema. Corticosteroids might reduce the harmful effects of brain swelling in CM but at the same time suppress the host immunity against malaria. Two published studies analyzed by Cochrane of 143 patients showed the deaths were evenly distributed in both arms (corticosteroids and no steroid**)** [20, 21] There were more episodes of gastro-intestinal bleeding and seizures in steroid arm. The reviewers concluded that the sample size being very small the studies were not strong enough to recommend steroids as an adjunct therapy. WHO does not recommend its use presently? but in view of the current knowledge of inflammatory mediators and its role in the pathophysiology of severe malaria a large scale randomized placebo controlled trail is necessary to conclusively prove or disprove its efficacy.

Osmotic agents like Glycerol, Sorbitol and Manitol are known to reduce ICP and increase intracranial pressure. Apart from renal filtration Glycerol and Sorbitol are metabolized in the liver and do not accumulate in patients with renal failure. Both the compounds have a short half life and altered glucose metabolism. Mannitol on other hand is exclusively filtered by the kidney and has the slowest elimination half life (2-4 hours). Entry into CSF is highest for Glycerol and intermediate for Mannitol The elimination from CSF is slower than serum and it's during this process a paradoxical rise in ICP may be encountered. Mannitol does not enter CSF in first pass and thus causes rapid dehydration of the brain tissue and thus lowers ICP. It also reduces ICP by prolonged dehydrating effect in brain tissue due to increase osmolality. The third mechanism postulated is by reducing blood viscosity it increases the cerebral blood flow causing reflex vasoconstriction and decrease in cerebral blood volume and thus reduction in brain swelling. Effect of mannitol in cerebral malaria has been studied by various authors; Newton et.al [22] from Kenya studied the effect of mannitol in 23 children with CM. Four had severe rise in ICP (>40cms of CSF) and low cerebral perfusion pressure (CPP < 40cmof CSF) two of them died and two had severe neurological sequelae. Nine had

intermediate ICP (20-30cm of CSF) and 10 had mild rise of ICP (10-20), all of them survived with out any sequelae. Thus mannitol could control mild and intermediate rise in ICP but had very little effect in severe intracranial hypertension due to CM. Cochrane data base till 2004 could analyzed due to lack of proper study design. Till date, there is no consensus regarding the use of mannitol in cerebral malaria. A trial by the authors showed brain oedema in 67% of cases with cerebral malaria as evidenced by CT scan, only a small number patients could be randomized to mannitol and non –manitol arm as many patients had acute renal failure or pulmonary oedema along with CM. The mortality which was the primary end point was similar in both groups. The authors opine that pending large randomized controlled trails it can be used as an adjunct therapy in patients who manifest evidence of raised ICP in CM.. It should be remembered that a rebound increase in ICP may occur during elimination phase. In a randomized clinical trial in Uganda in 2007, Namutangula et al. studied the effect of mannitol in 156 children. They concluded that mannitol has no beneficial effect. [23]

Desferrioxamine is an iron chelator used in patients of iron overload conditions like after multiple transfusions in thalssimia. It acts by preventing injury induced by oxygen free radicals which is a mediator in severe malaria. In a trial by Mohanty et.al.2002[24] in 45 patients of cerebral malaria which was a randomized placebo control study death was only 2 cases in the arm that received Deferiprone (oral desferrioxamine) died. In the placebo arm 4 patients expired. The fever and parasite clearance time shorter in the treatment arm versus placebo. All the patients received Injection. Quinine and other standard supportive management. This study showed that this could be a promising agent in the treatment of cerebral malaria. However the sample size was small for any definite conclusion, and being a oral drug the use of Deferiprone has the limitation of administration in severe malaria where the absorption may be erratic.

A double blind randomized placebo control trial of 83 patients of CM in Zambia the mortality rate was 17 in the Desferrioxamine group and 22 in the placebo group. The rate of recovery from coma was 1.3 times faster in the desferrioxamine group which had 42 children. The median recovery time was 20.2 hours versus 43.1 hour in placebo group. The parasite clearance 2.0 times faster than placebo.In this study desferrioxamine was given in a dose of 100mg per Kg of BW along with standard dose of Quinine for 72 hours in infusion and the control group had identical placebo infusion along with Quinine.[25], In another study from Zambia which included 352 children where desferrioxamine was infused over a period of 72 hours along with quinine compared to placebo the mortality was 16.3% in desferrioxamine group and 10.7% in the placebo group(adjusted odds ratio 1.8, (95% CI 0.9-3.6, P=0.074) The coma recovery time in survivors was not significantly faster than the placebo (odds ratio 1.2, 95% CI, 0.97- 1.6,P=0.089). This study did not provide any advantage of desferrioxamine over placebo in children of cerebral malaria as far as mortality and recovery from coma was concerned[26]

Cochrane review [27] assessed the usefulness of this agent in combination of antimalarial in seven randomized controlled trails involving 570 cases (including 435 children). No benefit or harm was shown in relation to mortality. The risk of seizures was less with desferrioxamine (relative risk, RR 0.80, 95% CL0.67-0.95), but adverse events were more common with desferrioxamine. The reviewers concluded that there is insufficient data to recommend the drug as an adjuvant to standard Antimalarial therapy. Large multi-center double blind placebo controlled trails are necessary to asses the potential benefit or adverse effect of this agent.

Pentoxifylline (PTX) is a phospho- diesterase inhibitor and acts by inhibiting TNF alpha, modifying the rheo-morphology, thus theoretically has a role in CM cases. The beneficial effect has shown that mice treated with PTX did not develop CM after

being infected with *P. berghei* ANKA in comparison to control who developed signs of CM and died with-in 2 weeks**.** [28] In 56 children where PTX was given 10mg /Kg at constant infusion along with quinine TNF was significantly less, coma recovery time was significantly short (6h. vs. 46h) trend towards lesser mortality. [29] In a recent study of 52 adult cerebral malaria patients Das et.al [30] patients receiving PTX along with quinine had faster coma resolution time and significantly lower mortality. The serum TNF was significantly decreased. The drug was well tolerated. However, another two trails of human CM did not support the above finding. In 51 cerebral malaria cases PTX did not decrease TNF alpha nor was there any decrease in mortality [31]. Similarly, another study from Thailand involving 45 patients of complicated malaria did not show any clinical benefit [32]. The studies till date have shown contradictory results. The sample size did not have enough power to conclude any inference. This agent merits a re-look with adequate sample size for definite conclusion.

N-acetyl cysteine (NAC) The lack deformability of pRBC and non pRBC is one of the mechanisms for cerebral malaria, NAC is considered to reverse this process. It inhibits TNF and is scavenger of free radicals. In 185 patients of severe malaria in Bangkok hospital the patients receiving NAC serum lactate normalized sooner in the NAC arm than placebo. There were no adverse events with NAC. [33]

Anti- TNF alpha monoclonal anti-bodies tried in a murine model prevented *Plasmodium berghei* induced cerebral malaria [34]. In a clinical trail single dose (250,500,1000,2000 units/kg of an ovine polyclonal specific fab fragment directed against TNF alpha given to17 adult patients of severe falciparum malaria immediately before injection Artesunate was compared with controls. The group receiving anti-TNF antibodies there was faster resolution of clinical symptoms and fever without any anaphylaxis and serum sickness like reaction. [35] In a double blind placebo control trail in 610 Gambian children the death was 19.9 in the trail group and 20.8 in the placebo group. There was very little survival advantage and the neurological sequelae were more in the anti- TNF group [36].

Agents for enhancement of macrophage CD 36 mediated phagocytosis of p.falciparum. Recently experimental studies have shown that human macrophages and monocytes with CD 36 ligands mediate a non –opsonic phagocytosis of p.falciparum parasites and they act as the first line of defense against malaria . Various drugs have been tried which up regulates the expression of CD 36 in macrophages and monocytes.. Asada et.al [37] reported that ligands of peroxisome proliferation activated receptor gamma (PPAR gamma) like prostaglandin 12 and troglitazone lead to up regulation of macrophage CD 36. In experimental animals PPAR Gamma agonist like troglitazone increases CD 36 expression and enhanced phagocytosis of parasitized RBC and decreases parasite induced TNF alpha. These findings open a novel method for the management of severe malaria...

Interleukin -12 IL 12 is a potent pro-inflammatory cytokine released by activated macrophages which confers protective immunity against malaria. It has a protective role against both blood and liver stages of infection[38].Though it has shown protection in animal models its role in the treatment of human malaria is limited as it is to be given prior to or on the day infection.

Interleukin 18- IL -18 is a pro-inflammatory cytokine induces INF Gamma, production from Th 1 cells, NK cells and activated macrophages particularly in the presence of IL-12. [39]. A study from Thailand show it can be a candidate for adjunct therapy in severe malaria.

Bacillus thuringiensis crystal proteins Crystal proteins extracted from bacillus thuringiensis were tested in *P berghei* infected mice for anti-malarial property. Following injections of 0.45and 1.5mg of the crystal protein the survival of the mice

was extended by 5 days, it was also shown that uninfected RBC can be protected against the parasite attack.[40].

Drugs with doubtful or harmful effect.

Cyclosporine-A In a murine model low dose of cylosporin –prevented cerebral malaria. The growth of p.falciparum was inhibited in culture medium. However in a double blind placebo controlled randomized trail from Vietnam it did not reduce mortality or morbidity in adult severe malaria cases. [41]

Low molecular weight dextran it was thought by reducing the blood viscosity it will improve cerebral circulation, it is well known the most cases of severe malaria have anaemia and the blood viscosity is already low. It can cause anaphylaxis and difficulty in blood cross matching. Presently WHO does not recommend its use in cerebral malaria [1]

Heparin procogulants and thrombocytopenia in malaria correlates well with the parasitaemia, serum levels of TNF alpha and clinical severity. Thus heparin or acetylsalicylic acid (ASA) which is used to prevent thrombosis and in case of ASA to prevent fever could be potentially beneficial. In a controlled randomized trail of 97 patients divided into 3 groups(33 received low dose sub-cutaneous heparin, 31 IV ASA and 33 only anti-malarial drugs) the mortality was not significantly different in any group [41]In view of the known adverse effects of both the drugs and little clinical benefit it is not recommended in severe malaria.

Conclusion

Cerebral malaria one the most common encephalopathies in the world is the major cause of mortality in African children. It also affects the none or semi-immune adults of South-East Asia. Till date the only treatment available is anti-malarial drugs. Though Artemesinin group of drugs has reduced mortality to some extent, but it is still not good enough. The quest for different approach has not yet yielded in any specific drug or therapy that can be unequivocally prescribed across the board. Though the literature abounds with various old or new drugs that has been tried in cerebral malaria none of them has conclusively proved its efficacy. Most of these trials suffer from inadequate sample size, non-randomization and ill defined end points. Recent insight into the pathophysiology of cerebral malaria has opened up new vistas for adjuvant therapy. Some the agents like osmotic diuretics, corticosteroids and PPAR gamma agonists (to name a few) needs large scale placebo controlled randomized trails as adjuvant therapy in cerebral malaria.

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FALCIPARUM MALARIA IN PREGNANCY

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INTRODUCTION

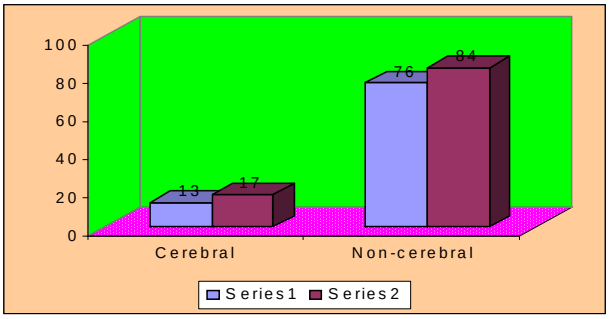
Few disease have had a greater impact on human social and economic development than malaria. Malaria is both preventable and treatable but continues to kill disproportionately children and pregnant women[11]. Various studies from Africa confirm that pregnancy is accompanied by greater prevalence and increased density of malaria parasite. The placenta is the preferred site for parasite sequestration and development, also called as placental malaria. The severity depends upon the background premunition. In areas of high transmission severe anemia is most common and associated with high mortality. In areas of low transmission or during epidemics, pregnant women are at high risk of severe malaria, cerebral malaria & death[11]. Falciparum malaria in pregnancy is a significant health problem in India. Pregnant women constitute an important high risk group for malaria infection, which result in low birth weight, abortion, premature labor, and increased perinatal mortality rate.

Magnitude of the Problem:

Most studies come from Sub Saharan Africa, where approximately 25 million pregnant women are at risk of P. Falciparum infection each year, of which 25% had evidence of placental infection at the time of delivery[2]. Malaria among pregnant women in low transmission areas shows - prevalence (6.2%), placental parasitazation (9.6%) maternal mortality 0.6 - 12.5%. In India about 1.5 - 2 million documented cases of malaria in pregnancy reported annually by NMCP (National Malaria Control Programme). Cerebral Malaria during pregnancy accounts for 50% mortality as compared to 20% in nonpregnant adult female. Meta-analysis of intervention trial suggest that successful prevention of malaria among pregnant women reduced the risk of severe maternal anemia by 38%, low birth weight by 43% and perinatal mortality by 27% among primigravida[2].

Figure 1 shows the number of cerebral malaria in pregnant and non pregnant women with malaria from our study.

Figure- 1



Series1- Pregnant Series2- Non pregnant

PATHOPHYSIOLOGY

Pregnancy increases susceptibility to falciparum malaria both in endemic and non-endemic areas. During pregnancy, down regulation of normal maternal immune response to prevent the rejection of conceptus, increased cortisol level, suppressed cell mediated immunity(Th1) and more reliant on humoral immunity(Th2) for protection. [10] There is also altered immune function of spleen, immune evasion by parasite. PLACENTAL MALARIA- Placenta is the main organ for malaria in pregnancy. Synthesis of immune suppressive factors mainly estrogen in placenta responsible for decreased cell mediated immunity at local site, favoring more parasite sequestration.[10] P.falciparum infected erythroblast express variant proteins on the surface which interact with various endothelial proteins of

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placenta (CSA-Chondroitin Sulphate A, HA-Hyaluronic Acid) and get sequestered there.[10] Intense sequestration of P.falciparum infected erythrocytes in placenta leads to microcirculatory obstruction in placenta and deficient nutritional supply to fetus. IFN ã & IL-2 were present only in women exposed to malaria. They cause syncytiotrophoblast necrosis, irregular thickening and scarring of trophoblastic membrane, breakdown of placental integrity.

In areas of stable malaria, adverse effect of of pregnancy is mainly seen in primigravida, most commonly severe anemia and low birth weight babies.[2] In some cases despite intense placental parasitemia the mother may be asymptomatic. In areas of unstable malaria, areas of low transmission and during epidemic pregnant women are increased risk of severe falciparum malaria irrespective of gravidity particularly in 2nd & 3rd trimester.[2]

Falciparum malaria during pregnancy increases the risk of certain complications . There is high incidence of cerebral malaria, severe anemia, pulmonary oedema and hypoglycemia.. **Cerebral malaria** probably occur as a result of heavy parasitemia and altered immune status of the patient. **Sever anemia** due to increased red cell destruction, ineffective erythropoesis, changes in erythrocytic membrane causing reduced life span of RBCs. [10] Deficiency of iron and folic acid associated with helminthic infestation further worsen the anemia particularly in the developing countries. Severe anemia may lead to congestive cardiac failure, can precipitate pulmonary oedema and contribute to increased maternal and perinatal mortality also cause LBW, prolonged labor, increased induction rate and operative deliveries.[10] **Hypoglycemia** is more commonly seen in falciparum malaria during pregnancy. Increased glucose demand by hyperparasitemia, increased metabolic demand of the febrile illness, increased peripheral requirement due to anaerobic glycolysis, failure of hepatic gluconeogenesis and glycogenolysis and quinine induced â-cell insulin hyper secretion. The risk of **acute pulmonary edema** is increased among pregnant malaria cases, can be attributed to sudden increase in capillary permeability with pulmonary capillary wedge pressure remaining normal. Pulmonary oedema may be precipitated by fluid overload, sudden increase in peripheral resistance, anemia or auto transfusion of hyperparasitemic blood from placenta at the time of delivery.

PATHOLOGY

Placenta is usually enlarged and may appear black due to deposition of malaria pigment .Parasitized RBCs are commonly observed on the maternal side of placenta and all stages of erythrocytic cycle of P.falciparum can be observed in the tissue section. Inflammatory masses of pigmented red cells, free pigment monocyte and fibrin are also characteristic finding. Trophoblasts show focal necrosis, basement membrane thickening, cytotrophoblast proliferation, macrophage infiltration and perivillous fibrin deposition.

CLINICAL FEATURES

The clinical manifestations of malaria during pregnancy may vary greatly according to the maternal immune status. Nonimmune pregnant women are susceptible to all complications of falciparum malaria. They are especially prone to develop cerebral malaria, hypoglycemia, acute pulmonary oedema, severe anemia and renal and hepatic failure as compared to non-pregnant female patients. There is increased risk of abortion, stillbirth, premature delivery and low birth weight babies. Immune pregnant women though susceptible to develop severe anemia, especially in primigravida the other manifestations are not very common. They are particularly at risk, because their malarial infection is often asymptomatic and may be overlooked. Low birth weight babies and increased risk of still birth is common in primigravida.

Cerebral malaria is common in pregnant women with P.falci-parum infection especially during the second and third trimester of pregnancy with a maternal mortality of approximately 50%. Hypoglycemia is a frequent complication of falciparum malaria and may often be severe. This may be present at the onset due to the disease process itself but more often it is seen to develop

after about 12 hours of quinine therapy. The hypoglycemia may be severe and recurrent. Patients may present with altered sensorium, convulsion and coma. There may be fetal bradycardia and fetal distress. Acute pulmonary oedema may be present at the onset or develop during treatment of malaria or may develop immediately following delivery. Severe anemia, secondary bacterial infection particularly pneumonia, urinary tract infection and multiorgan failure may occur during pregnancy contributing to the high maternal and fetal morbidity and mortality studies by Kocher et. al. from Rajasthan shows an increased incidence of severe complications including cerebral malaria, severe anemia and hepatic and renal failure in pregnant females in comparison to nonpregnant females.

Table-1: Clinical features of severe malaria.

Total	Pregnant (n=30)	Non-pregnant(n=160)
Age (in years)	18-36	16-60
Complications		
Hypotension	6(20%)	8(5%)
Hypoglycemia	1(3%)	2(1%)
Hepatopathy	11(37%)	45(28%)
Renal failure	5(17%)	37(23%)
Anemia	14(47%)	33(21%)
ARDS	5(17%)	11(7%)
Cerebral malaria	13(43%)	76(40%)
Death	10(33.7%)	31(19%)

Study conducted in P.G. Dept of medicine, S.C.B Medical College, Cuttack. ORISSA over a period of 2 years.

MANAGEMENT

Falciparum malaria in pregnancy may have a devastating outcome both for the mother as well as the child. Therefore all pregnant women with symptomatic falcilparum malaria should not only be hospitalized but also be kept in intensive care units.

CURRENT RECCOMENDATION FOR CASE MANAGEMENT[11];

1- Uncomplicaed falciparum malaria

In first trimester – 1st episode- Quinine 10 mg/kg body wt. TDS for 7 days. Preferably with clindamycin 5mg/kg body wt. TDS for 7days.

Subsequent episode- repeat treatment as above or ACT (artemisnin based combination therapy) or Artesunate 2mg/kg for 7days with clindamycin as above.

In 2nd & 3rd trimester -1st episode-ACT or Artesunate with Clindamycin

Subsequent episode - Artesunate with Clindamycin or Quinine with Clindamycin.

Prevention - Sulphadoxime & Pyrimethamine as IPT (intermittent preventive treatment)

2-Complicated Falciparum Malaria

Artesunate 2.4mg/kg through IV route at 0, 12 , 24 hours followed by same dose every 24 hour until patient can tolerate oral drug. Then 2mg/kg oral dose for total duration of 7 days. Clindamycin 5mg/kg TDS for 7 days.

Or

Quinine 20mg/kg loading dose given over 4hours of IV infusion. Then 10mg/kg every 8 hourly. Once patient able to take orally 10mg/kg TDS total for 7 days. Clindamycin 5mg/kg TDS for 7 days.

There is declining efficacy of quinine over Artesunate among pregnant malaria cases in South East Asea.[11]

Artesunate and Artemether are now recommended for pregnant women with severe and complicated malaria because they are faster acting and do not cause hypoglycemia.[11]

SUPPORTIVE TREATMENT

Since hypoglycemia is commonly seen in pregnant women blood sugar should be monitored daily and whenever necessary. Parenteral quinine should be infused with 10% dextrose, if hypoglycemias occur 25 to 50% dextrose should be administered and may be repeated. If possible oral glucose solution should be given through nasogastric tube or orally. Acute pulmonary oedema may be avoided by maintaining adequate fluid balance and monitoring CVP. Patient with pulmonary oedema should be kept in propped up position with oxygen inhalation and intravenous furosemide. Severe anemia should be treated with packed cell transfusion. Renal and liver function test should be performed routinely to detect complications early and institute

proper treatment Secondary bacterial infection should be diagnosed early and treated adequately.

Fever should be brought down quickly as high fever can lead to abortion, still birth and premature labor. Advice of obstetrician should be sought early and induction of labor, caesarian section or speeding up of 2nd stage of labor by should be considered in severe falciparum malaria in order to save the mother as well as the child.

CHEMOPRPHYLAXIS

In view of increased susceptibility to severe falciparum malaria and consequent poor maternal and fetal outcome chemoprophylaxis is recommended for all pregnant women in malaria endemic areas.

Non immune pregnant female should be discouraged to travel to malarious area particularly where multidrug resistant Falciparum malaria is prevalent.

There is no ideal drug for prophylaxis.

In chloroquine sensitive areas, chloroquine base 300mg once weekly is given.

WHO recommends in areas of medium or high malaria transmission IPT (intermittent preventive treatment) with sulfadoxime and pyrimethamine should be given at least on two occasions soon after quickening. The two doses should be given at least 4 week apart (1st dose in second trimester, 2nd dose in third trimester).This drug must be avoided during first trimester. In first trimester ITN (insecticide treated nets) encouraged along with chloroquine prophylaxis[8, 11].

Mefloquine in a dose of 250mg once weekly. Proguanil 100mg daily are also effective as chemoprophylaxis for malaria in pregnancy. They can be given all through out the pregnancy[8].

The chemoprophylaxis should be continued up to puerperium.

In endemic areas routine blood examination for malaria parasite should be done in all antenatal visits for prompt diagnosis and treatment.

CONCLUSION

Falciparum malaria continues to be a major health hazard for pregnant women. Increased susceptibility to the disease, proneness to develop severe falciparum malaria, increased risk of cerebral malaria, hypoglycemia, acute pulmonary oedema and multiorgan failure lead to very high maternal morbidity and mortality. The prognosis of fetus is adversely affected due to increased incidence of abortion, IUGR, still birth, premature labor. Early diagnosis and proper management is therefore essential in order to ensure a favorable progress and outcome of the pregnancy. In view of the high risk of severe malaria and consequent poor prognosis, chemoprophylaxis should be always advocated for pregnant women. IPT with SP (sulfadoxime & pyrimethamine) preferred as good no. of literature and trials are available. ITN (insecticide treated nets) should be encouraged for protection from the dangerous consequences of Falciparum malaria.

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Current Concept

OSTEOPOROSIS AND THE INTERNIST

Rohini Handa

INTRODUCTION

Osteoporosis is a common metabolic bone disease in clinical practice. It is characterized by reduced bone mass and micro-architectural deterioration in bone tissue. The result is an increased susceptibility to fragility fractures, common sites for which are the spine, hip and the wrist. With increasing life expectancy in India, osteoporosis is emerging as a significant public health problem.

DEFINITION

The World Health Organisation (WHO) has defined osteoporosis on the basis of bone mass measurement which is compared to the peak bone mass in a young adult of the same race and sex (T score).[1] Osteoporosis is bone mineral density (BMD) -2.5 or more standard deviations (SD) below the young adult reference mean. Osteopenia is defined as BMD between -1 to 2.5 SD below the young adult reference mean. Established or severe osteoporosis is defined as T score below -2.5 in presence of one or more fragility fractures.

It is to be emphasized that the WHO classification is derived from studies of white postmenopausal women and is not applicable to men, premenopausal women, or non-white postmenopausal women. Data from India show that BMD in Indians may be different from the Caucasians and the western reference values may not be applicable to Indians. The widespread vitamin D deficiency in India may also have an impact on BMD. BMD estimation carried out in healthy young individuals from Indian paramilitary forces with normal bone and mineral biochemical values revealed that 35%-50% of men and 14%-32% of women were osteopenic at different sites, while an additional 10% of men had osteoporosis of the lumbar spine despite optimal nutrition, good sunlight exposure and regular physical exercise.[2] This underscores the urgent need to have normative values of BMD from our country.

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PATHOPHYSIOLOGY

The trabecular (cancellous) bone is more affected by osteoporosis, despite the fact that it is cortical bone that comprises 90% of the skeleton. This is because trabecular bone has 20 times greater number of remodeling units/volume. Recently, the key cytokines involved in the development and activation of osteoclasts have been identified. RANK (receptor activator of NFêB), RANK ligand (RANKL) and OPG are the three cytokines that regulate osteoclast recruitment and function. Osteoclasts express RANK while osteoblasts express RANKL constitutively on their cell surface. RANKL, a member of the TNF superfamily of ligands and receptors, is essential for the differentiation, activation, and survival of osteoclasts. Osteoprotegerin (OPG), a soluble decoy receptor secreted by osteoblasts, blocks the interaction between RANKL and RANK and serves as a physiological regulator of bone turnover. Estrogen deficiency enhances the ratio of RANKL to OPG. Bone loss results both from oestrogen deficiency as well as by estrogen independent, age-related mechanisms like secondary hyperparathyroidism and reduced mechanical loading.

A lot of attention is currently being paid to the Wnt signaling pathway and LRP5, a member of the LDL receptor family.[3] The LRP5 and Wnt/ß-catenin play a central role in bone mass accrual and normal distribution. The LRP5 is a co-receptor of Wnt located on the osteoblast membrane between two other receptors, Frizzled and Kremen. Frizzled and LRP5 bind to Wnt, thereby stabilizing ß-catenin and activating bone formation. The Wnt signaling pathway has antagonists/inhibitors like Dickkopf protein (Dkk) and SOST gene product, sclerostin.

Better understanding of the disease pathophysiology has led to development of several targeted therapies for osteoporosis. Denosumab, a humanized monoclonal antibody to RANKL, mimics the function of OPG and is a promising agent for osteoporosis.[4] Similarly, inhibitors of sclerostin are a potential therapeutic target. Other agents in the pipeline are cathepsin K inhibitors. Cathepsin K is a tissue-specific cysteine protease expressed by osteoclasts that degrades bone and cartilage matrix proteins, including type 1 collagen.

CLINICAL FEATURES

The disease typically produces no symptoms (hence it is also called the "silent thief"). The first manifestation may be a low impact fracture defined as a fracture resulting from trauma equal to or less than fall from standing height. Fractures commonly occur in distal fore arm, vertebrae and hips, though any bone can be involved. Vertebral crush fractures lead to spinal deformities, kyphosis (Dowager's hump), loss of height and a protuberant abdomen. Patients may complain of early satiety due to abdominal compression and breathlessness. Not all fractures are symptomatic. Vertebral fractures, especially, may produce no symptoms and such 'morphometric' fractures require high index of suspicion for detection. Hip fractures are associated with excess mortality.

INVESTIGATIONS

Baseline investigations in a patient with osteoporosis should include blood counts, renal and liver function tests, serum calcium, phosphorus, alkaline phosphatase and urinary calcium excretion. In osteoporosis, these hematological and biochemical investigations are within normal limits and serve to rule out secondary causes.

The current gold standard to measure BMD is DXA (dual energy x-ray absorptiometry). DXA can be used for lumbar spine, proximal femur, forearm and even for assessment of total body composition. The radiation risk is negligible. Portable DXA can measure BMD at peripheral sites like heel, phalanges and forearm. DXA should ideally be performed at 2 sites: hip and spine (anteroposterior). Osteophytes may interfere with BMD measurement in the AP view in the elderly. Lateral spine DXA, though less precise, is less affected by spinal degenerative disease. Most treatments lead to a modest increase in BMD. The small magnitude of change in response to treatment necessitates that repeat BMD measurements be spaced fairly far apart, usually 2 years or more.

Quantitative ultrasound (QUS) is an inexpensive modality of measuring BMD. It may provide some idea about bone quality. The parameters measured include speed of sound (SOS) and broadband ultrasound attenuation (BUA) at the calcaneus. Different systems yield different values which are not comparable. The current role of QUS is as a screening procedure. It cannot be used to diagnosis osteoporosis or make treatment decisions. Patients with low QUS values should ideally be subjected to DXA for confirmation.

Resource constraints do not permit universal screening of all postmenopausal women in most countries. Screening for osteoporosis is warranted in postmenopausal women with risk factors (Table 1), patients with history of osteoporosis related fractures, patients with osteopenia or spinal deformities on spine x-rays, patients on long term corticosteroids (>3months), and men with hypogonadism/other risk factors.

Biochemical markers of bone turnover

provide an integrated assessment of global disease activity in contrast to DXA which is regional. One widely used resorption marker is N-telopeptide (NTx), which can be measured in urine and in serum. Biochemical markers do not help in diagnosis of osteoporosis or in prediction of fracture risk. These markers are usually employed to monitor response to treatment. One school of thought is that DXA should be used for initial diagnosis and urinary markers for assessing response to therapy. Drawbacks include lack of easy availability in India, lack of consensus on which marker(s) to choose, and as high as 20% variability in repeat measurements.

MANAGEMENT OF OSTEOPOROSIS

The management of osteoporosis may be divided into:

- **Nonpharmacologic Measures**
- **Pharmacologic Treatments**

Nonpharmacologic Measures

Nutrition and life style measures like adequate calcium/ vitamin D intake, weight-bearing exercises, avoidance of smoking/excess alcohol and prevention of falls are important aspects of osteoporosis management. Calcium and vitamin D through diet or supplements should be an integral part of all treatment protocols for osteoporosis. However, they should not be considered as the sole treatment of osteoporosis. The recommended calcium intake from all sources for most age and sex groups is between 1000-1500mg/ day and the recommended intake for vitamin D is between 400 and 800 IU. Dietary sources of calcium include dairy products (milk, cheese, yoghurt etc.), nuts, spinach, lettuce, chickpeas, sesame, tofu, sardines and fortified foods. There is no data to suggest that any one form of calcium supplementation like carbonate, citrate, lactate or gluconate is superior to the other. In general, calcium carbonate is best taken with meals since it requires acid for solubility while other supplements may be taken irrespective of meals. Low impact (one foot always rests on the floor) weight bearing exercises are beneficial. These may prevent bone loss but do not increase bone mass in postmenopausal women. Physical exercise improves neuromuscular coordination and reduces the risk of falls in the elderly. Other measures to reduce falls like close monitoring of vasoactive drugs, correction of visual and hearing deficits, proper environment with adequate illumination, non-slippery surface, hand rails etc. are important. In addition, hip protectors are also useful in prevention of fracture.

Ideally, prevention should begin from childhood itself with the aim to acquire optimal bone mass during growth. Peak bone mass is attained by the late 20's. Children and adolescents should have an adequate calcium and vitamin D intake. In addition, political will is needed to tackle the scourge of osteoporosis.[5]

Pharmacologic Treatments

The drugs available to treat osteoporosis may broadly be classified into agents that inhibit resorption and those that promote bone formation (Table 2).

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption by decreasing osteoclastic activity. These agents are resistant to metabolism by endogenous phosphatases and have a very long half-life in skeleton. Bisphosphonates are currently the 'first choice' drugs to treat osteoporosis. Commonly employed bisphosphonates include alendronate (70 mg weekly), risedronate (35 mg weekly) and ibandronate (150 mg monthly). Since bisphosphonates are poorly absorbed, they should be taken on an empty stomach with water and the patient should refrain from eating or drinking for at least 30 minutes. Gastrointestinal side effects are common with these drugs and include nausea, reflux esophagitis, and constipation. To minimize acid reflux, patients should not recline for one hour after a dose. To optimize treatment response all patients on bisphosphonates require adequate calcium and vitamin D. Recently, one a year intravenous zoledronic acid (5 mg intravenous infusion

over 15 minutes) has been approved for use in osteoporosis.[6] This may have the potential to reduce mortality after hip fracture.[7]

Bisphosphonates not only increase BMD at spine and hip in postmenopausal women with osteoporosis.but are also efficacious in preventing vertebral and non-vertebral fractures. These drugs are also useful in treatment of male osteoporosis and corticosteroid induced osteoporosis.

Hormone replacement therapy (HRT)

HRT means estrogens used alone or in combination with progestogens. HRT is effective in preventing clinical vertebral fractures and in preventing non-vertebral fractures, including hip fractures. It also increases BMD at all sites. There has been a marked shift in the paradigm with regard to HRT after the publication of the Women's Health Initiative (WHI) study.[8] Despite being effective, long term use of HRT cannot routinely be recommended for bone protection because HRT used for >5 years after menopause increases the risk of invasive breast cancer by 26%, the risk of coronary heart disease by 29% and the risk of stroke by 41%. Estrogen use without progesterone leads to irregular vaginal bleeding and the risk of uterine cancer. The risk of venous thromboembolism also increases substantially with HRT used in excess of 5 years. According to the current concept, long term HRT use for its bone or cardio protective effects in women over 60 is no longer recommended. It may be used short term (<5 years) for relieving menopausal symptoms.

Selective Estrogen Receptor Modulators

Raloxifene, a selective estrogen receptor modulator has mixed estrogen agonist and antagonist activity. It has estrogen like beneficial effects on bone and lipids but lacks estrogen like effects on breast and uterine tissue. The usual dose is 60 mg orally once a day without any relation to food. Raloxifene increases BMD at hip and spine and reduces vertebral fracture risk. The effect on risk of hip fracture is not known.

Parathyroid Hormone (PTH) - Teriparatide

Intermittent human PTH [rhPTH (1-34)] stimulates bone turnover and causes an increase in bone formation. It is effective in increasing BMD at all sites and in preventing vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. It is also useful in severe male osteoporosis and corticosteroid induced osteoporosis. The usual dose is 20mcg subcutaneous daily. The major deterrent to wide spread use in India is the cost.

Other Drugs

Nasal calcitonin (200 IU daily) is efficacious in preventing vertebral fractures in postmenopausal women with severe osteoporosis. However, it has not been shown to be efficacious in preventing non-vertebral fractures. It is effective in reducing the pain associated with acute vertebral fractures. Parenteral calcitonin is also available. It may be considered a 2nd choice drug for treatment of osteoporosis. Strontium ranelate is another 2nd line drug that has a dual mode of action. It increases bone formation and reduces bone resorption. It has been shown to cause early and sustained reductions in the risk of vertebral fractures. Fluorides, vitamin K, ipriflavone, anabolic steroids have virtually no role in treatment of osteoporosis.

Drug combinations in osteoporosis

According to the data available presently, combinations of 2 antiresorptives are believed not to confer added advantage over either agent alone in terms of better fracture prevention though there may be greater increase in BMD. Similarly, the effect of alendronate and PTH may not be additive. On the contrary, concurrent use of alendronate reduces the anabolic effect of PTH. However, prior treatment with bisphosphonates or raloxifene is not a contra-indication to subsequent treatment with PTH, if warranted.

Which Drug For Whom

The availability of several drugs for

ostoporosis has meant that clinicians need to make a rational, evidence based choice. Some dugs increase only BMD while others prevent fractures in addition. Of the latter, agents that prevent both vertebral and hip fractures are to be preferred over drugs that prevent only vertebral fractures. There is robust data to show that bisphosphonates prevent both vertebral and hip fractures. Also, they have the ease of once weekly/monthly oral administration. All this combines to make these agents the first choice. Raloxifene increases BMD at the spine and hip but reduces only vertebral fracture risk. It is appropriate in patients who cannot tolerate bisphosphonates due to gastrointestinal side effects. HRT use, and that too short term, is reserved only for patients who have menopausal symptoms. Despite being effective, the high cost of PTH and parenteral route of administration precludes its use as a first line drug except in very severe osteoporosis.

MALE OSTEOPOROSIS

Osteoporosis in women has relegated male osteoporosis to the background although 30% of the hip fractures and 20% vertebral fractures occur in men. Treatment options in men include bisphoshonates, testosterone and calcitonin. Bisphosphonates are agents of choice in idiopathic osteoporosis. Testosterone treatment is most effective in hypogonadal men where epiphyses have not closed completely.

OSTEOPOROSIS AND RHEUMATIC DISEASES

Osteoporosis is commonly encountered in chronic inflammatory rheumatic disorders. However, the problem remains under appreciated and under treated.[9] As many as 3/4ths of Indian women with RA have poor bone health. One in five patients have osteoporosis with an additional 55% having osteopenia. The low BMD scores are strongly associated with modified Sharp score.[10] Osteoporosis occurs in a significant proportion of patients with AS and lupus. In addition, corticosteroids too contribute to osteoporosis. Bisphosphonates can be used to treat osteoporosis in rheumatic disorders.

CONCLUSIONS

With the introduction of newer, effective agents like risedronate, ibandronate, teriparatide etc. physicians have a wide variety of drugs to combat osteoporosis. Physician awareness, patient education and resource sensitive, evidence based Indian guidelines are the need of the day.

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Table 1: Risk factors for osteoporosis

Genetic factors/Personal factors
- Low BMI (<19) - Familial prevalence - Early menopause (<45 years) - White/Asian > Blacks - Oophorectomy/hysterectomy
Life style factors
- Smoking - Alcoholism - High caffeine intake - Physical inactivity - Low calcium intake - Lack of exposure to sunlight
Drugs
- Long term corticosteroids (>3 months) - Dilantin sodium - Replacement therapy (thyroxine, hydrocortisone) - Heparin, warfarin
Medical disorders
- Primary hyperparathyroidism - Thyrotoxicosis - Addison's disease - Cushing's syndrome - Rheumatoid arthritis - Malabsorption sydromes - Chronic liver disease - Organ transplantation - Chronic renal failure - Prolonged immobilization
Men at risk for osteoporosis
- Hypogonadism

Table 2: Drugs used for Osteoporosis

Anti resorptives
• Bisphosphonates • Hormone replacement therapy • Selective Estrogen Receptor Modulators • Calcitonin
Stimulators of bone formation
▪ PTH (Teriparatide)
Agents with dual mode of action
• Strontium ranelate

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EARLY RHEUMATOID ARTHRITIS

DIAGNOSIS AND MANAGEMENT CURRENT STATUS

S. R. PAL

The management of rheumatoid arthritis has undergone a sea change since new tools and new concepts have been developed and validated highlighting the need for guidelines focused on early RA. Our aim is to achieve clinical remission early so as to prevent erosive disease, structural damage and long-term disability

Even in early rheumatoid arthritis, the activities of daily living are compromised. Within two years of onset of symptoms, the HAQ score is 0.8 – 1.04 (maximum = 3.0). Work capacity is restricted in one thirds in one year and work disabled in 40% in 3 years.

There is no consensus on how early is rheumatoid arthritis. For practical purposes, disease of duration of less than 2 years symptom onset is known as ERA. From 6 weeks to 1 year from symptom onset is known as very early RA (VERA) and disease of 1-2 years is known as late early RA (LERA).

Early RA is the time to strike hard as this is the narrow therapeutic window of opportunity. Initiating therapy even prior to development of erosions can help abort the disease and maintain drug-free remission and prevent structural damage and long-term disability.

There is no test and no diagnostic criteria to define early rheumatoid arthritis. An astute clinician picks up inflammatory arthritis early and once the definite subsets of arthritis (e.g. lupus, psoriasis, SSA) are excluded – one should estimate the risk of developing persistent and/or irreversible arthritis.

These cases of early inflammatory arthritis – unclassified – with high risk of developing persistent arthritis are defined as early rheumatoid arthritis. They do not fit into the classification criteria of RA.

Confirmation of the diagnosis of early RA is helped by the finding of high titre of anti-CCP antibodies by ELISA (1st & 2nd generation kits) The anti-CCP antibodies have a predictive diagnostic and prognostic value. They predict more erosive disease whereas RF predicts more of extra-articular disease.

Demonstration of acute synovitis with effusions or synovial thickening and increased vascularity on ultrasound examination of joints (and power Doppler study) helps confirm the diagnosis of early rheumatoid arthritis. Small joints of hands and feet are earliest picked up.

MRI picks up erosions earliest, but cost is a limiting factor. Ultrasound examination is a highly cost – effective and reliable imaging modality in the hands of skilled rheumatologists. Properly used and combined with anti-CCP antibodies, it can be used to select patients of early RA/early undifferentiated arthritis deserving early aggressive therapy.

Predictors of persistent and erosive disease include :

Number of tender and swollen joints

ESR, CRP

RF litre >50 units

anti CCP > 100 units

Radiographic erosions

In these subset of patients, very early use of effective DMARDs even before first radiographic

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evidence of erosions is advocated to prevent structural damage and disability. Early referral to a rheumatologist is the key/cornerstone to guaranteeing early diagnosis and therapeutic intervention.

The targets of management of early RA include :

to abort the disease – prevention ?

to prevent radiological damage and progression

to reduce inflammatory burden

to provide good quality of life and prevent disability

to prevent development of co-morbidities

The key recommendations for early RA include

- Lifestyle modifications – weight bearing exercises help reduce pain. Stopping smoking can prevent radiological progression of the disease.
- Pharmacological – oestroprogestins in women of child bearing age may prevent RA NSAIDs and particularly DMARDs reduce pain and DMARDs, BRMs and steroids help prevent radiological progression.
- Rehabilitative – physical fitness may prevent RA; To reduce pain, physical modalities, hydrotherapy and multidisciplinary intervention are helpful.

Treatment strategies include – combination therapy with conventional DMARDs : intensive therapy.

A combination of MTX + SSZ + high dose steroids in a step-down therapeutic strategy in 155 pts. With ERA show protracted effects on radiological progression compared to SSZ monotherapy. Results consistent with FIN-RACO study.

In the FIN-RACO study, 197 patients with RA of less than 2 years – 4 drug vs single DMARDs after 18 months – more patients of combination are in remission than those on monotherapy.

After 5 years less radiological progression and work disability are noted in the combination therapy group.

BRMs (particularly TNF a blockers) in early RA – 4 randomised controlled trials in disease of less than 3 years duration – TNF a blockers + methotrexate – increased rates of clinical remission and slowing of radiographic damage compared to MTX above.

Best study – 4 arms – sequential monotherapy, step-up combination therapy, step-dwon intensive combination therapy with high dose prednisolone, and infliximab and methotrexate. Results at end of 1 year show groups 3 & 4 show more rapid clinical response and a better radiographic outcome than groups 1 & 2. At the end of 4 years remission was maintained and radiographic progression arrested in the groups 3 & 4 (intensive therapy groups)

The Ticora study – in the patients with ERA – also support the proposition. Intensive treatment to reach a low DAS 44 score < 2.4 cause less radiographic damage than control group after 18 months of follow up.

Clinical remission today is an achievable goal. Cessation of smoking could prevent development of radiological damage and progression of R.A. It can prevent early undifferentiated arthritis progressing to RA with disability.

Glucocorticoid in early RA – There are several randomised controlled trials and 3 systematic reviews. Role of low dose glucocorticoids (<10 mg / day of prednisolone) – RCT in RA < 1 year duration – van Everdingen et al ® prednisolone group showed significantly less radiographic progression at 12-24 months. The Larsen score for RA is reduced with low dose glucocorticoids.

Another recent open study of 100 patients with undifferentiated arthritis – single dose of I.M or I.A – induces remission and is sustained in 50% of cases.

Regarding prognostic factors in early arthritis – 45 studies are available – 5 early arthritis, 40 in early RA. Some of the predictors / variables are as follows:

IgM or IgA RF

High ESR / CRP

Early radiographic evidence of erosions SJC correlates better than TJC anti CCP antibody

HLA – DRB I * 0401 & DRB I * 0404

Duration of cigarette smoking

Socially deprived areas

MRI

Strategies likely to yield best results in early RA include –

Identifying undifferentiated arthritis with potential to develop persistent and erosive arthritis. 6 studies have shown that classification criteria for established disease has little discriminant value during early months of the disease. Arthritis of more than one joint should be referred to and seen by a rheumatologist ideally within six weeks of the onset of symptoms.

Finally, practice points likely to influence outcome of ERA include – cessation of smoking, early referral to rheumatologist, very early intensive therapy for the poor prognostic group, keeping in mind the risk – benefit ratio and cost – effectiveness & monitoring disease activity and radiological damage.

Certain areas in ERA need probe and research

- ❑ Validation for diagnosis of early synovitis ultrasound / Doppler / MRI
- ❑ Accurate classification and diagnostic criteria for early RA.
- ❑ Prediction algorithms for persistent erosive arthritis and long-term disability
- ❑ Role of glucocorticoids in early RA (particularly very early RA)
- ❑ Intensive regimens and cure ? (long term remission)
- ❑ Therapeutic strategic in ERA tested on the basis of prediction models
- ❑ Studies with an appropriate design to determine the comparative efficacies and cost – effective ratio of different therapeutic strategies are required.

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ASSESSMENT OF THE SERIOUSLY ILL PATIENT

Samir Sahu

Prevention is better then cure. Early Identification of patient at risk of life-threatening illness makes. It easier to manage them appropriately and prevent further deterioration. Early identification also provides time for investigation and definitive treatment. The longer the Interval between onset of acute Illness and appropriate intervention, the more likely the patient condition will deteriorate, in many instances progressing to cardiopulmonary arrest. Several studies demonstrate that physiological deterioration precedes majority of cardiopulmonary arrest by many hours. Patient's with limited reserve are more likely to be susceptible to severe Illness and experience greater degree of organ system impairment Identifying patient at risk Involves an assessment of background health type of disease as well as the current acute physiology.

To asses the severity of the illness (how sick is the patient ?) requires measurement of specific physiological variables Measurement of vital signs - pulse rate blood pressure respiratory rate oxygenation temperature and unne output are required. Clinical monitoring helps to quantify severity, track trends and rate of deterioration and directs attention to those aspects of physiology that most urgently need treatment. The goal at this stage of assessment is to recognize that a problem exists and to maintain physiological stability while obtaining help.

Making an accurate diagnosis In the acutely ill patient often must take second place to treating life threatening physiological abnormalities Time for leisurely pursuit of differential diagnosis is not likely to be available. An accurate diagnosis is essential for refining treatment option once physiological stability is assured. The general principles of taking an activate history performing a brief directed clinical examination followed by secondary survey and organizing laboratory Investigations are fundamentally Important Good clinical skills and a disciplined approach are required to accomplish these tasks.

In the Initial assessment a brief history about the current problem and Information of background health is usually taken from witnesses & family members.

In the Initial examination patient must be fully exposed. Look, listen and feel The Initial examination must be brief and directed and should concentrate on level of consciousness, airway breathing and circulation. As treatment proceeds a secondary and more detailed survey should be conducted to refine the preliminary diagnosis and assess the response to Initial treatment. A full examination must be performed at some point and will be guided by the history and other findings.

The airway and respiratory system should be assessed first Tachypnoea is the single most Important indicator of critical illness.

The most common cardiovascular disturbance in the acutely ill patient is hypotension caused by hypovolemia or sepsis or both.

The Glasgow Coma Score (GCS) should be recorded during the initial assessment of CNS. Assessment of movement of limbs pupillary size &

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reaction should be documented More detailed assessment of central and peripheral sensory and motor function should be undertaken when time permits.

Good accurate and frequent charting is an essential part of managing critically ill patients The level of monitoring depends on the site of care and level of expertise. Monitoring is not therapeutic and is only useful when interpreted by trained Individuals. The respiratory rate heart rate GCS, BP core temperature fluid balance Inspired oxygen concentration and oxygen saturation should be changed in tile ICU central venous pressure and cardiac output may be recorded.

Additional investigation should be based on the finding of the history and examination Previous records should be reviewed and appropriate tests ordered Standard biochemistry, hematology microbiology & radiological tests should be performed as indicated. The single most useful evaluation in an acutely ill patient is an arterial blood gas analysis The presence of metabolic acidosis is one of the most Important Indicator of critical Illness.

The basic principles of resuscitation include ensuing a patent airway supplemental oxygen and restoration of circulatory volume III a severely ill patient establishing venous assess allow simultaneous blood sampling for laboratory tests. While performing these assessments an a interventions the context of the clinical presentation should direct attention is likely diagnosis and potential treatments. The history examination and laboratory test should be directed for clarifying the diagnosis and determing physiological reserve (respiratory, cardiac or renal reserve) it is particularly important to assess trend in response to treatment More experienced help must be obtained if tile patient's condition is deteriorating and if there is uncertainty about the diagnosis or treatment.

The key point in the assessment of the critically ill patient are as follows :

I. Early identification of patients at risk is essential for preventing or minimising critical Illness.

II. Resuscitation & physiological stabilization will often precede definitive diagnosis and treatment of underlying cause.

III. A detailed history is essential for making an accurate diagnosis determining the patient's physiological reserve, and establishing patients treatment preferences.

IV. Critical and laboratory monitoring of response to treatment is essential.

TABLE-1.1 FRAMEWORK FOR ASSESSING THE ACUTELY ILL PATIENT.

	PHASE-I Initial contact - first minutes (Primary survey) "What is the main physiological problem?"	**PHASE-II** Subsequent reviews (Secondary survey) "What is the underlying cause?"
History	***Main features of circumstances and environment*** * Witnesses, healthcare personnel * Main symptoms: pain, dyspnea, fatness. * Trauma? * Operative or nonoperative? * Medications/toxins?	***More detailed information*** * Present complaint
Examination	**Look; Listen; Feel** * Airway * Breathing and oxygenation * Circulation * Level of consciousness	**Structured review of organ systems** * Respiratory * Cardiovascular * Abdomen and genitourinary tract * Central nervous, musculoskeletal systems. * Endocrine, hematological systems.
Chart review documentation	**Essential physiology, vital signs** * Heart rate, rhythm * Blood pressure * Respiratory rate; pulse oximetry * Level of consciousness.	**Case records and note keeping** * Examine medical records if available * Formulate specific diagnosis. * Document current events.
Investigations	* Blood gas analysis (use venous if arterial access difficult). * Blood glucose.	* Laboratory blood tests. * Radiology. * Electrocardiogram * Microbiology.
Treatment	**Proceeds in parallel with the above** * Oxygen * Intravenous access + fluids. * Assess response to immediate resuscitation. * Call For More Experienced Advice and Assistance.	**Refine treatment, assess responses, review trends.** * Provide specific organ support as required. * Choose most appropriate site for care. * Obtain specialist advice/assistance.

TABLE-1.2 ASSESSMENT OF AIRWAY AND BREATHING

AIRWAY

Causes of obstruction

Blood, vomitus, foreign body, CNS depression, direct trauma, infection, inflammation, and laryngospasm.

LOOK For — Cyanosis, altered respiratory pattern and rate, use of accessory muscles, tracheal tug, altered level of consciousness.

LISTEN for — Noisy breathing (grunting, stridor, wheezing, gurgling). Complete obstruction results in silence.

FEEL for — Decreased or absent air flow.

BREATHING

Causes of inadequate breathing

Depressed respiratory drive:	e.g. CNS depression.
Decreased respiratory effort:	e.g. muscle weakness, nerve/spinal cord damage, debilitation, chest wall abnormalities, pain.
Pulmonary disorders:	e.g. pneumo/hemothorax, aspiration, chronic obstructive pulmonary disease, asthma, pulmonary embolus, lung contusion, acute lung injury, acute respiratory distress syndrome, pulmonary edema.

LOOK for — Cyanosis, altered respiratory pattern and rate, equality and depth of respiration, sweating, elevated juvular venous pressure, use of accessory muscles, tracheal tug, altered level of consciousness, oxygen saturation.

LISTEN for — Dyspnea, inability to talk, noisy breathing, percussion, auscultation.

FEEL for — Symmetry and extent of chest movements, position of trachea, crepitus, abdominal distension.

TABLE 1.3 : ASSESSMENT OF THE CIRCULATION

Causes of circulatory inadequacy

* Primary - directly involving the heart
  Ischemia, conduction defects, valvular disorders, cardiomyopathy.
* Secondary - pathology originating elsewhere
  Drugs, hypoxia, electrolyte disturbances, sepsis.

LOOK for — Reduced peripheral perfusion (pallor, coolness), hemorrhage (obvious or concealed), altered level of consciousness, dyspnea, decreased urine output.

LISTEN for — Additional or altered heart sounds, carotid bruits.

FEEL for — Precordial cardiac pulsation, pulses (central and peripheral) assessing rate, quality, regularity, symmetry.

* * *

Case Report

EXTENSIVE INTRACRANIAL CALCIFICATION IN A CASE OF IDIOPATHIC HYPOPARATHYROIDISM

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Abstract

An 18 year old girl presented with repeated carpopedal spasm to emergency department .She had history of convulsion since childhood and was on antiepileptic treatment. She had undergone surgery for bilateral cataract 2 years back.The diagnosis was missed until she got investigated for persistent seizures. Laboratory investigation showed hypocalcemia and decreased PTH levels. CT scan of brain showed extensive intracranial calcification involving basal ganglia, thalamus, corona radiata, subcortical white matter and cerebellum.She responded to high doses of calcium..

Keywords: hypoparathyroidism, calcification, tetany

Introduction

Hypoparathyroidism is an endocrine disorder caused by congenital disorders, iatrogenic causes, infiltration of the parathyroid glands, suppression of parathyroid function, or idiopathic mechanisms.[1]Idiopathic hypoparathyroidism is diagnosed when all the possible causes of hypoparathyroidism are ruled out.[1] The most common neurologic features in this condition are various motor disorders such as tetany, convulsion or muscle cramp, but involuntary movements such as parkinsonism or chorea is rarely encountered[2]. Basal ganglion calcification is recognized as a common manifestation of hypoparathyroidism, but calcification of the cerebral cortex is extremely rare.[5] We present a case of idiopathic hypoparathyroidism with extensive intracranial calcification.

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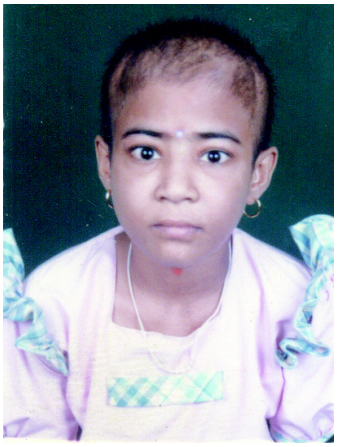
Case report



An 18 year girl presented to the department of medicine with repeated carpopedal spasms and intermittent spells of seizures. There was no history of psychosis or other abnormal movement. She gave history of recurrent attacks of generalized tonic clonic seizures since 5 years of age and was on antiepileptics (carbamazepine). She got operated for bilateral lenticular cataract 2 years back but there was no history of thyroid surgery. Her developmental milestones were normal. Family history was not suggestive.

General examination was normal except stunted growth and carpopedal spasm. Her vitals were stable. Neurological examination revealed hyperreflexia and positive chvostek's and trousseau's sign. Other systems were normal.

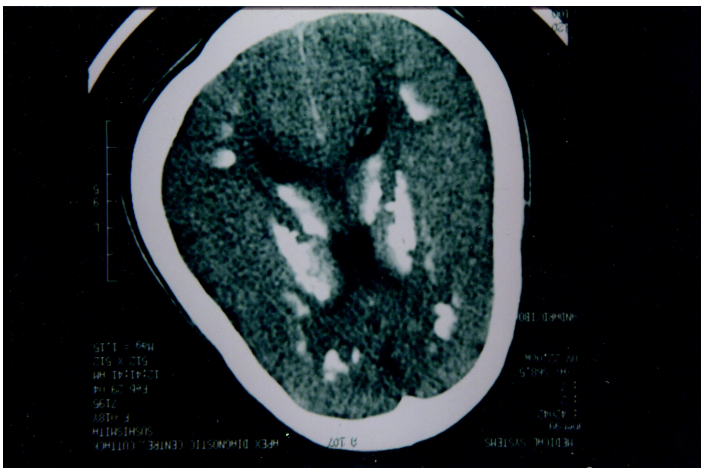
Investigations:Hb=9.0gm%,TLC=10,200/cmm,N78,L19,E2,M1,B0,TPC=2 lakh/cmm, S. bil (total)=0.3mg/dl, S. bil (direct)=0.1mg/dl, SGOT=42 IU/L, SGPT=33 IU/L, Alk Phos.=563 IU/L, S calcium(total)=5.0 mg/dl(8.5-10.1),S PTH=2.8(14.0-72.0 pg/ml),S. phosphorus=2.7 mg/dl(2.5-4.8). ECG showed QT_C prolongation(0.48s). CT scan of brain showed extensive intracranial calcification involving basal ganglia, thalamus, corona radiata, subcortical white matter and cerebellum.

The patient was diagnosed as a case of idiopathic hypoparathyroiism. Her tetany decreased with intravenous calcium gluconate. She got discharged with oral calcium, calcitriol and valproic acid.

Follow up-she has remained asymptomatic for last 3 years and there are no attacks of convulsion or tetany within this period.

Discussion

Hypoparathyroidism is an endocrine disorder caused as result of congenital disorders, iatrogenic causes (eg. drugs, removal of the parathyroid glands during thyroid or parathyroid surgery, radiation), infiltration of the parathyroid glands (eg. metastatic carcinoma, Wilson's disease, sarcoidosis) and idiopathic mechanisms.[1] In these cases there is either an apparent deficiency of PTH secretion or end-organ failure.[2] Idiopathic hypoparathyroidism is an uncommon condition.The pathogenesis of sporadic idiopathic hypoparathyroidism is unclear. Calcium sensing receptor (CaSR) plays a pivotal role in extracellular calcium homeostasis and is the presumed to be the putative autoantigen in hypoparathyroidism associated with autoimmune polyglandular endocrinopathy syndrome.[3]



In idiopathic hypoparathyroidism both calcium and PTH levels are low[4] where as in pseudohypoparathyroidism PTH levels are high with hypocalcaemia. In pseudopseudohypoparathyroidism increased PTH levels are associated with normal serum calcium and phosphorus levels .[4] Long standing hypocalcaemia gives rise to lenticular cataract which the patient suffered from at an early age for which she underwent surgery.

Radiologically, hypoparathyroidism causes calcification most often in bilateral basal ganglia.[5] The most common site is often globus pallidus.[6] Calcification can also occur in cerebellum, sub cortical white matter, corona radiata and the thalamus but are very rare.[6] This patient had extensive intracranial calcification. The mechanism of intracranial calcification in hypoparathyroidism has not been completely elucidated[7]. It may be related to the duration of hypocalcaemia and hyperphosphataemia than parathyroid hormone itself. Hyperphosphataemia promotes ectopic calcification in brain tissue in hypoparathyroidism.[7]

The immediate treatment for all types of hypoparathyroidism is calcium supplement with along with PTH in cases of acquired hypoparathyroidism.[8] To restore calcium levels in patients with symptomatic hypocalcemia, patients are treated with intravenous calcium gluconate.For maintenance and preventionof hypocalcemia, patients are treated lifelong with calcium supplements and $1,25(OH)_2D_3$(calcitriol) to stimulate absorption of calcium and phosphate from small intestine. A diet high in calcium and low in phosphorus is recommended.[4]

Symptomatic treatment is needed for seizures. Phenytoin and phenobarbitone are well known to cause vitamin D deficiency and hypocalcemia by decreasing intestinal absorption and increasing metabolism of 25 (OH) D3 in liver. Carbamazepine also interferes with 25 (OH) D3 metabolism in the

liver and its association in long term use with vitamin D deficiency has been reported.[9] A case of PHP-II like picture in anticonvulsant related vitamin D deficiency has also been reported previously.[10] Antiepileptics in patients of hypothyroidisms needs to be selective to avoid drug induced hypocalcaeimia

Conclusion

Extensive intracranial calcification can be a presenting feature of idiopathic hypoparathyroidism. Hypocalcemia manifests as tetany, seizure or syncope which are very difficult to differentiate at bedside without a proper history and observation.This patient had a missed diagnosis and was being treated as a case of iduiopathic epilepsy since childhood Treating seizure with antiepileptics in the setting of hypoparathyroidism for long periods can add to the problem of hypocalcemia. Serum calcium should be measured in all cases of epilepsy, dementia and cerebellar ataxia. Hypoparathyroidism is treatable if diagnosed early with appropriate doses of calcium and Vit D3.

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DELAYED CEREBELLAR ATAXIA FOLLOWING FALCIPARUM MALARIA: A RARE CASE REPORT

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ABSTRACT:

Delayed cerebellar ataxia is a rare acute self limiting complication of falciparum malaria [2]. This complication is predominantly found in Sri Lanka though few cases have been reported from India and Africa [2,4]. We have recently encountered such a patient in our hospital. The case is described below with pertinent literatures reviewed.

KEY WORDS:

Delayed cerebellar ataxia, *Plasmodium falciparum*

INTRODUCTION:

Delayed cerebellar ataxia found in falciparum malaria is usually an acute self limiting and isolated ataxia without cerebral involvement [4]. The patient usually shows features of midline cerebellar involvement and is characterized by cerebellar gait and truncal ataxia [1,4]. Most of the patients are afebrile before the onset of symptoms [1,4].

CASE REPORT:

A 45 year old engineer was admitted to the hospital in September '07 with complaints of difficulty in maintaining balance with a tendency to fall in all directions for the past four days. He developed high grade fever, intermittent in nature associated with chills and rigor and subsided with profuse sweating. He was admitted in the local hospital and was detected having falciparum malaria by MP slide and was treated with anti-malarials and antibiotics. The patient became afebrile after five days and was discharged. Four days later He developed instability of gait such that he lurched and fell in all directions – this left him unable to walk. He was then referred to our hospital for further investigations and management.

There was no history of diabetes mellitus, hypertension, tuberculosis or sickle cell disease.

Family history is also not suggestive of diabetes mellitus, hypertension, tuberculosis or sickle cell disease.

On admission the patient was found to be conscious afebrile. There was mild pallor, no cyanosis, icterus, clubbing, edema, Lymph node or thyroid enlargement, JVP was not raised, Pulse was 80/ min regular, B.P. 150/ 84 mm of Hg, Respiratory rate of 18/ min and temperature was 36.4 ° C.

Neurological examination revealed normal higher mental function. All cranial nerves were found normal. Motor system examination revealed normal bulk, tone and power. The gait was broad based with irregular stepping and a tendency to fall in all direction. No sensory impairment or autonomic involvement was found. On finger nose testing revealed past pointing; the knee heel shin test was found to be clumsy bilaterally. Disdiadochokinesia was present bilaterally. The deep tendon reflexes were normal, plantar was bilaterally flexor. The cranium and spine was normal and there were no signs of meningeal irritation.

The respiratory, cardiovascular, and gastrointestinal system was found to be normal.

INVESTIGATION:

On investigation Hb% was 11.2 gm/dl, DC N72 E3 L25; Total leukocyte count was 7100/cmm and ESR was 6 mm in 1st hr. Routine blood biochemistry ¾ Fasting blood glucose 110 mg/dl, urea

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28 mg/dl, creatinine 1.4 mg/dl, serum Na^+ 147mEq/l and K^+ 4.0 mEq/l. Malaria parasite by ICT was found to be positive. CT scan of brain was found to be normal and no abnormality was detected by pure tone audiometry bilaterally. CSF study was found to be normal.

The patient was diagnosed as having delayed cerebellar ataxia following falciparum malaria. He was treated with a full course of inj. Artesunate for 5 days. The patient rapidly improved and by the 5th day he was able to walk on his own. The cerebellar signs disappeared on the 6th day and he was discharged with advice after 7 days of admission.

DISCUSSION:

Neurologic features found in malaria are usually not consistent; the commonest being altered sensorium followed by seizures [1]. But cerebellar involvement is the most consistent neurological manifestation of complicated as well as uncomplicated malaria as Purkinje cells are susceptible to damage due to hyperpyrexia [4].

RBCs with parasitized *P. falciparum* adhere to the endothelial wall of capillaries in a certain phase of its cycle. Parasites derive some nutrition from endothelium. This phenomenon occurs maximally in the capillaries of brain [1]. Focal hemorrhage or non hemorrhagic infarcts in cortex, basal ganglia, thalamus, pons and cerebellum have all been described in cerebral malaria [1]. Immunologic mechanism, as a cause for delayed cerebellar ataxia has been postulated; cerebellar demyelination following falciparum malaria has been reported in several patients from Sri Lanka and India occurring several days after recovery [1,4]. The CT scan of brain is normal [1,2]. The disease has an excellent prognosis with complete recovery in 3 months [2,4]. The patients are treated symptomatically though some physicians prefer to use steroids.

CONCLUSION:

Cerebellar involvement in falciparum malaria may be due to selective clogging of cerebellar micro vasculatures with parasitized RBCs, perivascular hemorrhage, microscopic infarcts, shrinkage of purkinje cells and perivascular clusters of microglia, carrying a high mortality rate [1,3] or, may be due to immunologic mechanism as in the case of delayed cerebellar ataxia [1,4].

Delayed cerebellar ataxia is a rare complication of cerebellar involvement following falciparum malaria and may be considered in the differential diagnosis in patients showing cerebellar signs especially if the patient gives a past history of fever. This is the first reported case of delayed cerebellar ataxia from our institution.

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TUBEROUS SCLEROSIS IN ADULT : A RARE PRESENTATION

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ABSTRACT

A 25 year old male presented with repeated bouts of convulsion to emergency department. General examination revealed facial angiofibroma. CT scan of brain showed bilateral periventricular calcification suggestive of subependymal nodules of tuberous sclerosis. The patient was diagnosed as a case of tuberous sclerosis and put on antiepileptics (phenytoin sodium). He is asymptomatic for last 1 year

Keywords: tuberous sclerosis; angiofibroma, subependymal nodule

INTRODUCTION

Tuberous sclerosis is a rare genetic disorder with an autosomal dominant inheritance[1]. With an estimated prevalence of 3-10/100,000 worldwide[2], this neurocutaneous syndrome affects multiple organs like skin, brain, kidneys, eyes, lungs, teeth etc. The clinical triad of papular facial nevus, seizures and mental retardation is found in less than half of the patients. Thus the radiological hallmarks of this neurocutaneous syndrome are universally accepted as sufficient for diagnosis[3]. Although the usual age of presentation is between 2-6 years, it may present as early as infancy to late adulthood.

Here we report a late onset tuberous sclerosis presenting with status epilepticus to emergency department.

Case report :

A 25 year male presented to emergency department with repeated bouts of convulsions . There was no history of fever , headace ,vomiting, weakness or blurring of vision . There was no past history of convulsion, mental retardation or head trauma.

General examination revealed average body built, normal vitals and the presence of a butter fly shaped maculopapular rash on face involving both cheeks and bridge of the nose . There were two hyperpigmented plaques present above and below left eye.

Systemic examination including CNS revealed no abnormalities except bilateral papilledema. .

On investigations : Hb. =12.8 gm% ,TLC = 7,400 /cmm , N-80,L-18,E-2,M-0,B-0. TPC=3.2 lakhs, FBS=84.0 mg/dl, S.Urea=42.0 mg/dl, S.Creatinine=1.0 mg/dl.Other biochemical parameters like blood sugar, LFT and electrolytes were within normal range C.T. Scan of brain revealed periventricular calcification in bilateral lateral ventricles with cerebral edema suggestive of sub-ependymal nodules of tuberous sclerosis.

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Due to presence of two major criteria (table-1) like facial angiofibroma with forehead plaques and sub-ependymal nodules in CT scan, a diagnosis of tuberous sclerosis was entertained.

The patient is asymptomatic for last 1 year with anti-convulsant therapy (Sodium Phenytoin)

Table 1. Diagnostic Criteria for Tuberous Sclerosis Complex (1998)[4]

Major features	Minor features
Facial angiofibromas or forehead plaque Nontraumatic ungual or periungual fibromas Hypomelanotic macules (≥3) Shagreen patch (connective tissue nevus) Multiple retinal nodular hamartomas Cortical tuber Subependymal nodule Subependymal giant cell astrocytoma Cardiac rhabdomyoma, single or multiple Lymphangiomyomatosis Renal angiomyolipoma	Multiple randomly distributed pits in dental enamel Hamartomatous rectal polyps Bone cysts Cerebral white matter radial migration lines Gingival fibromas Nonrenal hamartoma Retinal achromic patch Confetti skin lesions Multiple renal cysts

- **Definite** – Either two major features or one major feature plus two minor features
- **Probable** – One major plus one minor feature.
- **Suspect** – Either one major feature or two or more minor features

Fig 1-facial angiofibroma with forehead plaque

Fig 2-CT scan of brain showing periventricular calcification suggestive of subependymal nodules of tuberous sclerosis

Discussion :

Tuberous sclerosis is a genetic disorder caused by mutation in TSC-1 gene on chromosome 9 (9q34) and TSC-2 gene on chromosome 16 (16p13)[1]. These two genes encode for proteins 'hamartin' and 'tuberin' respectively which act as tumor growth subpressors[1]. The name 'Tuberous sclerosis' is derived from the characteristic root like growth or 'tuber' in the brain, which later become calcified and sclerotic. The term tuberous sclerosis complex (TSC) is now widely used, emphasizing the variegated nature of its manifestations[1]. The criteria for diagnosing TSC have recently been revised (table-1)[4].

Skin Involvement :

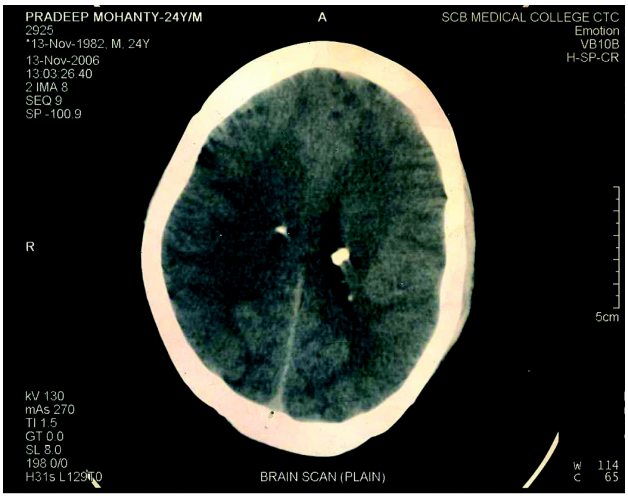
The characteristic cutaneous lesions are angiofibroma which was previously known by a misnomer 'adenoma sebaceum' (as it is not a tumor of sebaceous gland)[5]. These lesions appear in the face during middle to late childhood or adolescence in approximately 80% of patients. These red brown or flesh colored, smooth glistening, telengiectatic papules may extend from nasolabial folds to the cheeks and chin. The presence telengiectasia and the lack of comedones and pustules help to distinguish this eruption from acne vulgaris[5]. They may be observed in other areas like around nails (ungual fibromas), scalp and forehead.

Other skin manifestations include shagreen patches (large skin colored plaques with an orange peel / cobblestone texture in lumbosacral area), periungual fibromas, depigmented naevi and ash-leaf macules (ovoid, hypopigmented macules present over trunks and limbs). Café-au-lait spots also reported with increase frequency.[5]

CNS involvement :

Mental retardation occurs in 60-70% of patients. Almost all the patients with low IQ also have epilepsy whereas epilepsy occurs in 70% of those patients without mental retardation.[5]

Classical CNS involvement includes cortical tubers, subependymal nodules, subependymal giant cell astrocytoma and benign white matter lesions.[6] Tubers are benign lesions composed of dysmorphic



neurons occupying a cortical or subcortical location. They are detected by abnomal signal on MRI. or due to distortion of affected gyrus. Cortical tubers may calcify. By age ten, fifty percent of patients have calcified cortical tubers[7]. Subependymal nodules are found in nearly ninety-five percent of patients with tuberous sclerosis.[6] The commonest site is near the caudate nucleus along the striothalamic groove of the lateral ventricle. NCCT delineates periventricular and parenchymal calcification very well. Subependymal giant cell astrocytomas are histologically benign tumors located near the foramen of Monro. They are frequently calcified, appear heterogeneous on CT and show inhomogenous enhancement following contrast administration[8]. Associated obstructive hydrocephalous is a common symptom on presentation of the patient.

Renal involvement:

Renal lesions in tuberous sclerosis commonly consist of simple renal cyst and angiomyolipomas. Angiomyolipomas are benign in nature and rarely present as haematuria.[5] They may arise in renal cortex or medulla and are usually multiple and bilateral. They are present in fifty to eighty percent of the patients with tuberous sclerosis.[9] Renal cell carcinoma though rarely associated with tuberous sclerosis, may be its significant manifestations.[10]

Miscellaneous lesions:

Pulmonary findings in form of cystic lymphangiomyomas, and chronic fibrosis occur in less than one percent of patients with tuberous sclerosis.[6] Cardiac rhabdomyomas are true hamartomas and are found in approximately thirty percent of patients, predominantly children. Problems due to rhabdomyomas include mechanical obstruction and arrhythmia which occur almost exclusively during pregnancy or within the child's first year.[5,6] Retinal hamartomas may occur in some patients but usually do not impair vision. Vascular abnormalities occur in form of aneurysms of thoracic or abdominal aorta.[11]

Treatment

There is no specific treatment for tuberous sclerosis. Anticonvulsants are the mainstay of therapy. The choice of medication depends on the type of seizure. For infantile spasms, corticosteroids (ACTH or prednisolone) have traditionally been the first-line treatment, but in children with TS vigabatrin has been shown to be more effective.[12] Unfortunately, this drug can cause constriction of the visual fields and monitoring of visual fields should be done during treatment. Vigabatrin is not approved for use in the USA. For children with severe drug-resistant epilepsy, surgery to resect a cortical tuber acting as an epileptogenic focus can be beneficial.[13] Vagal nerve stimulation may be another option.

Prognosis

The prognosis for individuals with TSC depends on the severity of symptoms, which range from mild skin abnormalities to varying degrees of learning disabilities and epilepsy to severe mental retardation, uncontrollable seizures, and kidney failure. Leading causes of death include renal disease, brain tumour, lymphangiomyomatosis of the lung, and status epilepticus or bronchopneumonia in those with severe mental handicap.[14]

Conclusions

We report an unusual presentation of tuberous sclerosis manifesting in adult life with clinical and radiological signs suggesting a subependymal nodule. This provides a striking illustration of the extraordinary variation in expression of this disorder both with respect to age at presentation and severity of disease.

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ACUTE ISCHEMIC STROKE IN A YOUNG GIRL AFTER VIPER BITE

Das S.N*., Mohanty R*, Behera M.R., Choudhury A***, Jena S.K.***, Panda S.S***., Das P.K****.**

SUMMARY:

We report the case of a 22 year old girl who presented with right-sided hemiplegia and aphasia after being bitten by a viper. Follow up of this case suggested the brain injury was due to ischemic infarct. The mechanism of infarction in this case is believed to be the coagulation disorder caused by the toxins present in the snake venom.

INTRODUCTION:

Viperine snake bite primarily affects haemostatic mechanism leading most commonly to bleeding manifestations and renal failure. Neurological features of viper bite are much less frequent, and includes cranial and peripheral nerve symptoms, drowsiness, convulsion, blurred vision and loss of muscle co-ordination, sub arachnoid hemorrhage and cerebral haemorrhage[6]. However cerebral infarction is quite rare.

This case of a 22 years old girl who sustained ischemic cerebrovascular accident after a viper bite is presented and the possible patho-physiological factors are discussed.

CASE REPORT:

On 16th October, 2007 a 22 year old girl was bitten on the dorsum of the right hand. The relatives came with the patients and snake to the hospital which was identified to be viper (Saw scaled viper. *Echis carinatum*). The patient presented with severe pain at the local site and gum bleeding. In emergency department the patient was found to be disoriented, irritable, PR-100/min. all peripheral pulses were palpable. BP-120/80 mm Hg, CVS-Normal. Fang marks were visible on the dorsal aspect of right hand and there was cellulitis. Pupils were of normal size and reacting to light normally. There was no ptosis. The patient was administered 20 vials of ASV within 48 hrs. After 36 hrs of snake bite, patient developed right upper limb monoparesis which progressed to complete right hemiplegia over next 12 hrs. She was put on inj. Mannitol and conservative treatment thinking of possible cerebrovascular accident due to intra-cerebral hemorrhage. Patient became conscious, oriented but aphasic with hemiplegia on right side. Fundus examination was normal. All other cranial nerves were intact except right UMN facial palsy.

Patient was kept under observation for another 5 days and was discharged on 9th day of hospital stay. She was lost to subsequent follow up.

INVESTIGATIONS :

Hb-10.6gm%, TLC-14,200/mm3, DC-N/88, E/2, L/10, TPC-50,000/mm3,

Clotting Time-15min, Prothrombin time-Test-24, Control-14, FDP-Positive

Blood urea and S. creatinine were within normal limit. CT scan of Brain revealed multiple infarctions of left cerebral hemisphere.

ECG-Normal, ECHO-Normal, Protein C, S, Anti-thrombin C - Could not be done.

DISCUSSION :

Viperine bites accounts for nearly 50% of total snake bites in India[2,8]. Snake venom is a complex

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fluid rich in components having multiple effects[6]. The constituents are -

Proteolytic enzymes responsible for pain & local swelling, Polypeptide toxins e.g. viperotoxin which disrupts nerve impulse transmission and may lead to heart and respiratory failure, Proteases which can damage wall of blood vessels causing hemorrhage and muscle fiber destruction, Phospholipases, Collagenases and Thrombin like enzymes. It also contains Haemorrhagins, which are complement mediated toxins causing severe vasospasm, endothelial damage and increased vascular permeability, vascular occlusion and limb gangrene. This can damage major organs like kidney, heart and brain[2].

Hypovolemia due to increased vascular permeability as a part of capillary leakage syndrome contributes to the hyperviscosity[2]. Hyper-coagulation can be due to procoagulants in the venom such as arginine, esterase & hydrolase causing consumption coagulopathy[2].

Toxic vasculitis caused by certain species of viper can lead to thrombotic tendency[2]. Massive amount of snake venom produce intravascular coagulation with consequent ischemic sequelae to major organs. The cerebrovascular damage in patients with viper bite is due to

a) Direct toxic effects of venom

b) Shock

c) Arterial obstruction from thrombosis

In viper bites hemorrhage into the brain is uncommon. Non-hemorrhagic cerebral infarction is quite rare. This has been reported by Amertunga et.al. in which Russell's viper bite caused middle cerebral artery occlusion[9].

Basher and Jinkin, reported an infarction of left supraclinoid part of internal carotid artery after viper bite[3]. In a series of 309 snake bite patients Mosqura et.al. reported cerebrovascular accident in 8 cases (2.6%) of which 7 cases were hemorrhagic in nature and 1 was ischemic in nature[10].

So this rare complication of ischemic stroke in our case of viper bite could be due to triggering of intravascular coagulation cascade which might have resulted in formation of micro thrombi that led to multiple infarctions.

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A YOUNG MALE SLE PRESENTING AS RAYNAUD'S

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A 24 year old male admitted to S.C.B. Medical College hospital on 06.02.2007 for painful swelling and tenderness of both fingers and toes for 20 days, black discoloration of tips of fingers both sides and 2nd, 3rd & 5th toes right side for 10 days and pain & blue coloration of both hands and feet on exposure to cold.

No history of fever, joint pain, urinary abnormality, migrane, pain radiating to both upper limbs, respiratory symptoms, G.I. complain, ulcers in any part of the body nor symptoms relevant to cardiovascular system. Pt. was not a sickler nor suffering from any bleeding diathesis or hematological disease. Not a smoker nor alcoholic. Not on any styptic / ergot derivative, b-blockers or similar medication.

Presented at Kolkata, 2 years back in July, 2005 for sudden loss of consciousness and convulsion but without history of fever, trauma, vaccination, renal disease or rheumatic heart disease. No history of Raynaud's phenomenon in the past. Not a known diabetic / hypertensive and no such attack before this episode. Non of the family members had similar attack.

The investigation done at Kolkata in July, 2005 are normal and given in Table-1.

Patient was diagnosed to be a case of seizure disorder and discharged with eptoin. Subsequently he developed psychiatric manifestations like. irrelevant behaviour, echolalia and lack of concentration in studies. Patient gave up studies. There was no further convulsion and was alright till he developed the current problems in January 2007.

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On the day of admission patients sensorium was normal but had stammering speech, irrelevant talk with emotional outbursts. No fever, pallor, icterus, lymphadenopathy, abnormality in hair, cutaneous rash, dependent edema, CHF, thyromegaly. Pulse-88/min, regular, normal volume with all peripheral pulses well felt, no brachiofemoral delay and arterial walls were normal. Blood Pressure was 160/100 mm Hg (supine) 150/90 mmHg (standing). No abnormality detected in URT, Chest, Abdomen and Musculo-skeletal system. Examination of fingers & toes reveals raynaud's phenomenon with gangrene of the tip of the fingers and three toes. There was hyperesthesia of the palms and feet with erosion and destruction of the corresponding nails. There was no neurological abnormality. Results of laboratory test are shown in Table-2. Patient was treated with antihypertensives (Nifedipine retard and clonidine), IV antibiotics, anticonvulsant, topical antibiotic and steroid applications over fingers & toes. There was no significant improvement except for control of secondary infection.

Differential Diagnosis :

A young boy with Raynaud's phenomena and hypertension, the possible differential diagnosis includes 1) Peripheral vascular disease, but excluded as the peripheral pulses are normal with normal doppler study of limb vessels and renal vessels, 2) Thoracic outlet syndrome excluded as both upper and lower limbs were involved and no cervical rib on X-ray, 3) Syringomyelia was excluded as there was no neurological abnormalities, 4) Systemic sclerosis. Raynaud's phenomenon occurs in 80 to 90% of patients and presenting symptoms in 30% cases. But there was no skin, muscle, skeletal, visceral and esophageal involvement, 5) Mixed connective tissue disease. 30% of MCTD cases

presents with Raynaud's, but there was no systemic symptoms, skeletal or muscular abnormality and CPK values were within normal limits. 6) Rheumatoid arthritis, no musculo skeletal abnormality serological and radiological examination were normal. 7) Blood dyscrasia, myloproliferative disorders and paraproteinemia may be associated with Raynaud's, in this case Hb, PCV, ESR were normal, no evidence of venous or arterial thormobosis. 8) Idiopathic Raynauds with epilepsy. 9) SLE

Patients required further evaluated in view of :

- Seizure
- CNS manifestation like cognitive dysfunction and psychosis.
- Development of digital gangrene with Raynaud's Phenomenon.
- ANA Positive

Further investigation revealed (Table – 3)
Repeat ESR 07 mm in 1st hr, Anti-ds DNA- positive. Anti phospholipids antibody – negative

The patient was diagnosed as a case of SLE with CNS involvement and Raynauds and treated with methyl prednisolone, hydroxychloroquin and discharged with oral prednisone, hydrodychloroquine, antihypertensives & anticonvulsants. He improved and on follow up there was no Raynaud's or seizure.

Table – 1

Hb. 15G/dl	TLC-5900/cc	DLC-N57%	L20%
Comment of P.S.= normal			
FBG-84 mg%	Sr. Urea-30mg%	Sr. Cr. 0.8mg%	
	Sr.Na-134	Sr.K-4.1 mEq/L	
HBsAg, Anti-HCV & HIV – negative			
X-ray chest, ECG, EEG, USG of Abd & Pelvis - normal			
MRI scan of brain was within normal limits			

Table - 2

Hemogram			
Hb. 15.2%	ESR-06 mm 1st hr.	TLC-10400/cc	DLC-N81%
L 17%	P.S.-normal	TPC-3 lacs/cmm	PCV – 42%
Urine : Prot.-abs	RBC-abs	Pus cell-0-2/hpf	GFR-72.7 ml/min
Sr. Urea – 30 mg/dl	Sr. Cr. – 1 mg/dl	Sr.Na-136	Sr.
K-3.2 mEq/L			
FBG-78 mg/dl			
LFT – within normal limits			
CPK – within normal limits			
X-ray chest & lower cervical spine – normal, no cervical rib or thoracic outlet obstruction.			
ANA – Positive			
Rh. Factor – Negative			
USG of Abd. & Pelvis – normal		ECG-LVH	2D Echo – normal
Doppler study of limb vessels & renal artery – Normal flow pattern with no abnormality detected.			
Upper G.I. Endoscopy – Normal			

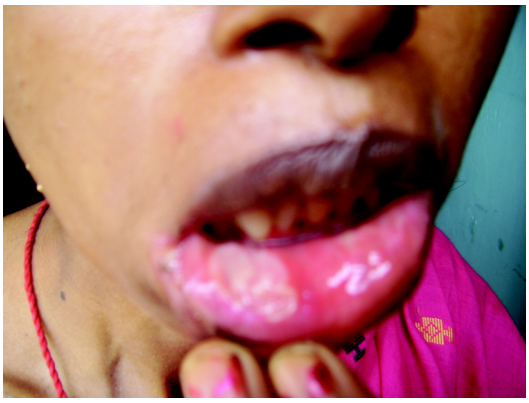
Table – 3

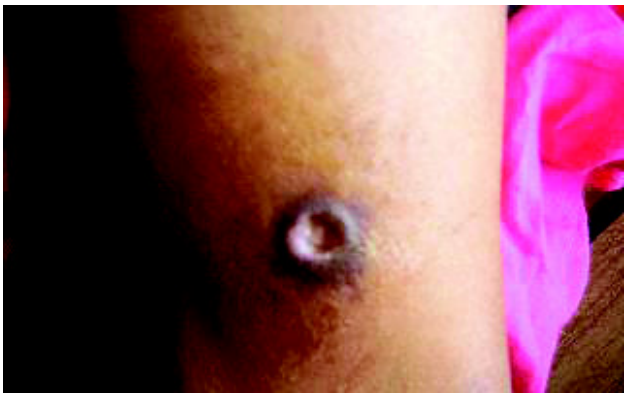
ESR – 07 mm 1st hour
Antids-DNA – Positive > 50mu/L
Antiphospholipid Ab negative <1.5 Iu/Ml.
(>15 Iu/ml positive)

Pictorial CME

BEHCETS DISEASE

J. R. Parida*, J.K. Panda*, J.M. Nayak****, S. Behera***, A Sahu**, N. Padhy**, H. Nanda*, B.K. Das*****

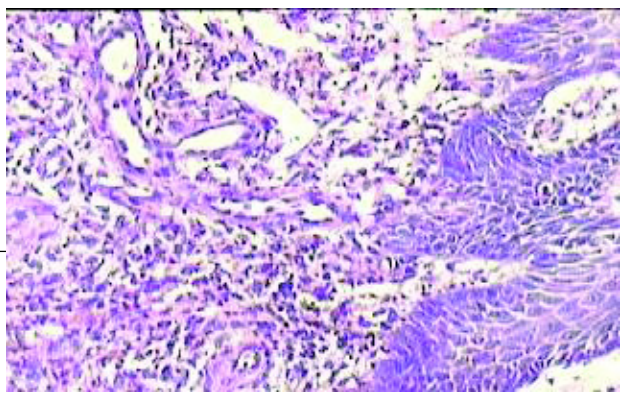




A 32 year female presented with intermittent fever, polyarthritis & multiple ulcerations in both upper &lower limbs for 3 months. She also had multiple ulcers in mouth cavity & throat for which there was difficulty in deglutition. Examination revealed multiple ulcers of varying size on bilateral thighs & legs which were tender with punched out margins. There was serosanguineous discharge from the ulcer bed. Multiple healed ulcers with hyperpigmented areas were present on bilateral arm & forearm. There were multiple tender apthous ulcers in the mouth. Pathergy test was positive. Biopsy from the margin of the ulcer showed lymphocytic vasculitis & dense perivascular infiltrate of mononuclear inflammatory cells in superficial & deep dermis. She was diagnosed as a case of 'Behcet's disease' and put on oral thalidomide 2mg/kg/d. After 2 months of treatment her ulcers healed and she became afebrile.

In the above clinical scenario, differential diagnoses likes inflammatory bowel disease(IBD) & cutaneous PAN (polyarteritis nodosa) are taken into consideration. Although it is well known that extra-articular manifestations like fever, arthritis& skin lesion can precede the onset of G.I. symptoms by 1 to 2 years in Crohn's diease ,positive pathergy test & histopathological evidence supports the diagnosis of Behcets. Multiple, tender, punched out ulcers in the limbs favours the diagnosis of cutaneous PAN, but mucosal (oral & pharyngeal) ulcers and synovitis are uncommon.Although patient with cutaneous PAN complain of joint pain adjacent to the ulcers, synovitis does not occur.

Histopathological Picture of biopsy from the ulcer site demonstrating intense infiltration of inflammatory cells



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