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Entecavir in treatment of CHB

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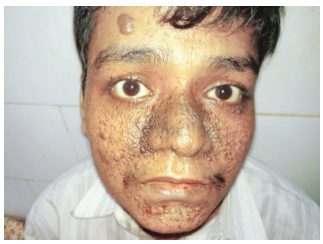

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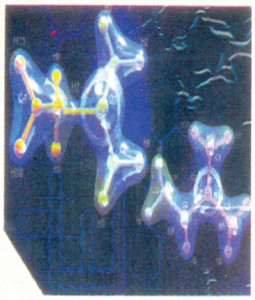

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Editorial

ENTECAVIR IN TREATMENT OF CHRONIC HEPATITIS B

B.L. Parija*, M.R. Behera**

Chronic hepatitis B virus infection is a major health problem affecting hundreds of millions of people worldwide. It may progress to cirrhosis and hepatocellular carcinoma and is responsible for almost 1 million deaths annually.[1] Eradication of HBV infection with currently available therapies is not possible. In endemic areas like South-East Asia and sub-Saharan Africa where transmission is primarily vertical or during childhood, most infections go on to chronicity.[2] In non-endemic areas such as western Europe and the U.S., transmission is primarily sexual and occurs in adulthood. When acquired during later age 95% of Acute HBV infection cases resolve spontaneously.[3] Universal vaccination of infants in both endemic and non-endemic areas will no doubt change this epidemiology over the coming decades.

Once chronicity develops, resolution of the infection as indicated by HBSAg loss and development of Anti-HBS is extremely rare. Thus the most realistic goal of therapy for chronic hepatitis B (CHB) is potent and durable suppression of viral replication aiming at arrest of progression and regression of the underlying liver disease.[4] More specifically in patients with HBeAg positive CHB, the endpoint and goal of treatment is HBeAg seroconversion and durable suppression of HBV to undetectable viral DNA level by real time PCR assays.[5]

Six drugs have been approved for the treatment of CHB. IFN.α, the pegylated form (PEG)IFN.α.2a and the nucleoside analogues Lamivudine (LAM), Adefovir Dipivoxil (ADV), Entecavir (ETV) and most recently Telbivudine (LdT).

Entecavir (ETV), a novel carbocyclic analogue of 2′ deoxyguanosine has been approved in 2005 in USA and in 2006 in Europe for naive and LAM resistant CHB treatment. The safety and efficacy of ETV were initially evaluated in a randomised placebo-controlled dose escalating study.[6] In another double blind randomised study the safety and efficacy of ETV was evaluated by Lai et al in 2002.[7] In a phase III double blind trial 714 treatment naive HBeAg positive CHB patients were studied by Chang et al in 2006 with ETV 0.5mg for 52 weeks.[8] In all those trials the high anti-HBV potency of ETV and its impressive efficacy interms of rapid HBV suppression to undetectable HBV DNA by most sensitive PCR assays was proved. This observation has made ETV monotherapy a very attractive option as first line treatment in CHB patients both HBeAg positive and HBeAg negative.

Study done by Patra et al in our institution has also observed with ETV for 40 weeks. The HBV DNA by PCR was undetectable in 64.29% cases and ALT normalisation was 100% and seroconversion was in 35.71% cases. The high anti-HBV potency of ETV in terms of rapid HBV suppression to undetectable levels of HBV-DNA combined with high efficacy to reduce serum ALT values to normal levels, and moderate HBeAg seroconversion rate of our patients is really impressive. Data from the current study indicate that clinical efficacy of ETV observed in other studies is maintained in our patients which is an encouraging observation for our physicians, hepatologist and patients as well. Though the study admitted certain limitations like small sample size, safety parameters, non-availability of patient data after 40 weeks, it is an useful study for all of us. Hence this warrants further studies to evaluate long term safety of the drug, development of ETV resistance, rebound increase in viral DNA load after 40 weeks of treatment obviously in a large sample size.

In CHB patients with LAM resistant HBV mutants particularly those with advanced chronic liver disease long term ETV monotherapy should be avoided because of the increased risk for emergence of multidrug resistant HBV strains. In near future combination of ETV with ADV or tenofovir may turn out as the most preferable long term treatment strategy.

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Original Article

A STUDY OF THE COAGULATION PROFILE IN FALCIPARUM MALARIA

S. Datta* L.D. Roul S. Das*****
J.K. Panda** N.C. Pattanayak***** S. Bhattacherjee********

ABSTRACT

Forty consecutive falciparum malaria cases alongwith ten age and sex matched controls were selected and evaluated clinically and hematologically for any coagulopathy. Among the 35% of cases with bleeding episodes, subconjunctival haemorrhage was the most prevalent manifestation. Thrombocytopenia, prolonged PT, prolonged aPTT, and raised D-dimer levels were observed in 85%, 80%, 70% and 85% of cases respectively. In the cases, the mean platelet count was 0.995±0.447 lac/mm³. INR was 1.71±0.62, aPTT was 35.25±9.45 sec and D-dimer level was 515±299.6 ng/ml. Serum D-dimer levels was significantly raised in complicated cases when compared to uncomplicated ones. Among those who died, three or more coagulation abnormalities were present and those having two or less coagulation abnormalities survived. The incidence of coagulopathy was more in cases with one or more organ dysfunction. Among complicated cases, 100% of those having nephropathy had raised D-dimer levels, and 92.3% of those with hepatic dysfunction had raised D-dimer levels. 90% of multiorgan failure, 88.9% of those with cerebral involvement and 50% of those without any organ involvement had raised D-dimer levels.
KEY WORDS: *Activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrin degradation products (FDP), disseminated intravascular coagulation (DIC), D-dimer.*

INTRODUCTION:

Malaria is a global problem caused by one of the four species of Plasmodium-falciparum, vivax, malariae or ovale. Of these, malaria caused by P. falciparum claims a special place because of its varied complications, involving multiple systems-renal, hepatic, cerebral, pulmonary, metabolic and haematologic[1].

The major changes of platelets during malarial infection are thrombocytopenia and platelet dysfunction. Thrombocytopenia occurs due to peripheral platelet destruction as a result of IgM and IgG attachment to the platelets, complement activation, and splenic sequestration, or due to consumption of platelets as a part of disseminated intravascular coagulation (DIC)[2-7]. Platelet dysfunction consists of platelet hyperactivity followed by hypoactivity [8-9]. Along with, DIC is of great concern in patients with falciparum malaria. It occurs due to release of procoagulants from parasitized RBC membrane [10] as well as intravascular lyses of RBC and platelets [11].

This study was conducted to observe the incidence of alteration in different coagulation parameters in falciparum malaria, and to correlate these coagulation parameters with clinical severity. Earlier studies had used FDP and platelet count for evaluation of bleeding abnormalities [12]. We took more definite objective parameters like PT, aPTT and D-dimer levels to assess the coagulation profile as has been recommended [13].

MATERIAL AND METHODS:

Forty consecutive adult cases diagnosed to be having falciparum malaria infection by either peripheral smear examination. or HRPII antigen detection by immunochromatographic test, or LDH detection by

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OptiMAL rapid malaria test were included in the study, along with ten age and sex matched controls. Those cases < 15 years of age, known cases of bleeding disorders, or on anticoagulant therapy, chronic liver or renal diseases were excluded. The cases included were evaluated clinically and biochemically. Also the different coagulation parameters were evaluated using various kits as detailed below.

A) Thrombocyte count.

B) Prothrombin time (PT) – Liquiplastin, Tulip Diagnostics, India.

C) Activated partial thromboplastin time (aPTT) – Liquiscelin E, Tulip Diagnostics, India.

D) D-dimer assay – Tulip XL, FDP, Tulip Diagnostics, India.

The tests were performed in accordance with the guidelines provided in the literature enclosed along with the kits.

Data was entered into MS Excel sheet and appropriate statistical methods were applied to obtain the results.

OBSERVATION:

The mean age of patients in the present study group was 37.2 ± 15.03 with male: female ratio of 1.86:1. The clinical presentation is given in table -1. Of the forty cases, fourteen cases had bleeding manifestations. The different bleeding manifestations are depicted in Fig-1. Subconjunctival hemorrhage was found to be most prevalent diathesis. Five cases were observed to have GI bleed, and three had hematuria and two cases had purpuric spots.

The comparison of coagulation parameters in cases and controls is depicted in table-3 and comparison of coagulation parameters in complicated and uncomplicated cases is depicted in table – 4. The platelet count, INR for PT, and aPTT were significantly altered in cases when compared to controls (table-3). The mean platelet count in cases was 0.995 ± 0.447 lac/mm^3.

Comparison of parameters in complicated and uncomplicated cases revealed that PT was significantly prolonged ($p < 0.01$) and D-dimer levels significantly raised($p < 0.05$) in complicated cases when compared to uncomplicated ones (table – 4). Relationships between coagulation parameter abnormalities, bleeding manifestations and mortality (table – 5) revealed that ten cases had three parameter abnormalities and twenty-two cases had four parameter abnormalities. Among the ten cases with three parameter abnormalities, four cases manifested with bleeding episodes, whereas among the twenty-two cases with four parameter abnormalities, ten had bleeding manifestations. Evaluation of mortality revealed that out of the ten cases with three parameter abnormalities, five expired, while out of the twenty-two cases with all parameter abnormalities, two cases died.

Correlation of organ involvement and coagulopathy revealed that out of the eight uncomplicated cases, six had coagulopathy, whereas all the complicated cases had coagulopathy (table-8). Chi-square test revealed that the presence of coagulopathy was significant in cases having one or more organ failure ($p < 0.05$) as compared to cases without any organ failure.

DISCUSSION:

In the present study, 45% of cases were in the age group 21-40 years with Male: Female ratio of 1.86.1. This might be because males have an outdoor lifestyle and Indian women are usually better covered with clothes. This observation is similar to the earlier reports[14].

TABLE 1: Clinical presentation of the study population

SYMPTOMS	NO	PERCENTAGE
Fever	36	95
Convulsions	5	12.5
Altered sensorium	24	60
Oliguria	8	20
Headache	7	17.5
Loose motions	1	2.5
Nausea/vomiting	13	32.5

*Multiple responses

Table 2: Pernicious Manifesatations Of Falciparum Malaria

MANIFESATATONS	NO	%
Cerebral manifestations(GCS ≤ 9)	18	45
Severe anemia(Hb<5g/dl or PCV <15%)	4	10
Renal failure (S creat > 3mg/dl)	14	35
Pulm edema	5	12.5
Hypoglycemia (RBS <40 mg/dl)	3	7.5
Hypotension/shock (SBP < 80 mm Hg)	3	7.5
Convulsions (>2 in 24 hrs)	5	12.5
Jaundice (S Bil > 3mg/dl)	23	57.5
Hyperparasitemia (>5%)	6	15
Bleeding	14	35

*Multiple response

Table 3: Comparision of Coagulation Parameters in Cases and Controls

	CASES	CONTROL	SIGNIFICANCE
Platelet count (lac/mm^3)	0.995± 0.447	2.69± 0.52	P<0.001
INR	1.71± 0.62	1.15± 0.002	P< 0.05
aPTT (sec)	35.25± 9.45	28.98± 1.66	P< 0.05
D-dimer (ng/ml)	515± 299.6	Not done	-

Table 4: Results of Different Coagulation Tests in Falciparum Malaria and Their Relation to Complications

Screening coagulation tests		No of falciparum malaria cases		Significance
		Complicated	Uncomplicated	
PT	Normal	4	4	p< 0.01
	Prolonged	28	4	
TPC	Normal	4	2	p> 0.05
	Reduced	28	6	
aPTT	Normal	8	4	p> 0.01
	Prolonged	24	4	
D-dimer	Normal	2	4	p< 0.05
	Raised	30	4	

Table 5: Relation between Coagulation Parameter Abnormalities (Thrombocytopenia, Prolonged PT, Prolonged aPTT, Raised D-dimer), Bleeding Manifestations and Mortality

Parameter Abnormalities	No.	No. With Bleeding	Death
None	2	0	0
One	2	0	0
Two	4	0	0
Three	10	4	5
Four (All)	22	10	2

Table 6: Coagulation Parameter Defects and Bleeding Manifestations Observed

PARAMETERS	NO.	PERCENTAGE
Thrombocytopenia	34	85
Prolonged PT	32	80
Prolonged aPTT	28	70
Raised D-dimer levels	34	85
Clinically overt bleeding manifestations	14	35

Table 7: Correlation of Organ Dysfunction and Raised D-Dimer Levels

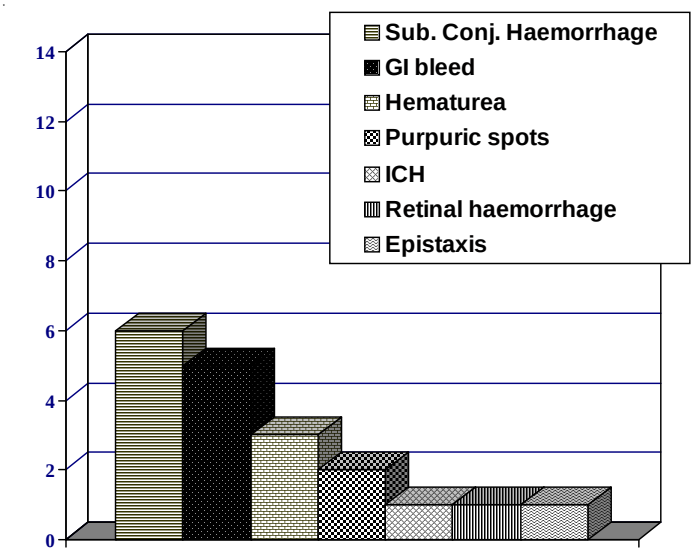
ORGAN DYSFUNCTION	NO. OF PATIENTS WITH RAISED D-DIMER LEVELS
None(n=8)	4(50%)
Hepatic(n=26)	24(92.3%)
Renal(n=14)	14(100%)
Cerebral(n=18)	16(88.9%)
Multiorgan dysfunction(n=20)	18(90%)

Table 8: Association of Organ Involvement and Coagulopathy

Coagulopathy	Organ(s) involved [out of cerebral, renal, pulmonary, hepatic]					
	None	One	Two	Three	Four	Total
Present	6	13	11	7	1	38
Absent	2	0	0	0	0	2
Total						40

$p < 0.05$

Figure 1- Showing prevalence of bleeding manifestations



Among the pernicious manifestations, jaundice was present in 57.5% of cases (table-2). Upadhyaya et al (1987) observed jaundice to be present in 6.67% of patients in series [15]. The incidence of jaundice present in the present study was therefore higher when compared to earlier studies.

In the present study, 35% of patients had bleeding manifestations. Transactions of Royal Society of Tropical Medicine and Hygiene, 2000, reports the incidence of bleeding in falciparum malaria cases to be <10% but Kocher et al (2003) [16] found bleeding manifestations in 25.52% of cases. The higher prevalence of bleeding diathesis in the present study supports the observation of Kocher.

The high incidence of thrombocytopenia (85%) in our study correlates well with the earlier publications, such as by Sharma et at (1992), who observed the incidence of thrombocytopenia to be 90%. But there was no relationship of thrombocytopenia and complications observed in the present study (table-4). When compared to controls, the cases also had prolonged INR, prolonged aPTT and raised D-dimer levels (table-3), which were of statistical significance. Similarly, prolonged PT and raised D-dimer levels in

complicated cases were also significant when compared to uncomplicated ones (table-4).

When the cases with organ dysfunction and raised D-dimer levels were correlated, it was observed that 100% of those cases with renal failure, 92.3% of those with hepatic dysfunction, 90% of cases with multiorgan failure, and 88.9% of those with cerebral malaria respectively had raised D-dimer levels. Besides, 60% of those with pulmonary edema had raised D-dimer levels. In earlier studies, Jaroonvesma et al (1972) observed raised D-dimer levels in 100% cases with cerebral malaria, whereas Sharma et al (1992) observed raised FDP levels in 75% cases with pulmonary edema. The presence of coagulopathy was significant in cases having one or more organ failure.

CONCLUSION:

Malaria is posing a challenging health hazard claiming heavy toll of lives. Falciparum malaria leads the list with all its dreaded complications, coagulopathy being one of the major determinants but often not evaluated in clinical practice. The present study showed that the incidences of coagulopathy was high in cases with falciparum malaria, where all parameters were altered when compared to controls. Also, the number of cases with coagulopathy was significantly raised in cases having one or more organ dysfunction.

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✦✦✦

Original Article

CLINICAL PROFILE OF LEPTOSPIROSIS IN A TERTIARY MEDICAL CARE CENTER OF WESTERN ORISSA, INDIA

D. K. Patel*, P Purohit, S. K. Jena***,**
S. Patel** & P. K. Padhi*****

ABSTRACT

Leptospirosis is an infectious disease caused by bacteria called Leptospira interrogans which has 23 serogroups and >200 serovars. It occurs worldwide, but it is most commonly acquired in the tropics. Outbreaks of this have been documented from various parts of the country. The diagnosis of leptospirosis is done by ELISA which detects IgM antibodies. 44 cases of leptospirosis confirmed by IgM ELISA test and were studied in details. 15-44 years of age group are infected. There were 32 males and 12 females. Farmers in rainy season were mostly infected. Most of the patients had fever(100%) followed by myalgia(95.5%), headache(90.91%), jaundice(86%), anemia(84.1%), vomiting(68.8%), oliguria(38.6%). 50% of cases had leucocytosis, 84.1% of cases had neutrophilia & 38.6% of cases had thrombocytopenia. 97.7% of cases had conjugated hyperbilirubinemia, 95.45% of patients had raised SGPT and 84.1% had raised SGOT. 70.45% of cases had increased urea level and 73% of cases had increased creatinine level. 31.8% showed renal failure. No mortality was detected in this study. For the treatment injection Penicillin or Ampicillin was used. ***Key words :*** *Leptospirosis, jaundice, malaria.*

INTRODUCTION

Leptospirosis is a worldwide zoonosis caused by Leptospira species which infect both human as well as other animals like Rats, field mice, pigs, sheep, goats, cattle & dogs. Leptospira are obligate aerobes (Spirochetes) with an optimum growth at temperature of 28-30^{-0}C and an optimum pH of 7.2 to 7.5. This infection has a great problem in tropical & subtropical regions which has suitable climatic & environmental conditions. In India leptospirosis was reported for the first time in Andamanns in 1920s and after that reports have come more frequently since 1980s especially from Gujurat (Clerke A.M. *et al* 2002), Mumbai, Kerala, Chennai (Ratnam *et al* 1994), and Andaman islands(Roy S. et al 2003) In Orissa it was first reported from Jajpur district following the super cyclone of 1999 (Sehgal *et al* 2002) and in Mayurbhanj district in November 1999 (Jena A.B *et al* 2004). Infection in human being can occur through direct contact with urine or tissue of infected animal or indirect contact with soil, water, or vegetation.

The clinical presentation of leptospirosis has got a broad spectrum varying from asymptomatic sub-clinical infections to multi-organ dysfunction. The common characteristics features of this infection are febrile illness, headache, continuous fever, prostration, severe myalgia & conjuctival suffusion. Severe leptospirosis (Weil's syndrome) is characterized by impaired hepatic and renal function, hemorrhagic diathesis with 5-10% mortality rate. Other features are rhabdomyolysis, myocarditis, pericardiatis, congestive heart failure, adult respiratory distress syndrome (ARDS), necrotizing pancreatitis, and multiorgan failure. Clinical manifestation can be divided into two distinct clinical syndromes, anicteric febrile illness and icteric leptospirosis. The second one is severe and has high mortality rate.

Leptospirosis is a potentially serious but treatable disease and a public health problem. This infection mimics severe malaria and frequently under diagnosed

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by physicians leading to inadequate treatment & death. This is because of lack of awareness about this illness & inadequate published literature in India. In view of this, this study was undertaken.

MATERIALS AND METHODS

This study was undertaken in department of medicine, V.S.S.Medical College & Hospital, Burla between June 2004 to June 2006. Patients admitted here having fever, headache and generalized body ache, with at least any one of the following set of symptoms and signs (1)Jaundice, (2) Oliguria, (3) Cough, hemoptysis and breathlessness, (4) Neck stiffness with altered sensorium & (5)Hemorrhagic tendencies including conjuctival suffusion and others were enrolled. Detailed history of all cases was taken, especially for chief complains with duration of illness, age, sex, personal and family history in a specified format. Leptospirosis was confirmed by anti-leptospiral IgM antibody by ELISA test (Adler B. *et al* 1982). Other laboratory investigations were done for renal function test, liver function test, CSF study and hematological parameters. During this study 44 cases of leptospirosis with varied presentation were enrolled.

OBSERVATION

There are 44 cases of leptospirosis patients were diagnosed clinically during this study period. The age, sex, incidence of infection in occupation, incidence in different months of a year, clinical sign and symptoms of patients, and different laboratory investigations were showed in table 1, 2, 3, 4,& 5. IgM ELISA positive for leptospirosis was found in one pregnant lady of 28wks of gestation. No mortality was detected in this study.

Table-1
Age and sex distribution of leptospirosis cases (N=44)

Age in years	Male		Female		Total	
	No.	%	No.	%	No.	%
15-24	10	22.73	3	6.81	13	29.55
25-34	9	20.45	4	9.1	13	29.55
35-44	10	22.73	3	6.81	13	29.55
45-54	1	2.27	1	2.27	2	4.54
55-64	1	2.27	1	2.27	2	4.54
65-74	1	2.27	0		1	2.27
Total	**32**	**72.73**	**12**	**27.27**	**44**	**100**

Table-2
Occupation of leptospirosis cases (N=44)

Occupation	No. of cases	Percentage
Farmer	28	63.64
House wife	5	11.36
Student	4	9.1
Others	7	15.91
Total	44	100

Table-3
Incidence of leptospirosis in different months.

Month	No. of cases	Percentage
January	2	4.54
February	1	2.27
March	3	6.82
April	1	2.27
May	2	4.54
June	6	13.64
July	5	11.36
August	9	20.45
September	4	9.09
October	5	11.36
November	3	6.82
December	3	6.82
Total	**44**	**100**

Tabe-4 Clinical presentation of leptospirosis patients (N=44)

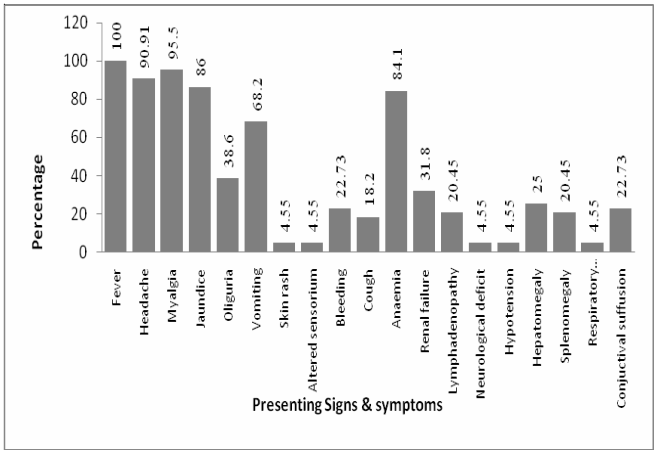

Table-5.
Laboratory investigations of leptospirosis patients (N=44)

Hb(gm/dl)	Range	**<5**	**5.1-10**	**10.1-12**	**>12**
	No. (%)	0(0.00)	33(75)	7(15.9)	4(9.1)
TLC(10^3/cmm blood)	Range	**<4**	**4-11**	**>11**	
	No. (%)	0(0.00)	22(50)	22(50)	
Neutrophile count(%)	Range	**<40**	**40-70**	**>70**	
	No. (%)	0(0.00)	7(15.9)	37(84.1)	
Platelets	Range	**<50,000**	**50,000-1lakh**	**1lakh-1.5 lakh**	**>1.5 lakh**
	No. (%)	0(0.00)	33(18.2)	9(20.4)	27(61.4)
Serum-Bilirubin (Total). mg/dl	Range	**<1**	**1-5**	**5-10**	**>10**
	No. (%)	1(2.3)	9(20.4)	9(20.4)	25(56.9)
Serum-Bilirubin (Direct). mg/dl	Range	**<0.3**	**0.3-5**	**5-10**	**>10**
	No. (%)	1(2.3)	12(27.3)	8(18.2)	23(52.2)
SGOT(IU/L)	Range	**0-35**	**36-105**	**0.6-175**	**176-300**
	No. (%)	0(0.00)	24(54.5)	15(34.1)	5(11.3)
SGPT(IU/L)	Range	**0-35**	**36-105**	**0.6-175**	**176-300**
	No. (%)	2(4.5)	15(34.1)	15(34.1)	12(27.3)
Urea(mg/dl)	Range	**10-20**	**20-60**	**60-100**	**>100**
	No. (%)	3(7)	13(29.5)	8(18.2)	20(45.3)
Urine examination	Range	**Albuminuria**	**Hematuria**	**Pyuria**	
	No. (%)	17(39)	2(4.55)	7(16)	
Serum-Creatinine(mg/dl)	Range	**<1.5**	**1.5-3**	**3-6**	
	No. (%)	12(27.3)	18(40.9)	14(31.8)	
Serum –ALP(IU/L)	Range	**<100**	**100-300**	**>300**	
	No. (%)	8(18.2)	29(65.9)	7(15.9)	

DISCUSSION

The highest incidence of leptospirosis was in 15-44 age groups. Other workers also found the peak incidence in the same age group (Jena A.B *et al* (2004), Margarita R.R *et al* (1999) & Claude Y. *et al* (1998). The incidence of leptospirosis in male to female ratio was 2.7:1. Margarita R.R *et al* (1999) reported the male to female ratio is 25:1. Jagadish C.K *et al* (2003) reported a ratio of 2.81:1 in his 84 cases of study in Manipal. Cases of incidence were higher (66%) in rainy season as humans frequently come in contact with contaminated water. Both Margarita R.R *et al* (1999) and Jena A.B. *et al* (2004) reported 100% of incidence in the same period. The infected persons are mostly belonging to farmers (63.64%) which are compatible with the study of Jagadish C.K. *et al* (2003) of 54.76%.

Out of the 44 cases of this study all 44 cases (100%) had fever, 40 cases (90.91%) had headache and 42 cases (95.45%) had myalgia which is compatible with the study of Bhardwaj R *et al* (2002). In an another study from Orissa 99% cases had fever and 63% had headache (Jena A.B. *et al* 2004). Headache was in the form of frontal headache in most of cases. Myalgia affecting thigh, calves and lower back was often severe. In our cases 86% of patients presents jaundice, 38.6% oliguria and 68.2% of cases had vomiting where it was 73%, 69% and 38.8% as reported by Margarita R.R *et al* (1999) respectively. Bleeding in the form of conjuctival suffusion was found in 22.73% but in another study by Dutta T.K *et al* (2005) the bleeding was in 10 patients out of 33 which were

in the form of melena, hematuria, retinal hemorrhage & subconjuctival bleeding. In this study hepatomegaly was observed in 25% of patients where as it was 21% by Dutta T.K *et al* (2005) and 24.6% by Berman S.J. *et al* (1973). Splenomegaly was detected in 20.45% of cases which is similar to the study of Speelman P. et al (2005). Lymphadenopathy was found in 20.45%, neurological deficit in 4.55% & hypotension in 4.55% of cases. In this study one case had right sided facial palsy, & another had left sided common peroneal palsy. Maldonado F. *et al* (2005) had reported a cause of bilateral facial palsy and suggested vasculitis as the cause. Respiratory manifestation is in the form of right side pleural effusion was found in 4.55% of the patients. Dutta T.K. *et al* (2005) had study 33 cases of leptospirosis of which 4 cases had pleural effusion, 1 case had adult respiratory distress syndrome(ARDS), 1 case of each had empyema & pneumonia.

In our study of 44 cases leucocytosis was observed in 22(50%) cases. Margarita R.R *et al* (1999) had reported in 69% of cases of leucocytosis in their study. 84.1% of cases had neutrophilia in the present study which is higher than that observed earlier by Claude Y. *et al* (1998). Thrombocytopenia was observed in 39% of cases in this study which is lower than that of the studies by Dutta T.K *et al* (2005), Claude Y. *et al* (1998) & Kishor K. *et al* (2001) who found it in 66.6%, 51% & 71.5% of cases respectively. The high bilirubin level seen in Weil's disease with mild to modest elevation of transaminases assists in differentiating it from viral hepatitis. 97.73% of cases had hyperbilirubinemia in our study but it was 73.6% reported by Margarita R.R *et al* (1999). 100% of cases had raised SGOT, 95.45% had raised SGPT and 84.1% had raised serum alkaline phosphatase which is similar to that of Margarita R.R *et al* (1999). Laurent D *et al* (2004) had reported moderate increase of serum transaminase level. Clerke A.M *et al* (2002) had reported a mild increase of serum transaminase level with hepatic involved in 71% of cases. Jagadish C.K. *et al* (2003) had also reported 65% with hepatic involvement in their study. Higher incidence of hepatic involvement in our case may be attributed to the late presentation of cases. In this study 70.45% of cases had increased urea level and 73% of cases had increased creatinine level. Out of 14 renal failure 6 underwent hemodialysis and all of these cases were recovered. Margarita R.R *et al* (1999) had reported an increase in level of serum urea and serum creatinine in 84.6% and 92.3% of cases respectively. Clerke A.M *et al* (2002) had reported involvement of kidney in 63.15% of cases. Christova I. *et al* (2003) had reported acute renal failure in 33.8% of cases. Four patients presented with bleeding manifestations & were given fresh blood transfusion. Non of the 44 cases of leptospirosis died in the present series which could be attributed to high degree of suspicion and early initiation of treatment and it needs further study for infection of leptospirosis. Out of 44 cases of leptospirosis, 37 cases were treated with injection Penicillin (1.5 million units i.v. 6 hourly), 7 cases treated with Ampicillin (500mg i.v. 6 hourly).

CONCLUSION

This study includes 44 cases of leptospirosis patients diagnosed by IgM ELISA test. The infection was prevalent in 15-44 years of age groups. Majority of the infection occurs during rainy season and mostly to the farmers. The most characteristics features of this infection are fever, headache, jaundice, myalgia, anemia, vomiting etc. In these patients there is an decrease in the level of platelets, & increase in the level of serum bilirubin, SGOT, SGPT, serum transaminase, urea, & creatinine. With early diagnosis & treatment all the patients recovered completely.

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Original Article

AN OPEN LABEL PROSPECTIVE STUDY TO EVALUATE THE EFFICACY OF ENTECAVIR IN HBeAg POSITIVE TREATMENT NAÏVE CHRONIC HEPATITIS - B PATIENTS

U.C. Patra*, N. Mohapatra, M. Nayak***, R. Panda****, M. Manjula*******

ABSTRACT

Background*: Entecavir (Baraclude) is a nucleoside analogue drug that has selective anti-hepatitis B virus (HBV) activity.It is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication,persistent elevations in serum aminotransferase and histologically active disease. We conducted a study to evaluate the efficacy of entecavir (ETV) in hepatitis Be antigen (HBeAg)-positive chronic hepatitis B (CHB) treatment naïve Indian patients in real life scenario.* ***Method:****This was a single center open label prospective observational study to evaluate the efficacy of Entecavir in chronic hepatitis B patients.A total of 28 patients were enrolled in the study from June 2009 to June 2010 .Parameters were evaluated at baseline and at 12, 24 and 40 weeks after the treatment, Efficacy of entecavir was assessed by evaluating hepatitis B virus DNA (HBV DNA), serum alanine aminotransferase (ALT) and sero-conversion.* ***Result:*** *The mean HBV DNA at baseline was 5.99 log [on a base-10 scale] IU/mL which decreased to 2.12 log IU/mL at the end of 40 weeks. Thus, there was a mean change of 3.87 log IU/m which was statistically significant (P<0.0001). Out of 28 HbeAg positive subjects, 10 (35.71 %) had become negative at the end of 40 weeks. Only 10.71% of the patients had normal ALT (<40IU/ l) values in the beginning which increased to 100% at the end of 40 weeks.* ***Conclusion:*** *Entecavir significantly improves virological, biochemical and serological markers in HBeAg positive treatment naïve chronic hepatitis B patients.* ***Key words****: Chronic hepatitis B, Entecavir, HBV DNA*

INTRODUCTION

Chronic hepatitis B affects an estimated 400 million people worldwide and causes more than 5 million deaths due to complications of chronic infection.[1] Nearly 40 million people out of the global HBV infection pool are from India and every year over 100,000 Indians die due to complications associated with chronic infection.[2]

Chronically infected patients with prolonged elevated HBV DNA level, elevated ALT level, and presence of HBeAg are at increased risk of developing progressive liver disease, cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC) and death.[1]

HBV DNA level of more than 2000 IU /ml (10^4 copies /rml) is a strong precursor for development of complications like cirrhosis and HCC.[3]

Patients with chronic HBV infection who have ALT levels that are near the upper limit of the normal range are at a significantly higher risk for complications of cirrhosis and HCC than patients with ALT levels that are less than half the upper limit of the normal range. The highest risk of complications of cirrhosis and HCC occurs in patients with ALT levels that are one to two times the upper limit of the normal range.[4]

Seropositivity for HBeAg and/or HBV-DNA > 2,000 IU/ml are significant risk factors for cirrhosis and HCC development, even in asymptomatic subjects with chronic HBV infection.[5]

The goal of treatment is to suppress HBV replication and ensure the loss of HBeAg with ALT

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normalization at the end of the treatment, thus decreasing progression of the liver disease to cirrhosis and HCC.

Drugs approved for HBV treatment include interferons, nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, and telbivudine).[6] Interferon requires parenteral administration, and causes many side effects especially in cases of cirrhosis.[7] A substantial percentage of patients, particularly those with high levels of viral replication, did not respond to treatment with interferon alfa, alone or after a short course of corticosteroids.[8] Nucleoside and nucleotide analogs are administered orally, they cause more profound HBV DNA suppression.

However these drugs are associated with rebound increase of HBV DNA levels or reactivation of hepatitis if discontinued prematurely. In addition, long-term use of these drugs is compromised by the development of resistance.[6]

ETV (Baraclude, Bristol-Myers Squibb) is a potent and selective inhibitor of HBV DNA polymerase.[9] In preclinical studies performed in chronic woodchuck hepatitis virus infections, ETV showed potent and sustained suppression of viral DNA and an absence of both viral rebounds and emerging ETV resistance (ETVr).[10] ETV reduced the covalently closed circular DNA viral reservoir to undetectable levels and extended the lives of treated woodchucks by preventing HCC.[10.] Therapy with ETV in HBeAg-positive CHB patients demonstrated superior histologic, virologic, and biochemical responses compared with lamivudine at 48 weeks.[1] In a study by Leung et al, comprehensive monitoring of genotypic and phenotypic antiviral resistance was performed on 673 ETV -treated nucleoside (naïve) HBV patients; only 3% of ETV-treated patients exhibited virologic rebound by the end of 96th week.[11]

We conducted a prospective observational study to evaluate the efficacy of entecavir in seropositive chronic hepatitis B treatment naïve Indian population in real life scenario.

METHOD

Study design

This was an open label prospective observational study to evaluate the antiviral efficacy of ETV in treatment naïve chronic hepatitis B patients.

Investigator from a single tertiary care center in Odisha, collected data on patients with HBeAg positive chronic hepatitis B, enrolled between June 2009 to June 2010 - they received 0.5 mg ETV once daily for a period of 40 weeks.The data for 28 patients were analyzed to evaluate the efficacy of ETV.

The study comprised of 4 visits, viz. baseline visit and visits after 12, 24 and 40 weeks of treatment.Of the 28 patients enrolled in the study all completed the study and were considered for evaluating efficacy data.

Patient selection

Patients meeting the following criteria were enrolled in this study: (1) men and women older than 16 years of age (2) patients with compensated liver disease documented by elevated serum ALT levels (3) patients having HBV DNA levels greater than 20,000 IU/ml; (4) hepatitis B e antigen (HBeAg)-positive; (5) nucleoside naïve patients; (6) compliant patients; and (7) women of childbearing potential willing to use an acceptable method of contraception to avoid pregnancy during treatment and for 8 weeks after completion of the study.

Patients with the following criteria were excluded: (i) if diagnosed or suspected as hepatic carcinoma patients; (ii) suffering with any serious disease besides CHB, including heart disease, immunologic disease, malignant tumor, etc. (iii) hypersensitive to nucleoside or nucleoside (acid) analogues or with a history nucleoside antiviral drug treatment; (iv) evidence of decompensated liver disease; (v) history of drug abuse or alcohol abuse; (vi) pregnant or lactating women and patients not using adequate contraceptive measures.

Intervention

Patients received medication as a part of their usual treatment. They were not exposed to any experimental investigations. After enrolment in the study, all patients received 0.5 mg of ETV orally on empty stomach once daily for a period of 40 weeks.

Data Collection

Data collection was done at baseline (visit 1) and at visits 2, 3 and 4 i.e. at 12, 24, 40 weeks of

treatment The data collected at baseline were demographics, laboratory investigations, co-morbid conditions, concomitant medications and drug allergies. At subsequent visits data useful to evaluate efficacy of ETV i.e. HBV DNA load, serum ALT and HBeAg were collected.

Assay Methodology

Serum HBV DNA was quantified using the TaqMan Real-Time polymerase chain reaction. The lower limit of detection was (< 20 IU /ml.)

Serum ALT level was quantified by local laboratory, normal value range 0-40IU/l,

Efficacy Analysis

The efficacy of antiviral therapy of chronic hepatitis B is measured using surrogate markers. These include undetectable levels of HBV DNA, normalization of ALT, and HBeAg seroconversion at the end of 40 weeks.

Statistical methods & analysis

The software package used for statistical analysis SAS software version 9.1.3

Method

Paired t-test was used for finding changes from the two visits when the data followed normality assumption and Wilcoxon signed rank test was used when data did not follow normality assumption. McNemar's test was used for paired categorical data for finding change between different visits.

OBSERVATION

Demographic Summary:

Demographics for all the subjects are shown in Table 1. The mean age of subjects was 37.6 years, with 22 years as minimum and 65 years as maximum. There were more male subjects (N=20, 71.43%) than female subjects (N=8, 28.57%). The mean (SD) weight was 60.1 kgs, N=28] with a minimum of 46 kgs and maximum of 75 kgs.

Efficacy analysis

HBV DNA (Viral load):

In Fig 2 represents undedectable levels of HBV DNA,, it was 0% in visit 1 which increased to 3.57 % in visit 2 , 32.14 % in visit 3 and 64.29 % in visit 4.

After considering the logarthimic transformation of the viral load, the mean HBV DNA (log) was gradually decreased from visit 1 (5.986 log IU/ml) to visit 4 (2.120 log IU/ml) it was statistically significant.$p<0.05$ It is graphically represented in Fig 3.

Serum ALT levels:

The mean of ALT in visit1 was 69.7 IU/L ± 25.88 IU/L. It decreased to 41.1 IU/L ± 17.98 IU/L in visit2, 27.1 IU/L ±5.44 IU/L in visit3 and 24.8 IU/L ± 2.39 IU/L in visit 4. Thus, there was a mean decrease of 44.90 IU/L ± 25.70 IU/L from the baseline to the end of the treatment at 40 weeks which was statistically significant ($P<0.0001$).

It was observed that the normal ALT level (d"40 IU) was 10.71% in visit 1, 60.71% in visit 2, 96.43% in visit 3 and 100% in visit 4, represented in Fig 1.

Seroconversion of HbeAg parameter:

Out of 28 HbeAg positive subjects in visit 1, 10 (35.71 %) had become negative in visit 4 as represented Table 2.

DISCUSSION

Although the efficacy of ETV to suppress the HBV DNA load have been demonstrated in various clinical trials there is limited data on its use in real clinical practice in India. This prospective, observational study assessed the efficacy of ETV in the routine clinical management of CHB treatment naïve patients. The present study demonstrated that ETV was associated with significantly higher rates of serologic, virologic, and biochemical improvement. Patients with undetectable levels of HBV DNA by PCR assay within

Table 1:
Demographic and disease characterstics at the base line

Demography	
Number of patients	N=28
Male/female (n%)	20/8(71.43%/28.57%)
Age (years)	37.6±10.86
Weight (Kgs)	60.5±8.43
Disease characterstics	**at baseline**
Mean HBVDNA	Log 5.99 ± 1.116 IU/mL
Mean Serum ALT	69.7 ± 25.88 IU/L
HBeAg positive	N=28(100%)

Table 2
HBeAg seroconversion

	Baseline	40 weeks
HBeAg positive	28(100.0%)	18(64.29%)
HBeAg negative	00(00.0%)	10(35.71%)

Figure 1 Bar graph for the ALT categorization from Baseline to 40 weeks

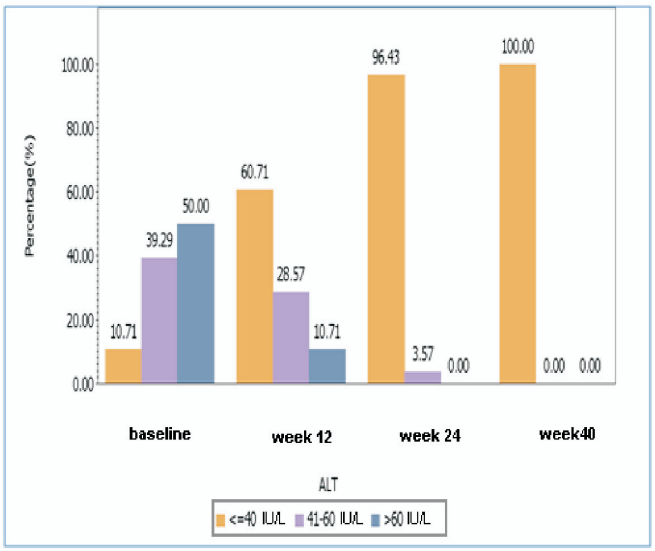


Figure 2
Bar graph for HBV DNA viral load

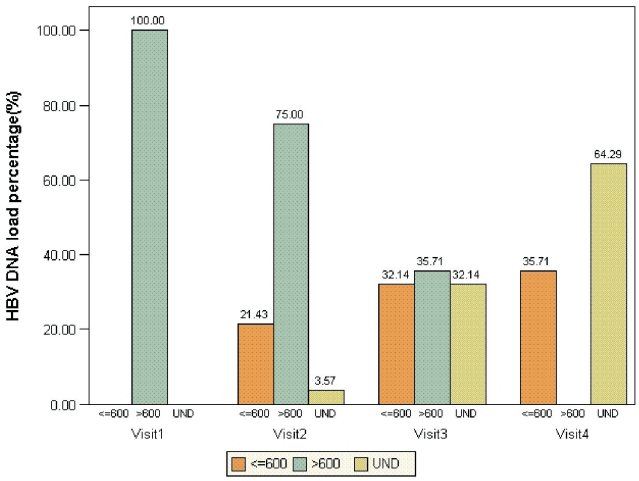
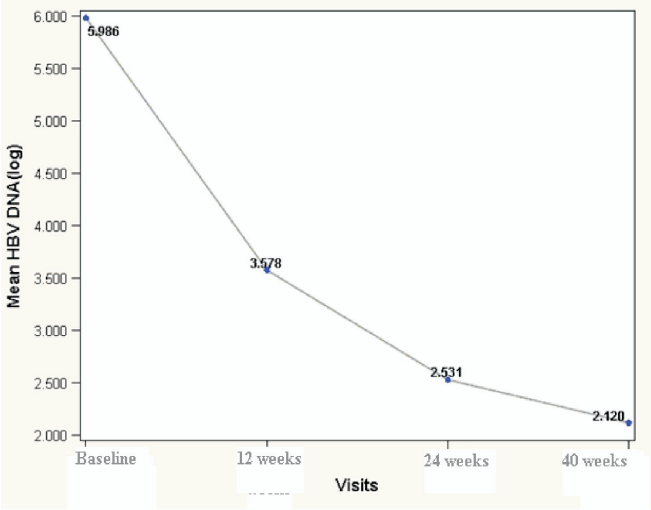


Figure 3 changes in HBV-DNA (log) viral load from baseline to 40 weeek



40 weeks after the start of treatment.was 64.29%.ALT normalization from base line to the end of treatment at 40 weeks was 100% and seroconversion of patients with HBeAg was 35.71%

The present results are in agreement with a study conducted by Chang et al which showed that more patients in the ETV group had undetectable serum HBV DNA levels than in the lamivudine group according to PCRassay (67 % vs. 36 %, P<0.001) and normalization of ALTlevels (68 % vs. 60 %,). The mean reduction in serum HBV DNA from baseline to week 48 was greater with ETV than with lamivudine (6.9 vs. 5.4 log [on a base-10 scale] copies/ml, P<0.001). HBeAg seroconversion occurred in 21% of entecavir-treated patients and 18% of those treated with lamivudine Patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic, and biochemical improvement are significantly higher with entecavir than with lamivudine.[12]

Study conducted by Fen-Yu et al on Entecavir in patients with HBeAg positive chronic hepatitis B patients concluded that entecavir was significantly more effective than lamivudine in suppressing viral DNA load to undetectable levels in patients who were nucleoside naïve and more patients achieved normalization of ALT levels at the end of 48 weeks.[13]

Serum HBVDNA rebounds with the development of viral resistence which is monitored by

genotypic analysis of isolates. In the current study with ETV in nucleoside naïve patients although development of viral resistence was not monitored, however it demonstrated that there was no virological breakthrough and viral rebound after 40 weeks of treatment,.these results are consistent with studies conducted by Colonno et al[10] and Tenny et al[14]

ETV demonstrates a potent anti-HBV activity and a low rate of emergence of drug resistance, with good safety and tolerability profiles. American association for the study of liver diseases (AASLD) and European association for the study of the liver (EASL) approved ETV as first-line therapy for treatment-naïve CHB[15,16]

The high anti-HBV potency of ETV, its impressive efficacy in terms of rapid HBV suppression to undetectable levels of HBV DNA by most sensitive PCR assays, combined with its high efficacy to reduce serum ALT values to normal levels, moderate HBeAg seroconversion rate of patients and rare development of resistence after long term use is demonstrated in various randomized clinical trials.[1,11,17,18,19]

Data from the current study indicate that clinical efficacy of Entecavir observed in other studies is maintained in patients receiving Entecavir in India under real clinical practice conditions.

LIMITATIONS

In this study safety parameters were not taken into consideration, data of the patients after 40 weeks of treatment was not available therefore further studies should be done to evaluate rebound increase in viral DNA load , development of ETV resistance and long term safety of the drug Sample size in this study was small and patients had no other co-morbid condition and no concurrent drug was administered,.futher studies can be conducted to evaluate the efficacy of ETV in chronic hepatitis B patients suffering from other co morbid conditions

CONCLUSION:

Among patients with HBeAg positive chronic hepatitis B who have not previously received nucleoside analogue, ETV significantly improves virological, biochemical and serological markers.

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Original Article

CLINICAL OBSERVATION OF SEVERE FALCIPARUM MALARIA IN PREGNANT WOMEN - HOSPITAL BASED STUDY FROM ROURKELA

D. Mishra*, M. Mohanty*, M. Bara*, S. K. Mishra**

ABSTRACT

***Background**: Malaria in pregnant women is associated with increased morbidity and mortality. The clinical course of malaria in pregnant women is associated with several problems in comparison to non pregnant women. Malaria during pregnancy and post partum period must be treated promptly as it is more severe, is associated with high parasitaemia, and is dangerous to both mother and foetus. **Subjects and Methods**: Rourkela is situated in the western part of Orissa which contributes a large number of falciparum malaria cases. The study was conducted at Ispat General Hospital. The clinical presentation of malaria in pregnant women was compared with non pregnant women. **Observations**: 475 female patients with malaria of whom 51 with pregnancy were studied. The complications were significantly higher in the pregnant women, viz., anemia (31.4% vs 8.3%), cerebral malaria (29.4% vs 9.7%) and acute renal failure (15.7% vs 3.1%). However, the incidence of jaundice was similar (23.5% vs. 18.9%). The mortality was four times higher than the non pregnant women (19.6% vs 4.5%). **Discussion**: Management of malaria in pregnant women is a challenging task. It needs intensive therapy due to presence of multi organ failure. Unless prompt attention is given, the prognosis is poor. Studies should be conducted for the safety and efficacy of prophylactic as well as curative treatment. **Key words:** Plasmodium falciparum, pregnancy, cerebral malaria, anaemia.*

INTRODUCTION

Malaria is a major public health problem of developing countries including India. Malaria in pregnant women is associated with increased risk of morbidity and mortality in both mother and the foetus. Gravid women are prone to develop severe complications not only during pregnancy but even in the post partum period. The outcome is often poor than the non gravid women[1,2,3] Scant data is available from different health care facility from India.[4,5,6]

MATERIALS AND METHOD

Study area:

Rourkela is situated in Sundargarh District of Orissa, India. It is located between 21^0 35/ and 22^0 35/ N and 83^0 32/ and 85^0 22/ E. It presents good ecologic conditions for malaria transmission with undulating uplands intersected by forested hills, rocky streams, and paddy fields. The climate is tropical with an annual rainfall of 160 – 200 cms. The maximum temperature is 40 – 46^0 C during hot dry summer (April to June) and minimum temperature of 5 – 10^0 C during winter (December & January). Highest transmission occurs between September to mid December which is just after the monsoon (mid June to September). Patients are admitted from all over the district of Sundargarh as well as from adjacent districts of Orissa, Chhatishgarh and Jharkhand.

The study was conducted at Rourkela, in Orissa state in eastern in India. The catchment area of the hospital includes a large township, adjacent suburbs, surrounding villages, forested and hilly areas; riverside

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small dwellings and mining settlements. The main river had two big tributaries, in addition to several rivulets and springs, water reservoirs.

Hospital:

Ispat General Hospital is a tertiary care centre catering to about two million people. from Sundargarh, and the adjacent districts of Orissa, Chhatisgarh and Jharkhand. There is facility for intensive care unit, renal replacement therapy, blood banking, clinical biochemistry and hematology, round the clock. The hospital is a regular training centre for "Severe malaria" for doctors. The annual admission to IGH is 28,000 to 30,000. About 2500 to 2800 pregnant women are admitted to the hospital per year.

Inclusion criteria

The study included all the female patients admitted to the Internal Medicine or Obstetrics & Gynaecology units of IGH, who have evidence of asexual falciparum malaria in their peripheral blood smear or the rapid diagnostic test positive for *P. falciparum* malaria.

Severe malaria:

Severe falciparum malaria was diagnosed as per the criteria of the World Health Organization.[1] In brief, the criteria are as follows:

The diagnosis of severe complicated malaria is considered when patients of falciparum malaria present with one or more of the following manifestations.

1. Cerebral malaria.
2. Severe anemia (Hb < 5 g/dl or PCV < 15).
3. Renal impairments (very low urine volume, serum creatinine > 3 mg/dl).
4. Jaundice (Serum bilirubin > 3 mg/dl).
5. Multiple convulsions.
6. Hypoglycemia (Blood glucose < 40 mg/dl).
7. Circulatory collapse.
8. Pulmonary edema or Respiratory distress (acidotic breathing).
9. Abnormal bleeding.

Clinical history and physical findings were recorded in a format. Particular attention was paid to neurological examination (including GCS), urine output, cardiovascular and pulmonary condition. A detail obstetrics history was collected and examined.

Blood was collected for investigations: haematological (haemoglobin, total and differential count) and biochemical tests (viz., plasma glucose, blood urea, serum creatinine, serum bilirubin, ALT, electrolytes and plasma bicarbonate). The patients were treated with antimalarials as per the national guidelines.

STATISTICAL METHODS:

The differences in various groups were analyzed by c^2 tests. The level of significance was considered only when the p value is less than 0.05 ($p< 0.05$). To find out the relative risk, we used the odds ratio with 95% confidence interval (RR, 95% CI).

RESULTS:

There were 475 female patients with proven asexual falciparum malaria in the peripheral blood. Of these 54 were associated with pregnancy while the others were non pregnant. There was no difference between the pregnant vs non pregnant group in the symptomatology (fever, headache, or vomiting)

However, the pregnant women were found to be associated with pallor, renal impairment and respiratory distress.

Cerebral malaria: Nearly 30% of the pregnant women had evidence of cerebral malaria as per WHO criteria. While about 10% of the non pregnant women admitted with malaria had CM.

Similarly, all the complications were significantly higher among the pregnant women than the non pregnant women (Table-1). However, there was no difference in the proportion of patients with jaundice in the two groups. (Table -1)

The mortality was four times higher among the pregnant women associated with malaria than those without pregnancy.

DISCUSSION:

The clinical course of malaria in pregnant women is often associated with multiple problems in comparison to non pregnant women. Malaria during pregnancy and post partum period must be treated promptly as it leads to adverse effect on both mother and foetus.

Pregnant women in non endemic areas or low endemic areas are susceptible to cerebral malaria, acute renal failure, jaundice, and anaemia. The mortality is higher than non-pregnant women. Immune pregnant women (from endemic areas) are susceptible to severe anaemia, especially primigravidae, but the other manifestations of severe malaria are unusual. In the present study from an endemic area of India, all the complications except jaundice were significantly higher among the pregnant women than the non-pregnant women. The mortality was also four times higher.

Cerebral malaria:

Pregnant women are vulnerable to develop cerebral malaria. In the present study the incidence of CM was thrice as common among the pregnant women.

Anaemia:

Increased incidence of maternal anaemia is associated with both maternal and perinatal mortality. It may be due to haemolysis, or pre existing nutritional deficiency. The malarial anaemia may be complicated by iron and/or folic acid deficiency anaemia. One third of the pregnant women had Hb below 5 gm/dl in the present study. This itself is a bad prognosticator. Often facility for safe blood transfusion is lacking in many centres in rural India, complicating the situation.

Pulmonary complications:

Pregnant women are vulnerable to develop pulmonary oedema, and acute respiratory distress syndrome (ARDS). The fatality with ARDS is more than 80%. In the present study, about a fourth had respiratory distress and nearly 10% needed ventilator support.

Severe falciparum malaria is lethal to the mother than the non pregnant women. In the present study, the mortality is four times higher. In a study from Bikaner, the mortality rate was 37.8% in pregnant females in comparison to non-pregnant females (14.8%); ($p < 0.001$). The incidence of various pernicious syndromes including cerebral malaria, severe anaemia (Hb < 5 g%) hepatic and renal failure were more in pregnant females in comparison to non-pregnant females.[5]

Table-1: Malaria in pregnant & Non-pregnant women

	Pregnant n= 51	%	Nonpregnant n=424	%	p
Duration of fever (in days)	6 (1-15)		5 (1-21)		NS
Severe anemia	16	31.4	35	8.3	0.0002
Acute renal failure	8	15.7	13	3.1	0.0003
Jaundice	12	23.5	80	18.9	0.44
Respiratory distress needing ventilator	5	9.8	11	2.6	0.007
Death	10	19.6	19	4.5	0.002

There is always a risk of multiorgan failure in pregnant women with poor survival. The prediction score for malaria[7] may be used for pregnant women.

It is pertinent that prompt attention should be given for prophylaxis in pregnant women. Studies should be conducted for the safety and efficacy of prophylactic antimalaria regimens. There must be an all out effort to train the village health workers for greater alertness for recognizing the red signals of severe malaria.[8] Prompt and free treatment for malaria should be included in Janani Suraksha scheme.

ACKNOWLEDGEMENTS:

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Original Article

STUDY ON LEVEL OF HIGHLY SENSITIVE CRP(hs-CRP) IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

The work entitled "Level of hs-CRP in Acute myocardial infarction was carried out in the dept of General Medicine of MKCG medical college, Berhampur during the period Sep 2008-Sep 2010. 50 patients of Acute myocardial infarction and 50 healthy controls were included and serum hs –CRP was estimated by ELISA technique. Cases were diagnosed using ACA/WHO task force criteria & different variables were studied using Chi-square analysis. The serum hs-CRP level was elevated in 96% of AMI and was with in normal limits in control group. Among different groups, STEMI cases had higher value of hs-CRP as compared to NSTEMI. Patients with higher BMI, diabetes, smokers, & those with higher LDL shows significant elevation of hs-CRP as compared to control group. This study shows the importance of inflammation in coronary events & the regular use of hs-CRP in addition to the routine blood sugar, lipid profile tests, may be helpful to reduce the final coronary event. ***Key words*** *: CRP, Highly sensitive CRP, Acute Myocardial Infarction.*

INTRODUCTION

Atherosclerosis remains the major cause of death and premature disability worldwide.Moreover current predictions estimate that by 2030,ischemia related CV diseases will responsible for 28% of all deaths globally.

A growing panel of markers of coronary risk presents a perplexing array to the practitioner.Markers measured in peripheral blood includes size fraction of LDL, level of CRP ,homocysteine, Lp(a), fibrinogen ,myeloperoxidase among many others.

Of these hs-CRP may well prove an exception in view of its robustness in risk prediction, its ease of reproducible and standardized measurement and this simple blood test may prove useful in the future in guiding therapy ,particularly in primary prevention

Inflammation has emerged as a key mediator of atherosclerosis. Substantial evidence indicates that inflammation plays a significant role in the transition from stable to vulnerable plaque and plaque rupture.

A growing number of studies report that inflammation plays a crucial role in the cell biology of atherosclerosis. Pathological and immunohistochemical staining studies have clearly shown a preponderance of inflammatory cells in the ruptured plaque of patients who have died of ACS. The importance of CRP lies here as a marker of inflammation.

CRP is a plasma protein, an acute phase protein produced by liver and adipocytes, originally discovered by Tillet in 1930. Its levels rise dramatically during inflammatory processes and measuring and charting CRP values can prove useful in determining disease progression or effectiveness of treatment. hs-CRP levels have received widespread attention because of multitude of prospective studies that have shown that high level of hs-CRP (>3mg/L) identify increased risk of CV events in CAD. In fact, hs-CRP seems to be at least as predictive of cardiac risk as cholesterol levels.

AHA and centre for disease control and prevention recommends hs-CRP as part of routine screening for those who are at intermediate risk for heart disease (Framingham risk score 10-20 %) hs CRP is primarily synthesized and secreted rapidly in liver 6 hours after an acute inflammatory stimulus. Serum levels of CRP with in 6 hour after the onset of AMI merely reflect a chronic and persistent

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inflammatory process and are not due to acute myocardial damage

MATERIALS AND METHODS

The present study was conducted to compare the serum hs-CRP level between patients presenting with AMI (STEMI&NSTEMI) and healthy controls 50 cases of AMI cases admitted to medicine dept. of MKCG MCH, Berhampur during the period 2008-2010 constituted the material of the present study. Fifty age and sex matched healthy subjects, comprising of relatives of patients constituted the control group.

Inclusion criteria

All diagnosed cases of AMI presenting with in 6 hour of onset. Diagnosis of AMI was done according to ACA /WHO task force criteria based on cardiac markers, ECG changes and ischemic symptoms

Exclusion criteria

Those presenting after 6 hours of onset of symptoms, H/O recent surgery or trauma with in the past 2 months, Malignancy, Febrile conditions, recent infections, acute or chronic inflammatory diseases, connective tissue disorders.

STUDY PROTOCOL

- Cases were selected on the basis of above inclusion criteria.
- Thorough history taking, clinical examination and relevant biochemical tests including ECG, chest X ray, lipid profile, blood sugar, serum cardiac markers.
- hs-crp estimation : 2 ml of venous blood is collected and hs-crp assay using solid phase enzyme - linked immunosorbent assay.

Based on hs-crp level patients are classified as low grade (<1mg/l), intermediate grade (1-3mg/l), and high grade (>3mg/l).

OBSERVATIONS

AGE AND SEX DISTRIBUTION

Age Group	Male	Female	Total
<50 Yrs.	2 (4%)	0	2 (4%)
50 - 60 Yrs.	11 (22%)	2 (4%)	13 (26%)
60 - 70 Yrs.	26 (52%)	5 (10%)	31 (62%)
>71 Yrs.	2 (4%)	2 (4%)	4 (8%)
Total	**41 (82%)**	**9 (18%)**	**50 (100%)**

URBAN, RURAL DISTRIBUTION

Resident Pattern	Male	Female	Total
Urban	15 (30%)	3 (6%)	18 (36%)
Rural	26 (52%)	6 (12%)	32 (64%)
Total	**41 (82%)**	**9 (18%)**	**50 (100%)**

SOCIO-ECONOMIC STATUS (SES) SPECTRUM OF ACUTE MYOCARDIAL INFARCTION

AMI	No. of cases	Percentage
ST Elevation	40	80%
Non-ST Elevation	10	20%
Total	**50**	**100%**

SERUM hs-CRP IN AMI PATIENTS

Serum hs-CRP (mg/l)	No. of cases	Percentage
>3 mg/L (high)	35	70%
1-3 mg/L (Moderate)	13	26%
<1 mg/L (Low)	2	4%
Total	**50**	**100%**

COMPARISON OF SERUM HIGHLY SENSITIVE C-REACTIVE PROTEIN LEVELS BETWEEN AMI & CONTROLS

Groups	Serum C-reactive Protein Level (mg/L)		
	Mean	S.D.	P Value
AMI (n=50)	3.20	0.84	P < 0.001
Controls (n=50)	0.33	0.07	

hs-CRP IN DIFFERENT AGE GROUP

Age Group (Yrs.)	No. of cases	Mean CRP (mg/L)
<50	2	2.15 ± 0.11
50 – 60	13	3.02 ± 0.56
60 – 70	31	3.22 ± 0.20
>71	**4**	**3.18 ± 0.88**

hs-CRP AMONG DIFFERENT TYPES OF AMI COMPARISON OF hs-CRP IN BOTH SEXES

Sex	No. of cases	Percentage	Mean CRP (mg/L)
Male	41	82%	3.26±0.14
Female	9	18%	3.26±0.76

hs-CRP IN SMOKER / NON-SMOKER

No. of cases	Percentage	Mean CRP (mg/L)
17	34	3.18 ± 0.76
33	66	3.00 ± 0.22

hs-CRP & BMI CORRELATIONSHIP BETWEEN PATIENTS OF ACS

BMI	No. of cases	Percentage	Mean CRP (mg/L)
<20	0	0	--
20-24.9	15	30	3.18 ± 0.76
>24.9	35	70	3.26 ± 0.11

DIABETES AND hs-CRP PROFILE

FBS (mg%)	No. of cases	Percentage	Mean CRP (mg/L)
<126	20	40	3.00 ± 0.66
>126	30	60	3.22 ± 0.88

hs-CRP & SERUM LDL CHOLESTEROL

Serum LDL (mg%)	No. of cases	Percentage	Mean CRP (mg/L)
100-110	15	30	3.08 ± 0.16
110-130	20	40	3.16 ± 0.22
>130	15	30	3.33 ± 0.19

SUMMARY

There were 40 patients (80%)with STEMI and 10 patients (20%) with NSTEMI. The serum hs-CRP level was elevated in 96%of cases of AMI and was with in normal limits in the control group. The mean hs-crp levels were 3.20mg/l and 0.33mg/l in AMI patients and healthy controls respectively. Among different groups STEMI had higher hs-crp value compared to NSTEMI. The hs–crp levels were high among patients having diabetes, high BMI, high LDL cholesterol& with smokers.

CONCLUSIONS

Significantly elevated hs-CRP in the early hours of AMI shows that hs-CRP can be taken as a serum marker of ongoing vascular inflammation and atherosclerosis. Nutritional and pharmacological modification of hs-CRP will result in decreased CV events needs to be studied.

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Original Article

STUDY ON THE IMPACT OF EARLY STATIN THERAPY ON THE DEVELOPMENT OF ATRIAL FIBRILLATION IN ACUTE MYOCARDIAL INFARCTION

R. Mohanty*, U. K. Patnaik**

ABSTRACT

Development of atrial fibrillation in acute myocardial infarction has an adverse prognosis on clinical outcomes. The aim of this study was to determine correlations between early statin therapy and development of atrial fibrillation in acute myocardial infarction. Patients with acute ST elevated and non ST elevated acute MI who were given statin treatment at various time frames were enrolled in the study. Out of a total of 256 patients, atrial fibrillation developed in 6.5% of patients without and in 3.7% of patients with early (~48 hrs of admission) statin therapy ($P < 0.001$). This observational study documents a definite correlation between atrial fibrillation and statin therapy at the early stage of acute myocardial infarction. ***Key words :*** *Statin, Atrial Fibrillation, Acute Myocardial Infarction.*

INTRODUCTION:

Statins are known to possess pleotropic properties some of which such as anti-inflammatory and antioxidant properties may be effective in preventing atrial fibrillation [AF].[1-3] A recent meta analysis of studies assessing the role of preoperative statin therapy in patients undergoing cardiac surgery showed a 33% reduction in the risk of developing AF[4]. An observational study showed a dose related effect of statin on atrial fibrillation after cardiac surgery, with higher dose statins having the greatest preventive effect[5]. We sought to see and analyze if there was any correlation between early statin therapy and the development of AF in acute myocardial infarction.

METHOD:

Men and Women aged> 18 years during the last 2 years were eligible for inclusion in the study if they were admitted to the ICU at the department of cardiology, VSS medical college, Burla and medicine department at SCB medical college, Cuttack, with an AMI within 48 hours of symptom onset. AMI was characterized by elevation of cardiac enzymes (CK-MB, Troponin-I or Troponin-T) with at least of one of the following:

a. Symptoms compatible with AMI.
b. ECG changes of AMI.
c. Appearance of pathological 'Q' waves.
d. Persistent ST elevation or depression.

All patients included in the study had Sinus rhythm at admission / at start of statin therapy. Early statin therapy was defined as initiation of statin therapy within 48 hours of admission.

The aim of the study was to evaluate:

a. Development of atrial fibrillation during hospital stay.
b. To see a potential dose- effect relationship between standard (40mg) and low (20mg) dose of atorvastatin.

The occurrence of atrial fibrillation was documented by continuous monitoring when in ICU and by repeated clinical examination and ECG recording when in the medicine ward.

RESULTS :

Out of a total of 256 patients (sinus rhythm on ECG at admission) 218 patients (85%) received early statin therapy. (Fig.1). Baseline characteristics according to statin use within 48 hours are given in table-1.

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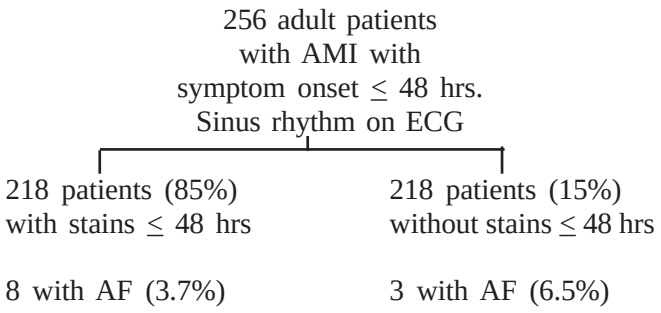

Fig.1 : Flow chart of population included in current analyses.

Atrial fibrillation developed in 5.1 % of the whole population: in 6.5% of patients who did not receive early statin therapy and in 3.7% of patients who did receive early statin therapy ($p < 0.001$). Other correlates of development of atrial fibrillation were age (74 ± 9 vs 65 ± 11 years, $p < 0.001$) sex (37% men vs 29% women, p=0.006), hypertension (70% vs 60% P=0.002), higher admission Killip Class (mean 1.8 ± 0.92 vs 1.34 ± 0.65, P<O.OOl). The incidence of AF was higher in patients with ST elevation MI (6.8%) vs patients with NSTE MI (3.5%). In an analysis of patients with STE MI given reperfusion therapy vs patients not given reperfusion therapy the incidence of AF was 4.7% vs 5.4% (P not significant).

Dose effect

Comparison between low dose and standard dose of statin showed a linear relationship between dose of statins and development of AF (It is to be noted that none of our patients received high dose of 80mg of atorvastatin).

DISCUSSION:

This is an observational study in two referral hospitals on the effect of early use of statins in patients

TABLE 1
Patient base line characteristics according to use of statin therapy within 48 hrs of admission.

Variable	Statin (n=218)	No Statin (n=38)
Age in years (SD)	74 (9)	65 (11)
Men, n(%)	197 (86)	33 (14)
Women, n (%)	21 (82)	5 (18)
Medical history, n (%)		
Hypertension	100 (46)	15 (42)
Diabetes mellitus	72 (33)	12 (31)
Hyperlipidaemia	52 (24)	8 (21)
Current smoker	61 (28%)	10(25%)
Type of AMI, n (%)		
STEMI with reperfusion	108 (49)	12 (32)
STEMI without reperfusion	59 (27)	7 (18)
NSTEMI	64 (29)	6 (16)
Anterior myocardial infarction, n (%)	147 (67)	21 (55)
Admission killip class 2:11,11(%)	46 (21)	8 (21)
Medications within 48h, n(%)		
Antiplatelet agents	210(96)	30 (80)
Beta blockers	186 (85)	24 (79)
ACE inhibitors	142(65)	14 (37)
Diuretic	126 (58)	16 (42)

admitted with acute MI, on the development of atrial fibrillation. The overall risk was reduced by approximately 40% by early use of statin increasing to about 55-60% at the standard dose of statin. It was also observed that 'patients given early statins were more likely to receive treatment with other evidence based therapies for acute economy syndromes.[6,7] The association between early prescription of statins and prevention of atrial fibrillation at an acute stage was independent of other factors by multivariable analysis. The findings from this study concur with other observational studies in different populations[8-12] that reported a reduction in the risk of AF with statin therapy. An ancilliary study from the GISSI-HF trial showed a strong trend to reduction in atrial fibrillation occurrence with rosuvastatin in patients with chronic heart failure[13]

MECHANISMS:

The pleotropic effects of statins such as preservation of endothelial function, anti-inflammatory and antioxidant properties may be independent of their lipid lowering properties.[14,15,16] These effects underlie the hypothesis that statins may reduce the risk of atrial fibrillation. In the peri-operative setting it has been suggested that the antifibrillatory effects of statins might be mediated by autonomic modulation, a factor that also might play a major role in the genesis of atrial fibrillation in AMI. The FAST-MI register database published its report as "The impact of early statin therapy on the development of atrial fibrillation at the acute stage of myocardial infarction".[17] This large observational study showed a definite benefit (OR 0.72) for patient treated with early statin therapy compared to those without, in the development of AF.

LIMITATIONS:

This is a non randomized observational study involving few number of patients and therefore limited by biases such as collection of non randomized data, incomplete or missing information, and inadequate numbers for statistical analysis to be foolproof. One of the major draw backs of the study was that there was no continuous ECG recording and therefore patient of paroxysmal AF have not been reported.

CLINICAL IMPLICATIONS:

Patients with AMI who develop atrial fibrillation are at a distinctly higher risk of developing complications as well as having higher morbidity and mortality rates. Management algorithms that include anticoagulation have their inherent difficulties especially in rural populations. Therefore the fact that statin use was associated with a lower risk of developing AF is important and its early use in AMI patients should be implemented.

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✦✦✦

Original Article

STUDY OF NOSOCOMIAL INFECTION IN INTENSIVE CARE UNIT

S.N. Das *, D. Ram, S. Ghosh****

ABSTRACT

Objective : *Study of Nosocomial infection among patients admitted to ICU of Medicine department, SCBMCH, Cuttack, between September 2010 to April 2011.* ***Result:*** *Total patients admitted were 40 with male to female ratio of 7:3. 17 patients (42.5%) had Nosocomial infections out of which Pneumonia was most common and seen in 9 patients.Enterococcus was the most frequent isolated organism. Mortality from Nosocomial infection was 35 %(6 out of 17).* ***Key words****: Nosocomial infection, Intensive care unit, resistance organism.*

INTRODUCTION:

Nosocomial infection (NI) is defined as an infection which develops 48 hrs after hospitalisation or within 48 hrs of discharge[1] that was not present or incubating at the time of admission.[2]

These infections now concern 5-15% of hospitalised patients and can lead to complication in 25-33% of those patients admitted to ICUs.[4]

Such infections are typically exogenous, the source being any part of the hospital ecosystem and may as well be iatrogenic.[5]

ICUs act as epicentres for NIs as the milieu provides an ideal scaffold for growth of resistant organisms and exotic flora.[6]

AIM AND OBJECTIVES:

To study the incidence of ICU acquired infections, to identify the predominant infecting organisms and their sensitivity pattern and evaluate the relationship between ICU acquired infection s and mortality among patients admitted to ICU of medicine department, SCBMCH, Cuttack between 01-09-2010 to 31-08-2011.

METHODS:

40 Consecutive patients admitted to the ICU of department of medicine, SCB medical college and hospital, Cuttack between 01-09-2010 to 30-04-2011 were taken into study and infections that occurred 48 hrs after admission to ICU were taken in to consideration.

OBSERVATION:

A preliminary analysis of this study scheduled to be completed after august 2011 was done.

40 Patients admitted between 01-09-2010 to 30-04-2011 were taken into consideration.

The most common organism isolated was Enterococci (20%).other organism were Staph. aureus, Klebsiella pneumonia, Acinetobactor baumanni, Pseudomonas aeruginosa.

Out of these NIs, 2 male had double infection and 3 had double organisms as the causative agents. Klebsiella pneumoniae was the most common organism implicated in causing pneumonia among ICU patients.

The most common organism implicated in NI urinary tract infection was E. coli and staph. aureus was most common source of blood stream infection.

After antibiotics sensitivity testing, it was inferred that E.coli was sensitive to linezolid, vancomycin, tigecyclin. Staphylococcus was sensitive to netilmycin, linezolid, and teicoplanin. Pseudomonas was found sensitive to netilmycin, tobramycin and amikacin. Acinetobactor sensitive to tigecyclin, netilmycin and meropenem and Klebsiella was found sensitive to gatifloxacin, azithromycin.

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TABLE-1(Age distribution of cases)

Age(years)	Male	Female	Total
10-30	8	2	10
31-50	8	5	13
51-70	12	3	15
71-90	0	2	2
Total	28(70%)	12(30%)	40

Table-1 shows the age and sex distribution of cases. Majority of the patients were in the age group 51-70 yrs and male predominance.

TABLE-2(Type of patients)

Type of patient	Male	Female	Total
CVA	6	5	11
Poisonings	11	0	11
Malaria	8	4	12
Miscellaneous	3	3	6
Total	28	12	40

(Miscellaneous: snake bite, enteric fever, periodic palsy,GBS)

Table-2 depicted that severe malaria with MODS was most common cause of ICU admission on an overall basis.

TABLE-3(Incidence of Nosocomial infection)

	Male	Female	Total
Total no. of patients	28	12	40
NIs	15	2	17
% of NIs	53.5%	16.6%	42.5%

Table-3 shows that out of 40 patients admitted to ICU, 17 patients had acquired one/two episode of NIs.

TABLE-4(Type of NIs)

Type of NIs	Male	Female	Total
Pneumonia	7	2	9
UTI	5	0	5
Blood stream infection.	3	0	3
	15	2	17

Table-4 depicts that pneumonia is the most common NIs overall as well as both among male and female.

TABLE-5(Type of organisms)

Type of organism	Male	Female	Total
Enterococcus sp	5	0	5
Klebsiella sp	4	0	4
Pseudomonas aeur.	2	1	3
Acenobactor baum.	4	0	4
Staph.aureus	3	1	4

TABLE-6(Mortality rate)

	Male	Female	Total
NIs	15	2	17
Death	4	2	6

Table-6 depicted that total mortality among NIs was 6 out of 17 (35%).4 were male and 2 were female.

The source of infection for staphylococcus was found to be the ICU wall, ambubag, oxygen mask; that for pseudomonas, Acinetobactor and Klebsiella was the suction Catheter and ICU bed for E.coli.

DISCUSSION AND SUMMARY

A prospective study done by Adrina cristna et al in an ICU of Brazilian University hospital involving 1886 patients during 2005-2008 showed that 383 (20.3%) patients had NIs out of which UTI(n=144: 37.4%)was most common. The most common organism was candidia albicans (18.5%) and the most frequent MDR pathogen were Acinetobactor baumanni and Pseudomonas.[9]

A prospective observational study done by Shabina et al in north India from 2004-2005 showed that 34.1% patients had NIs out of which pneumonia (77.3%) was most common. Acinetobactor, Pseudomonas, Candida were among the most frequent organism isolated.[11]

In a study done by A. N. Sahu et al on NIs in ICU at SCBMCH, Cuttack from Aug 2004-July 2006;out of 50 patients ,32 (64%) patients developed NIs of which pneumonia (n=25,50%) and the most common organism isolated was staph. aureus, VAP constituted 44%. Total mortality was 36% (n=18)

In our study done from Sept-2010 to April 2011, out of 40 patients, 17 (42.5%) patients develops NIs of which pneumonia (n=9, 57%) was most common and VAP constituted 33%.Enterococus was the most frequent organism isolated. Total mortality was 35% (n=6).

The contaminated ICU environment is one of the most common sources of infection. So, the key to control of antibiotics resistance pathogens in the ICU is rigorous adherence to infection control guidelines and prevention of antibiotic misuses.

Adoption of simple and workable barrier nursing measure, frequent hand washing ,change into clean lines wearing of protective gown, disposable mask, caps and shoes by ICU staff and visitors will result in decrease in the NIs. The importance of simple barrier precautions must be emphasized through repeated teaching of staff. The application of preventive measures should be approached through infection control protocol by the health care staff and must be a routine part of ICU patient care, there by reducing both mortality and ICU costs.

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✦✦✦

Original Article

MALE URINARY TRACT INFECTION - CHANGING TRENDS IN UROPATHOGENS

T. Karuna*, S. Khadanga**

ABSTRACT

Urinary tract infection (UTI) is less common among males <50 yrs. Escherichia coli is the most common organism which is responsible in 50-80% cases. Other gram-negative bacilli (Proteus, Klebsiella, Pseudomonas and Enterobacter) are less common. Gram-positive cocci are rare in male UTI and are found only in UTIs related to stone and urinary tract manipulation. In our study though Escherichia coli is still the most common organism isolated, its incidence has decreased to 38%.Non- Escherichia coli gram-negative bacilli related UTI has increased significantly. Gram-positive cocci once rare among community acquired male UTI, are not uncommon these days. Genitourinary tuberculosis must be kept in mind while dealing a case of sterile pyuria. Nitrofurantoin is more sensitive oral therapy than Quinolones. Linezolid should be added to Nitrofurantoin/ Quinolones if the symptoms or bacteriuria do not resolve. ***Key words*** *- urinary tract infection(UTI), gram-negative bacilli(GNB) Gram-positive cocci(GPC), Escherichia coli(E.coli). Coagulase-negative Staphylococci (CONS), acid fast bacilli (AFB).*

INTRODUCTION

Normally urine is sterile. UTI in male is less common than female. This is because of many factors such as- thicker transitional epithelium, longer urethra, more frequent voiding, separation from rectum by several centimeters of keratinized epithelium and antibacterial properties of prostatic secretion [(1)]. According to standard text books the diagnosis of UTI in male < 50 years is questionable in the absence of insertive rectal intercourse [(2)]. But contrary to this, in our clinical practice we frequently come across microbiologically proved UTIs in males < 50 years without history of rectal intercourse. Epidemiologically UTI is subdivided into nosocomial (catheter and other instrumentation related) and community acquired. Infections in either category may be symptomatic or asymptomatic. In the male population, acute symptomatic UTIs occur in the first year of life (often in association with urologic abnormalities); thereafter, UTIs are unusual in male patients under the age of 50[(3)]. The development of asymptomatic bacteriuria parallels that of symptomatic infection and is rare among men under 50 but common in elderly population both in males and females. The common causes of UTI in males are obstruction to the flow of urine(stone, stricture, tumor ,benign enlargement of prostate), nosocomial urinary tract manipulation (catheterization and other urologic procedures), lack of the circumcision , insertive rectal intercourse, decreased immunity (diabetes mellitus, malignancy, prolonged steroid therapy, HIV).

Most common organisms affecting the male urinary tract are gram-negative bacilli (GNB). E.coli causes 80% of acute infection in patients without catheter, urologic abnormalities or calculi[(2)]. E.coli as such is documented in 50-80 %(nosocomial and community acquired) of male UTIs in various studies[(3)]. Other GNB especially Proteus, Klebsiella, and Enterobacter spp. account for a smaller portion of uncomplicated UTIs. These organisms along with Serratia spp. and Pseudomonas spp assume increasing

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importance in recurrent infections and infection associated with urological abnormalities [4]. GPC (Staphylococcus aureus, Enterococci, CONS) play a lesser role. They cause UTIs in patients with renal stones or with previous instrumentation or surgery [2]. Pyuria in the absence of bacteriuria (sterile pyuria) may indicate infection with unusual agents such as C. trachomatis, U. urealyticum, Mycobacterium tuberculosis or with fungi. Alternatively, sterile pyuria may be documented in noninfectious urologic conditions such as calculi, anatomic abnormality, nephrocalcinosis, vesicoureteral reflux, interstitial nephritis, or polycystic disease [2]. Sterile Pyuria is documented in 40-70% of cases of male UTI in various studies [3].

In most instances, growth of 10^5 organisms per milliliter from a properly collected midstream "clean-catch" urine sample indicates infection. However, significant bacteriuria is lacking in some cases of true UTI. Especially in symptomatic patients, fewer bacteria (10^2–10^4/mL) may signify infection. In urine specimens obtained by suprapubic aspiration or "in-and-out" catheterization and in samples from a patient with an indwelling catheter, colony counts of 10^2–10^4/mL generally indicate infection. Conversely, colony counts of $>10^5$/mL in midstream urine are occasionally due to specimen contamination, which is especially likely when multiple bacterial species are found [2].

Since data from this part of world regarding the uropathogens of male UTI and their sensitivity to antibiotics are lacking we wanted to study this aspect of male UTI.

MATERIAL AND METHODS.

Inclusion criteria

1. Male in the age group of 15-50.
2. Symptoms of UTI- dysuria and / or frequency and / or urgency and / or suprapubic pain with or without fever.
3. Pus cell in urine > 5/H.P.F

Exclusion Criteria

1. Prior history of instrumentation or catheterization
2. Other co morbid conditions.

100 male patients of male UTI were included in the study. The patients were followed up in OPD or IPD depending on the severity. All the patients were subjected to TLC, DLC, blood urea, serum creatinine and urine –routine, microscopic, culture and sensitivity. All the patients were given Ciprofloxacin 500 mg twice daily orally / IV till the culture sensitivity report. Those patients who presented with sterile pyuria, were screened for early morning urinary AFB.

RESULTS

In our study we observed that more than 2/3rd (69%) cases did not yield any organism after 48 hours of aerobic incubation. Out of the rest 31 cases Candida spp, was isolated in 4 samples which are most probably contaminants. Only in 27 samples we recovered either GNB or GPC. Out of the 27 cases, 4 samples showed multiple organisms and all of them were GNB. Among those 4 samples, 2 samples showed E.coli, Eenterobacter, one sample showed E.coli+Pseudomonas and the other one showed Klebsiella+Pseudomonas. Usually male UTI is caused by mono pathogen and whenever multi-pathogens are isolated the less common pathogen is considered as contaminant[2]. According to this principle our 2nd pathogen is considered to be contaminant and they are not considered in any calculation. Out of the rest 23 samples, GNB were isolated in 18 samples, and GPC were isolated in 5 samples. Among GNB the most common organism was E.coli (9 cases), 2 cases were Enterobacter and 1 each from klebsiella, pseudomonas and proteus. In 4 samples we recovered unusual GNB (Citrobacter-1, Acinetobacter-1., morganella-2).

Among the GPC Entercocci was the most common isolated species (4 cases) followed by 1 each of Staphylococcus aureus and CONS.

Among those patients in which we did not receive any organism, we performed early morning urinary AFB study and out of the 69 cases we recovered AFB from 3 samples.

Among the GNB, Nitrofurantoin was the most sensitive oral drug(18/ 22) followed by Quinolones(15/ 22).among the GNB, Piperacillin-tazo. was the most sensitive(18/22) injectable followed by Amikacin and Imipenam(17/22).

Among the GPC Linezolid was the most sensitive oral drug (4/5).Vancomycin was sensitive to all GPC.

Among 69 cases of sterile pyuria we recovered urinary AFB in 3 samples(3 out of 100 total cases).

Table-1
CULTURE CHARACTERISTICS (n=100)

No growth	69
GNB	22
GPC	5
Candida	4

Table-2
ORGANISMS ISOLATED AMONG GNB (n=22)

E.Coli	9
Klebsiella	1
Pseudomonas	1
Proteus	1
Enterobacter	2
Citrobacter	1
Morganella	2
Acinetobacter	1
E. Coli + Pseudomonas	1
E.Coli+ Enterobacter	2
Klebsiella+ Enterobacter	1

Table-3
ORGANISM ISOLATED AMONG GPC (n=5)

Staph aureus	*1*
Enterococci	*3*
CONS	*1*

DISCUSSION

As reported from almost all earlier studies *E.coli* was the most common uropathogen isolated in our study . *E.coli* was isolated from 50-80% of samples in various studies. We observed that *E.coli* was responsible only in 38%of cases (12/31). The incidence of non- *E.coli* GNB (10/31), was more in our study than in any previous studies. Usually *Klebsiella,Proteus* and *Pseudomonas* are more common in this category. But we recovered some unusual GNB such as *Citrobacter, Acinetobacter* and *Morganella.(*4/31 cases). So, though E.coli is the most common uropathogen in our study, Non-E.coli GNB related UTI definitely increasing. According to standard text books the empirical therapy for male UTI is Ciprofloxacin. But in our study Nitrofurantoin was the most sensitive oral drug followed by Ciprofloxacin[5-10]. Among injectables Piperacillin was most sensitive followed by Amikacin and Imipenam.

GPC are more commonly recovered from sexually active females. Among males they are more commonly found with relation to stone or nosocomial UTI. But in this study we recovered GPC in community acquired male UTI, which clearly indicate that GPC are becoming more common uropathogens. Enterococci was the most common uropathogen among GPC. Almost all of them were sensitive to Linezolid and Vancomycin.

We could not get any data regarding the incidence of genito-urinary tuberculosis among sterile pyuria cases. We recovered urinary AFB in 3 samples out of 69 sterile pyuria cases. Sterile Pyuria is reported from 40-70% in various studies[3]. In our study we got 69% of the cases (69/100) were sterile after 48 hours of aerobic incubation.

CONCLUSION

Though *E.coli* is still the most common uropathogen, the non-E.coli GNB and GPC related male UTI is definitely increasing. Nitrofurantoin is more sensitive than Quinolones in our study. Linezolid should be added if the symptoms and / or bacteriuria persist with Nitrofurantoin/Ciprofloxacin. Genito-urinary tuberculosis should be suspected in non-resolving sterile pyuria cases.

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ANNOUNCEMENT

31ST APICON 2011
12TH, 13TH NOVEMBER 2011
VENUE : SAHEED BHAWAN, CUTTACK

Chairman Organising Committee	Chairman, Reception Committee	Organising Secretary
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	Before 30th Sep. 2011	After 30th Sep'11	On spot
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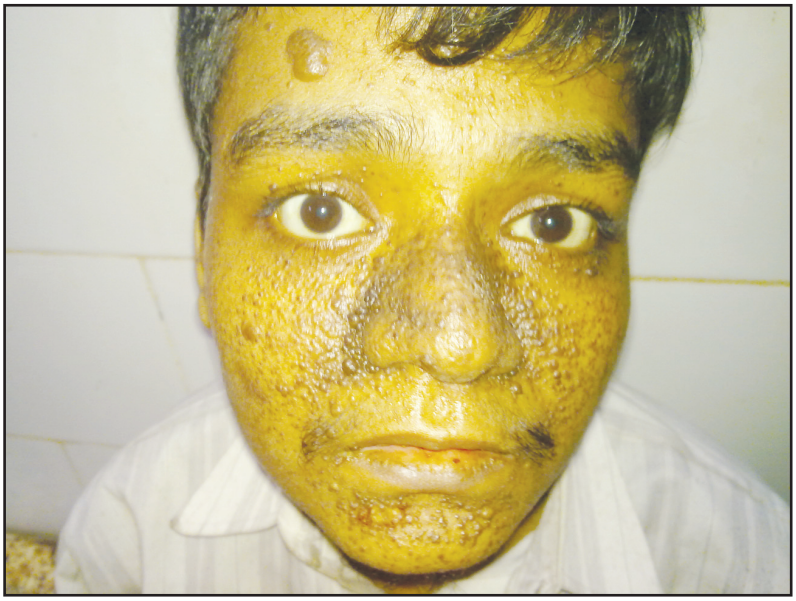
Pictorial CME

TUBEROUS SCLEROSIS

M.R. Behera*



(Adenoma sebaceum over face)

A 16 year old male presented with chief complaints of repeated bouts of generalised tonic clonic consulsions for last two days without any history of fever. He had history of similar attacks since childhood and on irregular medication with oral phenytoin. He discontinued his primary school studies because of mental retardation. Clinical examination revealed : vitals were normal, multiple papulonodular lesions over face, mainly over nasolabial folds known as "Adenoma Sebaceum". Systemic examination revealed no abnormalities except mental retardation and left side extensor plantar. Routine investigations revealed no abnormality. CT scan of brain showed multiple subependymal calcifications near both lateral ventricles, EEG showed generalised seizure activity. Final diagnosis of **tuberous sclerosis** (TS) was made basing on history of convulsion, mental retardation, adenoma sebaceum over face and characteristic CT scan findings. Patient was managed with anticonvulsants.

TS, also known as 'Bournvilles disease' is an autosomal dominant multisystemic disease characterised by hamartomatous lesions in various organs of body like skin, brain, retina and viscera. Clasically 2/3rd of the cases present with EPILOIA (Epilepsy, Low Intelligence, Adenoma Sebaceum). TS may manifest as Facial angiofibromas (Adenoma Sebaceum), Collagenous skin patch (shagreen patch), hypomelanotic ash leaf spots, subungual/gingival fibromas, multiple renal or bone cysts, retinal hamartomas, renal angiomyolipoma, lymphangiomatosis, cardiac rhabdomyoma, cortical tubers/subependymal nodules, subependymal giant cell astrocytoma. It is caused by a mutation of either of two genes, TSCI and TSC2. Adenoma sebaceum can be treated with laser theray. In severe and resistant epilepsy cases neurosurgical intervention can be considered. In symptomatic cerebral tumors, management is to debulk the tumour. Patients with mild TS usually lead a normal life. However, patients with severe mental retardation or uncontrollable seizures usually have a bad prognosis.

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Review Article

OXIDISED LDL - ROLE IN THE PATHOGENESIS AND MANAGEMENT OF CORONARY ARTERY DISEASE

T.K. Mishra*, B. Das, S.N. Routray*, C. Satpathy**, H.N. Mishra*****

ABSTRACT

Role of cholesterol in alterations of normal blood flow and damage to the endothelium is a well recognised phenomenon. Data from meta-analysis suggest that many individuals continue to demonstrate disease progression and develop clinical end points inspite of LDL-C levels that are at target level. This has sparked considerable interest on the contribution of oxidative stress to cardiovascular events. According to the oxidation hypothesis of atherosclerosis, the LDL particle in its native form is not atherogenic. However, oxidatively modified LDL can be taken up by macrophages via scavenger receptors, subsequently leading to formation of foam cells, endothelial dysfunction and progression of atherosclerosis. Several studies have shown strong correlation between ox-LDL and' risk for Subclinical atherosclerosis as well as myocardial Infarction. Efforts are on to reduce ox-LDL. ***Key words:*** *Oxidative stress, Oxidised LDL (ox-LDL), Reactive oxygen species (ROS), Triglyceride rich, lipoproteins (TRLs).*

INTRODUCTION

Cardiovascular disease is the leading cause of global morbidity and mortality despite advances in clinical management. Rudolf Virchow, recognised as the father of modern pathology, recognised the role of cholesterol in alterations of normal blood flow and damage to the endothelium in patients with coronary artery disease (CAD). With 60% of cholesterol transported in the blood stain being associated with low density lipoprotein (LDL), intervention that can reduce LDL-C have been demonstrated to reduce cardiovascular morbidity and mortality. However, data from meta-analysis suggest that many individuals continue to demonstrate disease progression and develop clinical end-points, in spite of LDL-C levels being at target level.[3] In the present article, we shall review evidence for presence of oxidatively modified lipoproteins, its association with cardiovascular disease and impact of lipid-lowering interventions on oxidative stress.

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In recent years, considerable interest has been placed on the contribution of oxidative stress to disease progression and cardiovascular events. Increased oxidative stress describes a state of imbalance in which anti-oxidant processes are inadequate to protect the body from assault form excess levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS)'. According to oxidation hypothesis of atherosclerosis, the LDL particle in its native form is not atherogenic.[5] However, oxidatively modified LDL can be taken up by macrophages via scavenger receptors, subsequently leading to formation of foam cells, endothelium dysfunction and progression of atherosclerosis. While oxidised LDL (ox-LDL) has been the focus of research, ROS can initiate oxidative modification of other lipoproteins, which may also contribute to the progression of atherosclerotic disease.[7]

Detection of Oxidised LDL

Plasma lipoproteins can be modified in vivo either by free radicals (one-electron oxidants) or by nonradical oxidants (two-electron radicals)'. Non-enzymatic oxidation results from the interaction of

plasma lipoprotein with either ROS or RNS. These free radicals, or one-electron oxidants, include metabolites such as superoxide anion ($0°_2$), hydroperoxyradical ($H00_2$), peroxi radical (RO'2) nitric oxide (NO'), and nitrogen dioxide (NO_2) As already stated, oxidative modification can also occur via nonradical oxidants, or two-electron oxidants. Among these are hydrogen peroxide (H_20_2), Ozone (0_3), and hypochloritde ('OCI). In addition to direct oxidative modification by either ROS or RNS via nonenzymatic processes, specific enzymes present in the body can initiate oxidative modification of plasma lipoproteins. Among these are NAD(P)H oxidases, xanthine oxidase, nitric oxide synthase, and lipoxygenases.[8] These pro-oxidant processes are an integral component of normal metabolism.

Lipid hydroperoxide is one of the by-products of lipid peroxidation and is one of the most common measures for the overall lipid peroxidation level. It is expressed as thiobarbituric acid reactive substance (TBARS), which can be measured by spectrophotometry, fluorometry or by high performance liquid chromatography. An ELISA kit based on the 4E6 antibody that recognises oxidative epitopes on Cu^2+ modified LDL is also available.[9]

Oxidised LDL and CAD Risk

In the Health, Aging, and Body composition cohort (HABC), individuals with high ox-LDL had greater risk for myocardial infarction (Relative risk: 2:25; 95 CI 1.22-4.15).[10] In the Coronary Artery Risk Development in Young Adults (CARDIA) study, higher concentration of ox-LDL was associated with increased incidence of abdominal obesity, hyperglycaemia and hypertriglyceridemia.[11] A case-control study Indicated that individuals, with documented CAD had higher ox-LDL levels(3.1 Vs 1.3 mg/dL, $p < 0.001$).[12] However, there was no association between ox-LDL levels and the disease severity. In the Multi Ethnic Study of Atherosclerosis (MESA), data from 879 persons demonstrate that individuals with subclinical atherosclerosis had higher levels of oX-LDL.[13] The presence of subclinical atherosclerosis in the study was defined as plaque occurrence in carotid arteries with greater than or equal to 25 stenoses, ankle-brachial pressure index less than 0.9 and coronary artery calcium score greater than or equal to 200 Agamon units. In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), ox-LDL was strongly predictive of cardiovascular events in patients with stable CAD.[14] This relationship was independent of the traditional risk factors and inflammatory markers such as hsCRP. In a study of subjects examined after admission to the emergency room for chest pain, patients with documented myocardial infarction had acute elevations (56%, $p < 0.05$) in the levels of ox-LDL between the time of enrollment (in the emergency room) and time of discharge (3-4 days post-event.)[15] An acute increase in ox-LDL was not observed in other subjects, who included individuals with unstable angina stable CAD and individuals with normal coronary arteries.

Mechanism of atherogenesis By OX-LDL

The presence of ox-LDL in the arterial wall is associated with increased risk for foam cell formation and plaque vulnerability. The arterial wall has high propensity to retain ox-LDL resulting in a 70-fold difference in concentration of ox-LDL in the plaque, as compared with plasma. The residence of LDL in the atherosclerotic lesion is significantly longer than in normal vessel.

Intermittent exposure of the endothelium to high glucose concentration is associated with generation of reactive oxygen species (ROS). During the interaction of triglyceride rich lipoproteins (TRLS) with lipoprotein lipase anchored to the arterial wall via heparin sulphate proteoglycans. TRLs will be seeded with ROS generated in the sub-endothelium. The enrichment of TRLs with polyunsaturated fatty acids, which are highly susceptible to oxidative modification, would enhance the efflux of ROS from the arterial wall. In the atherosclerotic patient, inflammation within the arterial wall generates more ROS. When the antioxidants mechanism associated with enzymes such as superoxide dismutase and para-oxonase is not adequate, the net

result is accumulation of oxidised epitopes on plasma lipoproteins. Excess of ox-LDL and the presence of activated macrophage in the inflamed arterial wall results in the accumulation of oxidised lipoproteins in the arterial wall.~ A snapshot measurement of OX-LDL levels in fasting plasma may not be adequate to reflect the complex dynamics of these processes.

Is ox-LDL protective?

There is actually one school of thought which suggests that the formation of ox-LDL is a part of normal physiology, and under normal conditions, is antiatherogenic.[17] Exercise and consumption of diet high in polyunsaturated fatty acids are currently recommended as part of a healthy lifestyle that reduces cardiovascular risk. Both of these are however, associated with high oxidative stress. The acute generation of oxidatively modified epitopes is protective because it stimulates the immune response and upregulates the antioxidant response system. However, for the high-risk patient, who is in a pro-oxidative state, the excess oxidative stress and impaired antioxidant defence mechanism would result in the generation of more oxidised lipoproteins with prolonged lifespan.

Intervention for Increased ox-LDL

Animal experiments have shown that regression of atherosclerosis process is associated with reduction of total blood cholesterol, apo-lipoprotein B(APOB) and ox-LDL.[8] In human subjects, treatment with pravastatin (40 *mg/day)* has shown reduction in IgG and IgM-apoB immune complexes, which are markers of LDL oxidation.[18] Pharmacological reduction in post-prandial hyperglycaemia has also been shown to be associated with reduction in post-prandial levels of OX-LDL in plasma.[20] However, changes in markers of LDL-oxidation have not been correlated with observed changes in the arterial wall, as assessed by quantitative coronary angiography or intravascular ultrasound.[21]

Summary and Conclusion

According to oxidation hypothesis of atherosclerosis, native LDL is not atherogenic, but oxidatively modified lipoproteins, specifically LDL, can be widely taken up by macrophages with subsequent formation of foam cells and contribute directly to the progression of atherosclerosis. While ox-LDL has been the focus of research, ROS can initiate oxidative modification of other lipoproteins, which may contribute to the progression of atherosclerotic process. Nonenzymatic oxidative modification results from the interactions of plasma lipoprotein with either ROS or RNS. Individual, with subclinical atherosclerosis have been shown to have high level of ox-LDL. High ox-LDL is also associated with greater risk of myocardial infarction. The arterial wall has a high propensity to retain ox-LDL resulting in 70-fold difference in concentration in the plaque as compared with plasma. In human subjects, treatment with statins has shown reduction in level of markers of LDL oxidation such as IgG and IgM - apo B immune complexes. However, none of these changes in markers of LDL oxidation has been correlated with changes in the arterial wall in human beings.

The presence of ox-LDL is a necessary stimulus for antioxidant production. In high-risk individuals, the presence of high levels of oxidised epitopes symbolises failure of antioxidant protection system to compensate for the generation of oxidised epitopes.

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Review Article

MOLECULAR BIOLOGY OF AGING BRAIN

D.N. Moharana*, R.K. Dalai, N. Dhal***, M. Behera*****

Consequent upon exuberant increase in the lifespan, ageing of population is an obvious feature of the process of demographic transition. The glimpse of an elderly was one the three realities of human life that had made the Prince Siddhartha renounce the world and become 'BUDDHA' about 2500 years ago. Being old often means to be ill demented, weak, unattractive, nonproductive, dependant and abused. But the truth ultimately prevailed and the definition of old in the Madrid Convention changed to "persons who give us light are old and to be sincerely cared for."

Temporal profile of Histobiological changes of human brain

Pre-natal development

Developmental neurobiology concerns itself with the development of the brain. The process of neurogenesis populates the brain at a faster rate.

Adolesence:

Rapid neurogenesis, synaptic modulation and recruitment.

Adult below 50:

Rapid genesis, recruitment and utilization of the synapses. Synthesis of the neuro transmission, modulation of the function of the Telencephalon.

Adults beyond 50:

Brain aging is the major risk factor for most common neurodegenerative disease, including Alzheimer's Disease, Cerebrovascular Disease, Parkinson's Disease and Amyotrophic Lateral Sclerosis. Other risk factors, including genetic mutations, female sex, low educational attainments and head injury contribute much less to the risk of these disorders. The molecular biology of brain aging is poorly understood and this is of importance when one seeks to understand the pathogenesis of Alzheimer's Disease.

There are few informative studies on the molecular biology of brain aging in the absence of neurodegenerative disease. In large part this deficit is attributable to the paradox that many individuals without clinical disease before death are found at autopsy to have extensive evidence of brain neurodegeneration and, conversely, some die with clinical features of disease but show few signs at autopsy of degeneration. The hypothetical concept of cognitive or brain reserve was devised to explain these types of discrepancy between clinical features and brain pathology the human brain shows a decline in function and a change in gene expression. This modulation in gene expression may be due to oxidative DNA damage at promoter regions in the genome. Genes that are down-regulated over the age of 40 include:

- GluRl AMP A receptor subunit
- NMDA R2A receptor subunit (involved in learning)
- Subunits of the GABA-A receptor
- Genes involved in long-term potentiation e.g. calmodulin 1 and CAM kinase II alpha.
- Calcium signaling genes
- Synapatic plasticity genes
- Synaptic vesicle release & recycling genes Genes that are upregulated include:
- Genes associated with stress response and DNA repair

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- Antioxidant defence

Normal aging is distinct from Neurodegenerative disease. DNA damage due to oxidation increase as the brain ages, possibly due to impaired mitochondrial function. Neuroinflamation is a common feature of aging in the mammalian brain. Astrogliosis (measured by immunobistochemeistry of FGAP) increases with age in mouse, rat as well as human brain.

Though brain aging is a common phenomenon, there are many centenarians who age gracefully and look mentally very active at the sunset years of life. The prevalence rates of mental disorders in the older people points towards a larger section of elderly age group having a significant amount of morbidity. The incidence of mental disorders in elderly increases exponentially as age advances. Dementia is the most common disabling mental disorder of old age, the incidence mounting to as high as 20% in those beyond 80 years.

Brain ageing or Age Related Mental Decline (ARMD) or Age Related Cognitive Decline (ARCD) is defined as progressive nature of psychomotor retardation leading to loss of mental ability to adopt to environment in a previously active normal person. It is symptomatically characterized by memory loss, lack of concentration, incoordination, vertigo, tinnitus and speech disturbances. Recent data confirms that ageing is accompanied by authentic cognitive decline, which in particular distinguishes it from early dementia because of depression. Sometimes the temporal profile of mental decline progresses through stages of cerebral ageing without mental decline which is termed as Benign Senescent Forgetfulness. In this context it is wise to make a clear cut definition of cogpition. It is the various thinking processes through which knowledge is gained, stored, manipulated and expressed, can be broken down into a variety of functions including memory, language, praxis, Visio spatial, perceptual function, conceptualization and flexibility. Any change in cognition is interesting as well as complex, especially when it is related to aging. Standard measures of overall intellectual functioning, such as Wechsler Adult Intelligence Scales, generally show some age-associated decline, usually with a distinction between verbal abilities, that tend to be preserved, where as non-verbal or performance abilities, tend to deteriorate.

Assessing intellectual abilities at the bedside or clinic is based more on a general evaluation of the patient's behavior than on a single informal test.

Life-span is a complex task, mainly because of three reasons: the cohort effect, inclusion of subjects with early manifestations of illness, and presence of physical illness which may affect an organ through which cognition may be expressed.

The cohort effect ascribes differences in performance between groups to their living in different time period and thus having been exposed to various environmental influences.

Arthritis, hearing deficits, and visual changes are three common conditions that interfere with the motor and perceptual abilities upon which testing of cognitive depends.

It is important to delineate the age-associated changes in cognition from those occurring due to disease. Unfortunately, there is little information available that can help make this distinction in the early stages. Benign senescent forgetfulness and age-associated memory disorders are two terms that refer to non pathological memory impairments. As memory impairment can also progress to a global, intellectual decline.

Disorder of cognition are suggested by decline in non-memory function such as language, praxis, vi suo spatial perception and dysfunction in every day activities. Neuropsychological testing is helpful in unclear cases.

Age associated changes in cognition occur due to any of the following reasons:

i) decline in the number of large pyramidal cells

ii) decrease in the branching of brain dendrites

iii) decline in brain volume (cerebral atrophy)

iv) neurochemical changes (decline in acetylcholine, dopamine, serotonin and noradrenaline)

v) qualitative quantitative changes due to vascular insufficiency.

In addition, numerous studies of central neurotransmission during the aging process have been conducted mainly on animals and it is likely that advanced neuroimaging techniques shall be utilized for the purpose of neurochemistry studies in man.

Aging is also associated with a number of vital events which constitute a source of stress and chronic stress in associated with progressive and selective impairment of meso cortical dopaminergic activity.

Complaints of memory loss and cognitive dysfunction can be symptoms of major or unipolar depression, but these symptoms are often reversed on treating depression.

The clinical characteristics of cerebral aging distinguish it from dementia and depression.

Electrophysiological data also distinguish if from these diseases. EEG reveals a reduction in the modification of the topographical distribution of the various frequency bands; the latency and amplitude of the P300 wave are minimally different from those of elderly subjects with normal cognitive functions. The P300 wave indicates impairment of attention, and its distribution is more extensive than in normal subjects.

Many alterations in the brain structure have been described in association with aging but in view of the complexity of the histological changes is very difficult to comment to what extent the changes are pathological and up to what extent the changes are physiological. The external changes are thickening and fibrosis of the dura and leptomeninges, sometime with calcification. The brain atrophies to some extent and the loss of cerebral substance has been estimated to be about 100gm. The internal structures involved are lentiform nuclei and the cerebral vasculature. The ventricles become larger with ependymal granulations. There is lipofuscin deposition. There is about 20 to 40% loss of neurons in the spinal cord and 1 to 2% annual reduction in the number of hippocampal nerve cells. There is accelerated apoptosis. There is reduced dendrictic arborization and synapse formation and neuroaxonal atrophy. The inclusion bodies in the aging brain has been described to be upto in 30% of cases. They are hyaline, eosinophilic and polygonal in nature. The Lewy bodies are characteristically widely distributed. The Neurofibrillary tangles are characteristics of Alzheimer's Disease but found in other cases of senile dementias. Senile plaque are interstitial tissue degenerations found in electron microscope are universal in nature but more commonly found in the hippocampus, amygdale and nucleus of Meynert.

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CURRENT CONCEPT

RECENT INSIGHT INTO MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

A.K. Sahu*, J.K. Panda, P.K. Padhi*****

INTRODUCTION

Glomerulonephritis[1] is a syndrome characterised by hematuria, proteinuria, hypertension, renal insufficiency and RBC cast in urine.Its clinical presentation varies from asymptomatic hematuria or proteinuria (or both), acute nephritis, rapidly progressive renal failure to chronic nephritis.These varied clinical features are the result of different expressions of inflammatory glomerular injury.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS[2]

It is a pattern of glomerular injury seen in a variety of disease processes, characterised by *diffuse mesangial cell proliferation & thickening of capillary walls* due to *subendothelial extension of mesangium*. So it is also called as *mesangiocapillary glomerulonephritis or lobar glomerulonephritis.*

CLASSIFICATION[3]

Type I Disease (Most Common)
- Idiopathic
- Subacute bacterial endocarditis
- Systemic lupus erythematosus
- Hepatitis C ± cryoglobulinemia
- Mixed cryoglobulinemia
- Hepatitis B
- Cancer: Lung, breast, and ovary (germinal)

Type II Disease (Dense Deposit Disease)
- Idiopathic
- C_3 nephritic factor-associated
- Partial lipodystrophy

Type III Disease
- Idiopathic
- Complement receptor deficiency

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SECONDARY CAUSES[4]

Infectious diseases- Viral: Hepatitis B and C, HIV

Bacterial: shunt nephritis, visceral abscess, infective endocarditis.

Systemic immune complex diseases - Mixed cryoglobulinemia ,SLE ,Scleroderma,Sjögren's

Hereditary deficiencies of complement components

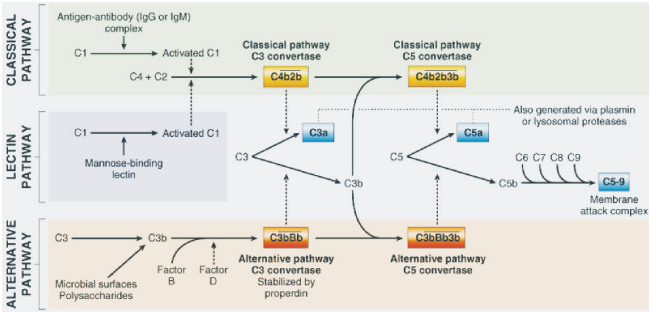
Hypocomplementemic urticarial vasculitis

Neoplasms- Leukemias and lymphomas, Carcinomas,Light-chain disease and plasma cell dyscrasias.

Chronic liver disease - Chronic hepatitis,Cirrhosis

Miscellaneous- Partial lipodystrophy, α1-Antitrypsin deficiency, Cystic fibrosis, Drugs (e.g. heroin, α-interferon), Sarcoidosis, Sickle cell disease, Hemolytic uremic syndrome.

PATHOGENESIS OF MPGN :



COMPLEMENT CASCADE

The final common pathway in the pathogenesis of all types of MPGN is the formation of membrane attack complex (MAC) which mediates further injury & proliferation.[2]

PATHOGENESIS OF MPGN – I[5]

- Type I MPGN results from chronic antigenemia and the generation of nephritogenic immune complexes that preferentially localize to the *subendothelial spaces*.

• These immune complexes activate the complement system via the *Classical pathway*, leading to the generation of-

1-chemotactic factors (C3a, C5a) that mediate the accumulation of platelets and leukocytes

2-membrane attack complex (C5b-9) that directly induce cell injury.

Leukocytes release oxidants and proteases that mediate capillary wall damage and cause proteinuria and a fall of glomerular filtration rate. Cytokines and growth factors released by both exogenous and endogenous glomerular cells lead to mesangial proliferation and matrix expansion.

PATHOGENESIS OF MPGN – II[5]

• This type is mainly due to the *uncontrolled* systemic activation of ***Alternative pathway*** of Complement cascade.

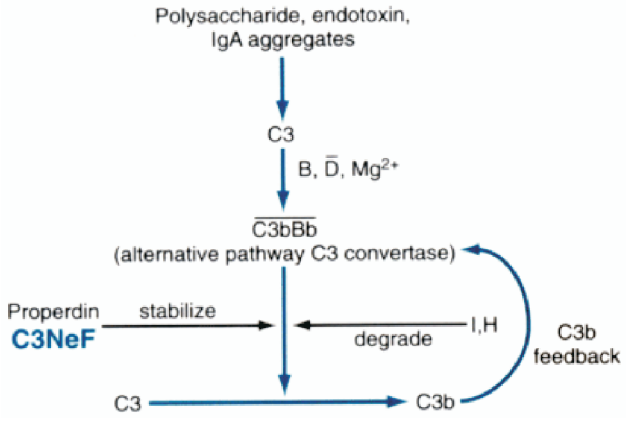
• There are 3 mechanisms behind this –

1-C3NeF mediated

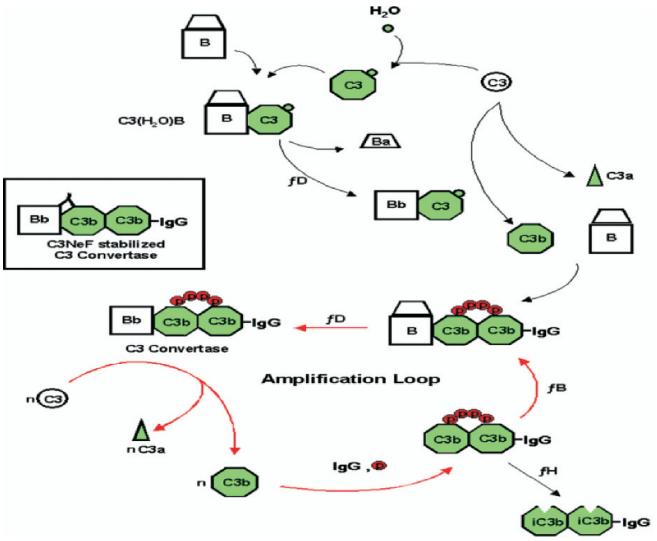
2-Factor H mediated

3-Factor D mediated

C3NeF :-



C3 Nephritic factor is an IgG autoantibody which binds to and prevents the inactivation of C3 convertase (C3bBb) in alternative pathway.So C3 is continuously activated to form C3a & C3b leading to formation excess of membrane attack complex (MAC).



Factor H :-

Factor H is a *negative regulator of alternate C pathway* i.e. it inhibits C3 convertase (C3bBb)of alternative pathway. If there is *mutation of factor H* or *formation of autoantibody against factor* H then alternate pathway is unregulated and there is excess formation of MAC leading to glomerular injury.

Factor B & Factor D :-

Circulating C3NeF can also cause complement mediated lysis of adipocytes thereby producing high concentration of *Adipsin(Factor D).*This *factor D cleaves Factor B* and activates the alternate C pathway. This complement mediated lysis of adipocytes gives a peculiar appearance to the patient called **ACQUIRED PARTIAL LYPODYSTROPHY.**

PATHOGENESIS OF TYPE-III :-

Type lll MPGN is mainly mediated by NeFt i.e. *Nephritic factor of terminal pathway.* This NeFt is a slow acting factor which stabilises a properdin dependent C5 convertase (C3bBb3b).So there is persistent activation of C5 leading to formation of high amount of MAC.This induces glomerular injury.

PATHOGENESIS OF MPGN IN SPECIFIC CONDITION: *CRYOGLOBULINEMIA*[6]

- **CRYOGLOBULINS** are monoclonal or polyclonal immunoglobulins which precipitate reversibly as the serum is cooled below core body temperature .i.e. *precipitate at 4°C and again liquify when brought to 37°C.*
- These Cryoglobulins are of 3 types :-

Type-I : single monoclonal Ig associated with Plasma cell dyscrasia.

Type-II: mixed cryglobulins of both monoclonal(IgM) & polyclonal types.

Type-III : mixed polyclonal

Type II & III are called mixed cryoglobulins found in connective tissue disorders,lymphoproliferative diseases & infective conditions like HCV.These cryoglobulins in serum denote a systemic inflammatory syndrome involving small & medium sized blood vessels due to immune complex deposition.50-60% of patients with chronic HCV infection develop Type II cryoglobulins composed of *IgM kappa monoclonal Ab directed against polyclonal antiHCV IgG.*10-20% of such patients with detectable cryoglobulinemia have features of cryoglobulinemic MPGN.These cryoglobulins are recognised by circulating leucocytes & intrinsic glomerular cells and produce inflammatory mediators which cause glomerular injury leading to MPGN.

CLINICAL MANIFESTATIONS IN MPGN :-

MPGN primarily affects *children and young adults (6 to 25years).*No sex predilection. In children, MPGN is frequently idiopathic, whereas in adults , MPGN is commonly associated with cryoglobulinemia and HCV infection. Patients with MPGN may *present in one of four ways,* as follows[1,3]

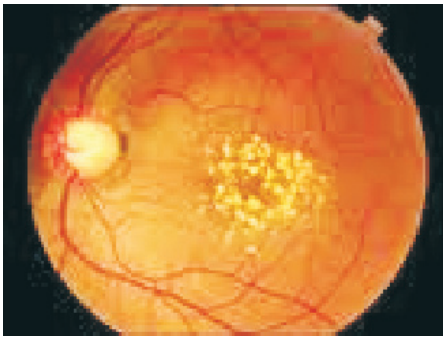
1. Nephrotic syndrome (40–70%)
2. Acute nephritic syndrome (20–30%)
3. Asymptomatic proteinuria and hematuria detected on routine urinalysis (20–30%)
4. Recurrent episodes of gross hematuria (10–20%).

A respiratory tract infection may precede the diagnosis in 50% of patients.Hypertension is found at presentation in one third of patients but occurs more frequently with progressive disease.Renal failure occurs in >50% of patients.The anemia is out of proportion to the degree of renal failure and is related to complement-mediated lysis of red blood cells. Compared with children,adults are more likely to have renal insufficiency and hypertension and less likely to have hematuria at onset. Types of MPGN can't be distinguished based on clinical presentation. However, the presence of associated extra-renal manifestations, such as DRUSEN or ACQUIRED PARTIAL LYPODYSTROPHY (APL), suggests type II MPGN.[1,3]

ACQUIRED PARTIAL LYPODYSTROPHY (APL) is the loss of subcutaneous fat in upper half of body which usually precedes the onset of kidney diseases by several years & results in peculiar facial appearance.[5]

Misra et al reported that 83%of APL patients have low C3 levels & have polyclonal C3NeF.20% develop MPGN II after a median of 8yrs after onset of APL. Compared with APL patients without renal disease, those with MPGN II have-an earlier age of onset of lypodystrophy(12.6 ± 10.3yrs Vs 7.7 ± 4.4yrs; $p<0.001$) and higher prevalence of C3 hypocomplementemia (78% Vs 95%;p=0.02). This link between APL & MPGN II is related to effects of dysregulation of alternate pathway of C cascade in both adipose tissue and kidneys.[7]

DRUSEN[8] : Whitish yellow deposits lie *within ocular Bruch's membrane*, beneath the retinal pigment epithelial cells.In contrast to the drusen formed in ARMD, in type ll MPGN, it occurs in early age and detectable in 2nd decade of life.Initially it doesn't affect vision,but as disease progresses,vision can deteriorate due to development of subretinal neovascularisation, macular detachment and central serous retinopathy. Risk of decrease of vision is 10%.



EVALUATION OF PATIENTS WITH SUSPECTED MPGN

History

- Preceding upper respiratory tract infection
- Urinary symptoms; oliguria, hematuria, frothy urine, etc
- Symptoms of anemia; fatigue, pallor, etc
- Uremic symptoms; anorexia, vomiting, etc
- Symptoms suggestive of secondary MPGN; jaundice, joint pains, weight loss, etc
- Blood transfusion

Examination

- Blood pressure
- Anasarca
- Stigmata of chronic liver disease
- Features of cryoglobulinemia; acrocyanosis, peripheral neuropathy etc
- Ophthalmic examination for DRUSEN
- Features of partial LIPODYSTROPHY

Investigations

- Hematology: full blood count,
- Biochemistry, creatinine clearance, 24-h urinary protein or urine protein/creatinine ratio, immunoglobulin electrophoresis, angiotensin-converting enzyme, á1-antitrypsin
- Immunology: complements (C3,C4, CH50), C3NeF, ANA, ANCA, rheumatoid factor, cryoglobulins
- Microbiology: HCV, HBV, HIV, blood cultures
- Radiology: chest X-ray,
- Histopathology: kidney biopsy

HISTOPATHOLOGY MPGN – I

LIGHT MICROSCOPY[1,3]

1- *Hyperlobulated glomerular tufts due to global increase in mesangial cellularity & matrix with diffuse endocapilary proliferation*.cellularity increased due to infiltration of mononuclear cells and neutrophils.

2- *Diffuse thickening and duplication of the glomerular basement membranes (GBM*) seen with Periodic acid–Schiff and silver stains !known as *tram-tracking, splitting, or reduplication* of the GBM.

It results from the presence of *subendothelial deposits* i.e. mesangial cells, infiltrating mononuclear cells, or even portions of endothelial cells interpose themselves between the endothelium and BM,forming an inner GBM like layer.The proportion of cells to matrix varies with duration of disease.In advanced cases ,lobular centers get sclerosed completely mimmicking KW lesions.Glomerular crescents are present in 10% cases of MPGN -I.Presence of *eosinophilic hyaline globules in capillary lumina* suggests MIXED CRYOGLOBULINEMIA.*Vasculitis* affecting small and medium sized renal vessels is strongly associated with cryoglobulinemic MPGN.

IMMUNOFLUROSCENT MICROSCOPY

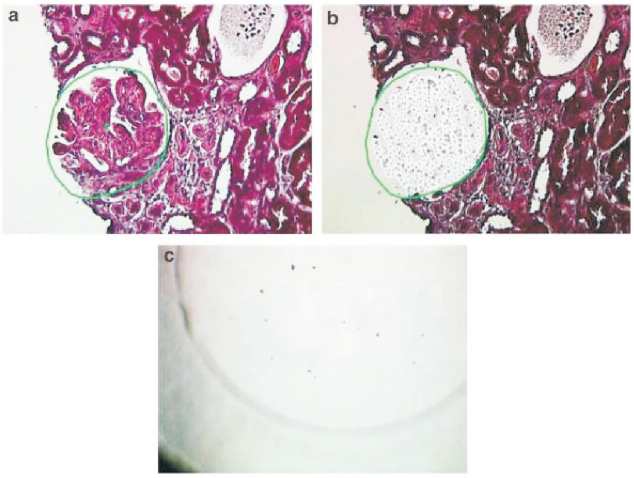
Strongly positive staining for C3 and, less frequently,for IgG and IgM, in a *fine to course granular pattern* along the glomerular capillaries.Early complement components (C1q or C4)and properdin are also frequently present.Intracapillary globular structures stained for Ig & C corresponds to hyaline thrombi in light microscopy and suggests cryoglobulinemic MPGN.

HISTOPATHOLOGY of MPGN TYPE-II[5,9]

LIGHT MICROSCOPY - the pathognomic feature of Type II MPGN is presence of *DENSE DEPOSITS*. There is presence of elongated, brightly eosinophilic, variably refractile deposits within the GBM.The deposits may be continuous and ribbon-like or periodically interrupted, thereby having the appearance of a “string of sausages” . On silver-stained specimens, these intra-membranous deposits appear to be light brown and surrounded by darker lines forming a double contour.Similar deposits may be seen in the tubular basement membrane and Bowman’s capsule.

Sethi S et al took 8 patients of confirmed cases of Dense Deposit disease & isolated the glomeruli from paraffin embeded tissues.Compared to glomeruli from

5 controls, they found that all the glomeruli from patients with DDD contain components of the alternative pathway and terminal path.Factor C9 was also uniformly present. In contrast, in nine patients with immune complex–mediated membranoproliferative glomerulonephritis, glomerular samples contained mainly immunoglobulins and complement factors C3 and C4.[10]



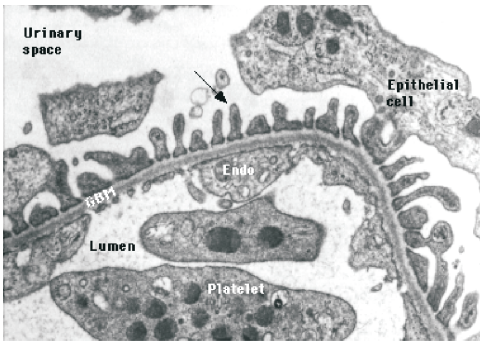
Laser microdissection of a glomerulus of DENSE DEPOSIT DISEASE :- (a) Glomerulus to be microdissected; (b) Vacant space on slide following microdissection; (c) Fragments of the microdissected glomerulus in the microcentrifuge tube cap.

Immunofluorescence microscopy shows staining for C3, usually in a linear or granular pattern along the glomerular capillaries, and in the mesangium. *Immunoglobulin is not detected*, indicating that the dense deposits are not classic Ag-Ab immune complexes.However, segmental IgM or less often IgG and rarely IgA have been reported. Early complement components are usually absent.

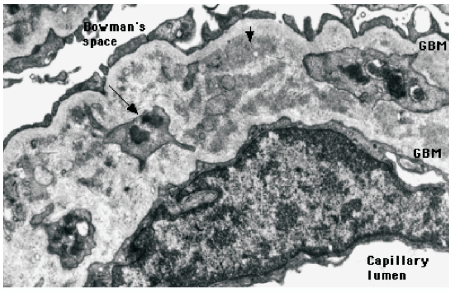
Features observed on electron microscopy is *a layer of highly electron-dense material within the lamina densa* of the glomerular capillary basement membrane that *splits into two layers.*

HISTOPATHOLOGY of MPGN TYPE-III

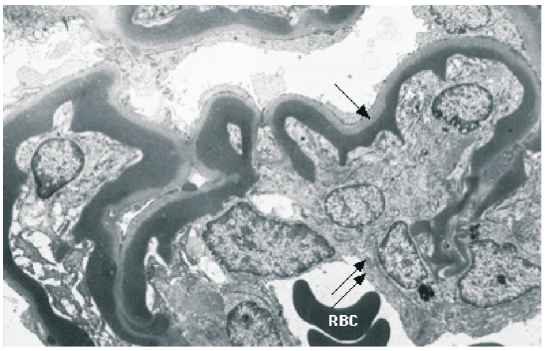
MPGN III has some features in common with those seen in *type I MPGN*, such as *double contours of the GBM and subendothelial deposits*. It also shows widespread *subepithelial deposits* similar to those seen in *membranous glomerulonephritis*. Hence,it is also named as mixed membranous & proliferative GN. However, *hypercellularity is often less prominent* than in type I MPGN.[1]



Normal glomerulus Electron micrograph of a normal glomerular capillar loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin and no electron dense deposits are present. Two normal platelets are seen in the capillary lumen. Courtesy of Helmut Rennke, MD.



Type 1 MPGN Electron micrograph in type 1 membranoproliferative glomerulonephritis shows marked thickening of the glomerular capillary wall by immune deposits (short arrow) and by interposition of mesangial cell processes (long arrow). There are two layers of the glomerular basement membrane (GBM) surrounding the mesangial interposition that account for the double contour appearance on light microscopy. Courtesy of Helmut Rennke, MD.



Type 2 membranoproliferative glomerulonphritis Electron micrograph in type 2 MPGN (dense-deposit disease) showing dense, ribbon-like appearance of subendothelial and intramembranous material (arrow) and narrowing of the capillary lumen due to proliferation of cells (double arrow). Courtesy of Helmut Rennke, MD.

COMPLEMENT LEVELS IN SERUM OF MPGN PATIENTS

TYPE OF MPGN	PATHWAY INVOLVED	COMPLEMENT LEVELS
Type I & Cryoglobulinemic MPGN	Classical pathway	C3 low /normal C4 low CH50 low
Type II	Alternate pathway	C3 low C4 normal CH50 low
Type III	Both alternate & terminal pathways	C3 low C4 normal C5-9 low

DISEASE COURSE IN MPGN[9,11]

Spontaneous fluctuation in severity of clinical picture is seen.Children tend to have a more acute presentation and a slower decline in renal function than adults.50% of patients progress to ESRD within 10 years of diagnosis.90% of patients have renal failure after 20 yrs. Features suggestive of an adverse outcome include-nephrotic syndrome,renal dysfunction at onset and persistent hypertension,presence of crescents in histopath study. Type II MPGN is associated with worst prognosis.

TREATMENT OF MPGN

1. CORTICOSTEROIDS[12]

A prospective, multicenter, randomized trial conducted by the International Study of Kidney Disease in children (ISKDC) demonstrated the beneficial effect of ALTERNATE-DAY STEROID THERAPY on renal survival in *pediatric patients* with MPGN. 80 children, predominantly with type I MPGN were randomized to receive either 40 mg/m2 of prednisone every other day or placebo for a mean duration of treatment of 41 months. Treatment failure (30% increase in serum creatinine) occurred less frequently (40%) in patients treated with prednisone than in those who received placebo (55%).61% of the treatment group versus 12% of the placebo group had stable renal function at the end of the study. While corticosteroid therapy seems to be effective in children, there is no convincing evidence that steroids are effective in modifying disease activity or disease progression in *adults* with idiopathic MPGN.

2. *CYCLOPHOSPHAMIDE*[13]

In one study by *Faeda et al,* 19 pediatric and adult patients with MPGN were treated with an intensive and prolonged regimen *of pulse methylprednisolone plus oral prednisone and cyclophosphamide.*Of the 19 patients, 15 achieved complete remission and three achieved a partial remission. They concluded that cyclophosphamide is effective in inducing remission and halting the progression of MPGN to ESRD. Cyclophosphamide is generally beneficial in patients with rapidly progressive renal failure or a recent deterioration in renal function, especially those with crescents on histopathology.

3. MYCOPHENOLATE MOFETIL[14]

MMF is an anti-proliferative agent that is being increasingly used for treating patients with various forms of immune-mediated renal disease. In idiopathic MPGN, preliminary studies suggest that the combination of MMF and corticosteroid can reduce proteinuria and may preserve renal function.

4. CYCLOSPORINE[15]

The efficacy of cyclosporine was tested in a recent trial involving 18 patients with refractory MPGN who also received small doses of prednisolone (0.15 mg/kg/day). Long-term reductions in proteinuria with preservation of renal function was observed in 17 of the patients, suggesting that cyclosporine can be considered in corticosteroid resistant primary MPGN.

5. PLASMA EXCHANGE[16]

Plasma exchange has not been studied in a controlled manner. Success has been reported for the treatment of typeII MPGN recurring after transplantation.There is some evidence that patients with Factor H deficiency may benefit from plasma exchange.

6. ANTIPLATELET THERAPY[17]

Platelet consumption is increased in MPGN and platelets play a role in glomerular injury. The combination of ASPIRIN (975 mg/day) and DIPYRIDAMOLE (275 mg/day) was found to have useful effects on renal function in a randomized double-blind placebo-controlled trial in 40 patients with idiopathic MPGN, including children .Another study reported a clinically significant reduction in proteinuria in patients treated with aspirin(500 mg/day) and dipyridamole (75 mg/day), but very little change in the GFR

CONCLUSION

MPGN represents 10% cases of GN undergoing renal biopsy.Among the primary renal causes of

NS,Idiopathic MPGN accounts for 4% in children & 7% in adults. Most affected age group is 6 to 25 i.e.children & young adults.Type l is mediated by immune complexes & classical C pathway whereas Type ll (DDD) is by alternate pathway.Type lll has histopath features of both type l MPGN & MGN.Types of MPGN cant be distinguished basing on clinical features.Type ll has worst prognosis.Steroids & immunosuppressants like CYCLOPHOSPHAMIDE, MMF are mainstay of treatment of IDIOPATHIC MPGN. Several drugs are coming up targeted to the COMPLEMENT PATHWAY & INFLAMMATORY MEDIATORS.

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Brief Communication

UNFOLDING THE MYSTERY OF ONCOGENESIS : ROLE OF ADIPONECTIN

S. Mohanty*

Adipose tissue is no longer considered inert, but an active endocrine organ. Adiponectin is secreted by adipocytes. Adiponectin is considered as a link between obesity, insulin resistance and diabetes.

Obesity (especially when BMI > 40 kg/m^2) predisposes to development of some cancers. Endometrial cancers, breast cancers (especially after menopause), cancers of colon, rectum, esophagus, kidney, pancreas, ovary, cervix, liver, gall bladder etc.. have higher incidence in obese persons.

This obesity related higher incidence of cancers is mediated by adiponectin, as suggested by some workers.

EVIDENCE ATTRIBUTING ADIPONECTIN AS A CAUSATIVE ROLE:

1. Adiponectin and Breast cancer :

Work et al (2001) observed increased incidence of breast cancer in postmenopaused obese women[1]. Mastoros et al (2004) proposed that adiponectin level might underlie the association between breast cancer and obesity.[3] Later on it was confirmed by other studies.[4,5]

Lower circulating adiponectin level was associated with higher incidence of breast cancer. This was independent of age, menopause status, hormone receptor status, and status of estrogen receptor. Additionally, it was noticed that lower the serum adiponectin level, more aggressive the tumor.

2. Adiponectin and Endometrial Cancer :

Serum level of adiponectin is inversely related to endometrial cancer. This inverse risk of endometrial cancer is independent of possible effects of SGF-I, IGF-II, IGFBR-3, leptin and BMI.[1,3,4,6]

3. Adiponectin and Cancer Colon

In a large prospective health professional follow-up study, Wei et al (2005), found that plasma adiponectin level and colorectal cancer are inversely related. Individuals in the highest adiponectin quintile had an approximately 60% reduced risk as compared to individuals with lowest quintile.[7]

4. Adiponectin and gastric cancer :

Plasma adiponectin level was lower in patient with gastric cancer, especially in fundus.[8]

5. Adiponectin and prostate cancer :

A small case-control study by Goktas et al (2005), indicate that adiponectin level is lower in patients with prostate cancer as compared to normal individuals and individuals with BHP.

6. Adiponectin and leukemia :

Adiponectin suppresses the growth of myelomonocyte cell line and induces apotosis in myelomonocytic progenitor cells (leukemia lines).[9] Circulating adiponectin is inversely related with AML but not ALL.

ADIPONECTIN AND ADIPONECTIN RECEPTORS : GENERAL INFORMATION :

Adiponectin is secreted by adipocytes. It consists of three domains - a signal peptide, a collagen like motif and a globular domain. It exists in two forms in circulation - one low molecular weight (LMW) oligomer, that is hexamer (two trimers). The other is high molecular weight (HMW) oligomer consisting of four to six trimers.

There are two types of adiponectin receptors - Adipo R1 and Adipo R2. The first one is expressed ubiquitously. It has high affinity for LMW adiponectin and low affinity for HMW adiponectin. Adipo R2 has intermediate affinity for both and predominantly expressed in liver.[10]

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MECHANISM OF ACTION OF ADIPONECTIN[10]

1. Indirect effect through altering hormone and cytokine level :

In obesity reduced adiponectin levels lead to insulin resistance and compensatory hyperinsulinemia. Increased insulin level leads to reduced liver synthesis and blood levels of insulin like growth factor binding protein I, ($IGFBP_1$) and $IGFBP_2$ and probably reduced synthesis of $+GFBP_1$ in local tissue. This leads to increased bioavailability of IGF1 which in turn promote cellular proliferation leading to oncogenesis.

2. Direct effect of adiponectin on carcinogenesis:

Adiponectin selectively binds to several mitogenic growth factors - PDGF BB, basic HGF, HBEGF etc. These factors induce proliferation in different tissue. Adiponectin inhibits them. Adiponectin also inhibits nuclear factor - KB which is a transcription factor and upregulates cellular proliferation in carcinoma breast.

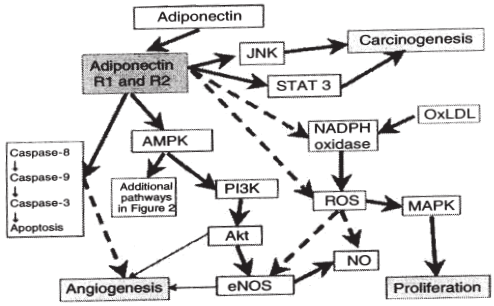

Figure 1 Multiple potential signalling pathways for adiponectin. Abbreviations: R1 and R2, adiponectin receptor type 1 and 2; AMP kinase, adenosine 5′-monophosphate (AMP)-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; oxLDL, oxidized low-density lipoprotein; PI-3K, phosphatidylinositol-3-kinase; Akt, agarose kinase target or protein kinase B; ROS, reactive oxygen species; NO, nitric oxide; eNOS, endothelial NO synthase; MAPK, mitogen-activated-protein-kinase. The solid arrows and dotted lines reflect stimulatory and inhibitory effects, respectively. Modified from Goldstein and Scalia: JCEM, June 2004, 89(6):2565.

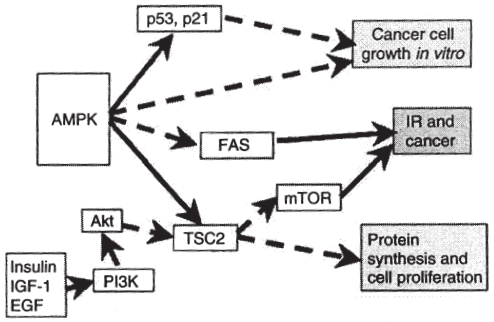

Figure 2 Possible molecular mechanisms of regulation of tumour cell growth by AMPK (12). Abbreviations: AMP kinase, adenosine 5′-monophosphate (AMP)-activated protein kinase; PI-3K, phosphatidylinositol-3-kinase; Akt, agarose kinase target or protein kinase B; mammalian target of rapamycin (mTOR); fatty acid synthase (FAS). The solid arrows and dotted lines reflect stimulatory and inhibitory effects, respectively.

3. Signalling pathways linking adiponectin with carcinogens (Fig.1, Fig.2).

Several signalling molecules such as 5′ AMP activated protein kinase (AMPK), nuclear factor-KB (NF-KB), peroxisom proliferators activated receptors (PPAR)-α, p38 mitogen-activated protein (MAP) kinase are known to mediate adiponectin induced metabolic effects.

CONCLUSION :

Adipose tissue has gained the status of an endocrine organ. Adiponectin, secreted by adopocytes, not only plays role in insulin resistance and obesity; but also is important in oncogenesis. Low serum level of adionectin may serve as a risk factor for cancer. On the otherhand adiponectin per se or adiponectin analogues may prove to be effective in preventing and managing cancer.

In addition, PPARγ agonists or adiponectin receptor agonists (e.g. osmotin) may be useful in future while managing cancer.

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Case Report

INTRAVASCULAR HEMOLYSIS IN BLACK PHENYL POISONING - TWO CASE REPORTS

L.K. Dash*, P.K. Mohanty, C.R. Khatua***, G.P. Nayak******

ABSTRACT

Black Phenyl is widely used as disinfectant in domestic and hospital environment. This is easily available for suicidal poisoning. Often considered, wrongly, as of little consequence to the persons who consume, it can be devastating as it contains a mixture of toxic coal tar acids, phenolic compounds and coal tar oils in varying proportion. Poisoning with phenol compounds may occur by ingestion, inhalation, and absorption through skin. Death may occur within a few hours due to respiratory or circulatory failure or within some days due to hepatic or renal failure. Hemolytic anemia (intravascular hemolysis) following phenol poisoning is rarely reported in the literature. We report two cases of black phenyl poisoning following ingestion who presented with intravascular hemolysis. ***Key words:*** *Black Phenyl, Coal tar acids, Phenolic compounds, Poisoning, Intravascular hemolysis;*

INTRODUCTION

Phenolic compounds were used as antimicrobial agents as early as 1815.These are produced by fractional distillation of coal tar. Various phenolic compounds include phenol, cresols, xylenols, propylphenol, tretramethyle phenol, diethyl phenol,napthols etc[1]. Kucheinmeister in 1860 and Lister in 1867 used phenol (carbolic acid) in dressing of surgical wounds. The black phenyl is a powerful germ killer used for homes, hospitals and other places of human inhabitation and it contains 40% w/w coal tar acids, phenolic compounds and coal tar oils. This can be consumed by human beings mainly with a suicidal intention because of easy availability as household sanitizers. Phenol and its derivatives like dinitrophenol and pentachlorophenol are very toxic substances with a toxicology rating of 4[2]. Poisoning may occur by ingestion, inhalation, and absorption through the skin. We report two patients who developed haemolytic anaemia jaundice and hemoglobinuria following ingestion of black phenyl. Cases of intravascular haemolysis through inhalation of phenol compounds have been reported[3], but intravascular hemolysis following ingestion of black phenyl is rarely reported in the literature[4].

CASE REPORT-1

A 33 years old previously healthy male was admitted to Medicine Department for weakness, easy fatigability and dark brown colour urination for 2 days. Two days prior to that, he had ingested black phenyl, a phenolic preparation for which he was treated with gastric lavage at peripheral hospital and discharged on the same day. There was no history of taking any drugs, other toxic substances or chronic alcohol ingestion. On examination he had pallor, icterus, tachycardia (heart rate 104/min) and blood pressure was 106/74 mmHg. Systemic examination revealed no abnormality. The blood hemoglobin (Hb) concentration was 3.8 gm/dl, white cell count 9,300/mm3, reticulocyte count of 3.8%, Total platelet count (TPC) of 2.2lacks/cmm and MP (QBC) was negative. Peripheral blood smear showed anisocytosis, normochromia with increase in polychromatic cells without any spherocytes, eliptocytes, ovalocytes and premature cells.. Serum total bilirubin was 5.4 mg/dl with an indirect fraction of 5.2 mg/dl; serum AST, ALT & alkaline phosphatase levels were 180u/l, 29u/l and 134u/l respectively and prothrombin time was 14 seconds (control of 13 seconds). Serum LDH was 911 U/L. Sickling test and coomb's (both direct and indirect) test were negative. G6PD level was normal. Urinary bilirubin was absent.

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Centrifugation of patient's blood showed dark brown discolouration of plasma suggestive of hemoglobinemia(Fig-2). Serial urine samples collected over seven consecutive days showed gradual change of colour from dark brown to light brown and then to normal(Fig.-1). During the hospital stay, he was transfused with 4 units of whole blood after which his hemoglobin level increased to 10.8 gm/dl.. Gradual improvement occurred with resolution of tachycardia, jaundice, and colour of urine. His serum billirubin level came down to normal after 11 days and he was discharged on the 12th day. He came back for check-up after 15 days and was free from symptoms.

Fig-1: Change of urine colour from Day-1 to Day-7 from left to right
Fig-2: Colour of plasma after centrifugation

CASE REPORT-2

A 32 years Female attendant of our hospital came to emergency department after two hours of consuming black phenyl preparation. She was treated with gastric lavage and admitted to ward. There was no history of taking any drugs or other substances other than the black phenyl. On examination she was afebrile with a heart rate of 96 beats per minute; blood pressure was 118/76 mmHg. The rest of the clinical examination did not reveal any abnormality. On next day, she had cola coloured urination. The hemoglobin concentration was 7.0gm/dl, white cell count 8,200/mm3, reticulocyte count of 2.7%, TPC of 2.5lacks/cmm, MP (QBC) was negative and peripheral blood smear showed normochromia, anisocytosis and polychromasia without any ovalocytes, eliptocytes and spherocytes and premature cells. Serum total bilirubin was 1.9 mg/dl with an indirect fraction of 1.1 mg/dl; serum AST, ALT & alkaline phosphatase levels were 140u/l, 85u/l and 113 u/l respectively. Serum LDH was 1132 U/L. Her G6PD level was normal. Sickling test and coomb's (both direct and indirect) test were negative. Bilirubinuria was absent. Serial urine samples showed gradual clearing and change to normal over 9 days period (Fig-3). Centrifugation of patient's blood sample showed dark brown plasma suggestive of hemoglobinemia. During the hospital stay, she was transfused with 2 units of whole blood on separate occasions. Thereafter, her Hb was increased to 10.3 gm/dl. Gradually she improved and she was discharged on the 12th day. On follow up after 15 days she was feeling better and healthy.

Figure-3: Change of urine colour from Day-1 to Day-9 from left to right

DISCUSSION

The above two reported cases presented with features of intravascular hemolysis after ingestion of black phenyl which is a mixture of coal tar products including phenolic compounds. Both cases developed hemoglobinuria (with an average duration of 9 days), anemia which was improved with blood transfusion and there was accelerated erythropoiesis as evidenced by rise in reticulocyte count. There are many reports on the toxic injury with phenols including cases with fatal outcome[2, 4, 5]. Acute toxicity causes intense burning sensation in mouth, throat, and stomach. It also depresses central nervous system especially respiratory center. Liver may be damaged. In severe cases hemolysis and methemoglobinemia is a characteristic feature[6]. Phenol is rapidly absorbed into the blood and there may be hyper- or hypo-thermia, tachycardia, tachypnoea, pronounced general weakness, nausea,

dizziness, headache, convulsion, coma and shock leading to death.The exact mechanism and the compounds involved in hemolysis are speculative. It is excreted chiefly in the urine and also by the liver, salivary gland, stomach, lungs and skin[6, 7]. Crude phenol and its derivatives like dinitrophenol, pentachlorophenol can interfere with the oxidative phosphorylation in cells[2]. Storage of energy in the form of adenosine triphosphate is prevented, thereby leading to a compensatory increase in the basal metabolic rate which is responsible for most of the principal clinical features of the toxicity of such substances. The main source of energy in red blood cells is anaerobic glycolysis. Energy is stored in the molecules of adenosine triphosphate, a process that might be prevented by the toxic effect of the phenols. Due to shortage of energy, red blood cells cannot continue to perform their vital functions like maintaining the osmotic equilibrium across the cell membranes, the cation pump and cell deformability. This metabolic handicap may lead to premature lysis of the red cells[3].Considerable progress has been made in the understanding of the mechanism that protect the red cell against oxidants[8]. These include G6PD, the entry enzyme to the hexose monophosphate shunt that generates NADPH, and related enzyme systems that maintain glutathione (GSH) in the reduced form and protect hemoglobin from irreversible oxidation by the oxidants like phenol and its derivatives. Heinz body anemias are found in individuals with defects in these protective mechanisms when they are exposed to oxidants in the form of chemicals or drugs that normally are not hemolytic [9, 10, 11, 12].

In our two reported cases, there was mild elevation of serum transaminases suggesting mild hepatic injury. But both the cases exhibited features of severe intravascular hemolysis.

In the singular case report on internet search we found N.Santa et al.[5] reported one case with hemolytic anemia following ingestion of a phenol derivative. The case history in the case they reported and our first case was similar. In their case the patient was discharged on same day after gastric lavage from emergency department who presented again 2 days later with features of hemolysis. In our 1st case, the patient was treated in a peripheral hospital and discharged on same day who visited our medical college hospital 2 days later with severe anemia due to intravascular hemolysis. These happenings indicate that the doctors attending these two cases initialy did not appreciate the toxic potential of the black phenyl. Thus it underscores the importance of creating awareness amongst doctors working in peripheral hospitals and residents in emergency department to realize that patient consuming black phenyl should not be discharged on same day as he can develop severe intravascular hemolysis and succumb at home. Such patients should be carefully observed in hospital and timely transfused with blood to tide over the phase of excessive hemolysis.

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Case Report

RECURRENT PYOPERICARDIUM IN SYSTEMIC LUPUS ERYTHEMATOSUS

S.K. Mahapatra * P.C. Dash N.R. Murmu** A. Acharya*****

ABSTRACT

A case of systemic lupus erythematosus (SLE) presented as pyopericardium who was first time diagnosed as SLE and not received any treatment is reported here with review of literature.
Key word: *SLE, Pyopericardium.*

INTRODUCTION:

Systemic Lupus Erythematosus(SLE) is a common autoimmune disorder with multisystem involvement. The most common cardiac manifestations of SLE are pericardial involvement, pericarditis, pericardial effusion, and tamponade. Pyopericardium can be a complication of SLE who is usually on steroid or immunosuppressive therapy.

Case Report:

A 18 year old female was admitted to Medicine Department with complaints of Intermittent swelling of face for 1 year, fever for 3 days, breathlessness and decreased urination for 1 day.

On examination there was moderate pallor, raised JVP periorbital puffiness and pitting pedal oedema. There was multiple erythematosus rashes all over the body and subconjuctival haemorrhage.

Her blood pressure was 110/70mm Hg, Pulse – 98 / min , Respiratory rate – 36/Min. On cardiovascular examination apex was not localized and Left second intercostal space was dull on percussion.

Laboratory investigations showed : Hb – 8.4gm %, total leucocyte count – 8,000/mm^3 , DC N88, L-12, Urine – albumin ++, RBC – 30-40/HPF, pus cell 10-12 / HPF, granular cast was present. ESR – 90mm in 1st hr., TPC – 2.04 lac / cmm, RBS – 104 mg/dl, S.urea – 103mg/dl, S.Creatinine – 2.3 mg/dl.

Antinuclear Antibody – 2.52 – positive (Homogenous) Anti dS DNA – positive (1:320).

Her abdominal ultrasonography report showed moderate ascitis, B/L pleural effusion.

2D ECHO report showed – there was moderate pericardial effusion with early tamponade. Patient was diagnosed to be a case of SLE with Nephropathy with bilateral pleural effusion and pericardial effusion.

Patient was started with methyl predenisone 1 gm daily with IV antibiotic (Piperacillin-Tazobactum + Linezolid)

Pericardiocentesis was done and 150ml of frank pus was aspirated and sent for cytological & biochemical examination and Gram staining which showed 1000/cmm cells with 70% polymorphs. Gram staining showed gram negative cocci.

Patient improved after pericardial aspiration to deteriorate again after 5 days with recurrent pyopericardiumand died in the hospital.

DISCUSSION :

Pericarditis is the most common cardiac manifestation of SLE (12-47%)(Wallace DJ et al)[1]. However according to Sturfelt G et al[2], 3% cases of SLE have pericardial effusion. In general, the echocardiogram is more sensitive then clinical diagnosis

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with 19-54% of patients having pericardial effusion. Shearn M etal[3] reported pericardial tamponade even in treated patients. A study done by Marks AD[4] et al included SLE patients with uremia as the cause of pericardial tamponade. Pericardial haemorrhage caused fatal pericardial tamponade in one anticoagulated patient (Leung WH et al)[5]. According to Zashin SJ et al[6] cardiac tamponade is rare. However this complication does occur and on rare occasions may be the presenting manifestation of SLE. MC cuiston C.F. et al[7] emphasized that acute pericardial effusion has been noted less frequently with an incidence of 8% to 18% and most of the effusions are small but occasionally are massive and tamponade have been noted. The fluid does not have any special character and has been variously described as turbid, serosanguinous, clear or pale yellow. CDR MD et al [8] reported infectious pericarditis with tamponade in SLE both by bacteria and fungi. Harvey etal[9] reported 2 cases of purulent pericarditis as the manifestation of Lupus erythematosus who were on steroid therapy. In our patient Echocardiography was done and report came as pericardial tamponade and 150ml frank pus was drawn through pericardiocentesis and SLE was diagnosed clinically and with investigations like ANA and Ds DNA. Patient was first time diagnosed to be a case of SLE in the hospital after admission who had not received steroid or any other immunosuppressive drug prior to hospitalisation. Pyopericardium in SLE have been described and presumed to be due to immunosuppression by steroid or immunosuppressive drug. Our case is unique due to fact that patient on diagnosis of this disease (SLE) presented with pyopericardium.

CONCLUSION :

A 18 yrs female presented with Pyopericardium in a case of SLE without prior diagnosis or was not on steroid treatment. So, although rare, pyopericardium can be a presenting manifestation of systemic Lupus Erythematosus.

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Case Report

AN UNUSUAL CAUSE OF RECURRENT HEMOPTYSIS

K. P. Tripathy * , P.K. Behera, R. Panigrahi *** , A. Devi *****

ABSTRACT

A 27 year old female who presented with repeated hemoptysis and to whom ATT was started in a peripheral hospital was thoroughly investigated and found to have an intralobar pulmonary sequestration in left lower lobe. Here we report the case in view of rarity. ***Key words :*** *Pulmonary sequestration, hemoptysis, Intralobar, Extralobar.*

INTRODUCTION:

Intralobar pulmonary sequestration was first described by PRYCE in 1946[1] . Since then several reports and reviews have appeared in literature with presentation in childhood as well as late in third decades[2-4]. Cases mostly present with repeated chest infection and minor hemoptysis but cases with fatal hemoptysis has also been reported[6]. We report a case in her late twenties who presented to us with recurrent hemoptysis for around six months.

CASE REPORT:

27 Yr muslim female presented to us with complaints of coughing out of blood on and off for nearly six months. It was associated with intermittent cough and scanty expectoration, at times with blood tinged sputum, but hemoptysis was never massive. There was also history of intermittent low grade fever, but no history of weight loss, loss of appetite or night sweats. She was neither a known case of rheumatic heart disease nor there was any history of dyspnea on exertion, orthopnea or PND. She was non-diabetic, non-hypertensive. There was history of contact with pulmonary TB as her husband was a known case of PTB, detected 2 yrs back and had completed ATT. She was mother of two children with regular menstrual periods. She was treated with antibiotics from time to time along with ATT for short period at a peripheral hospital and discontinued ATT.

On clinical examination she was of average body built with pulse rate 87/min, BP 110/70 mm Hg and mild pallor. There was no icterus, cyanosis or clubbing. JVP was not raised and no dependant edema was present. No significant lymphadenopathy was found.

On examination of respiratory system coarse crepitations heard over left infraaxilary and infrascapular area. No other significant findings noted. Examination of CVS, abdomen and CNS revealed no significant findings. With this clinical presentation and examination findings provisional diagnosis of non resolving left lower lobe pneumonia, left lower lobe bronchiectasis , left lower lobe pulmonary TB or malignancy was thought of including rare presence of intralobar pulmonary sequestration.

On investigation, Hb. was 9.5gm%. TLC - 12,000/cmm, ESR 40mm, blood urea 30mg/dl, serum creatinine 1mg/dl. FPG 90mg/dl. X Ray of chest showed a homogenous opacity in the left lower lobe adjacent to cardiac shadow. CT angiography of chest showed the opacity to have a separate blood supply from aorta confirming the diagnosis of intralobar pulmonary sequestration. The case was treated conservatively with antibiotics and referred to cardiothoracic surgeons where she was planned for surgical resection of the sequestrated segment.

DISCUSSION:

Pulmonary sequestration is an uncommon

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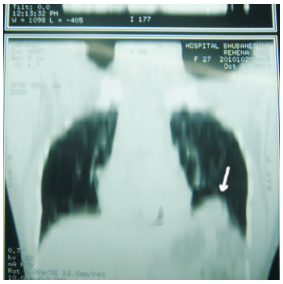
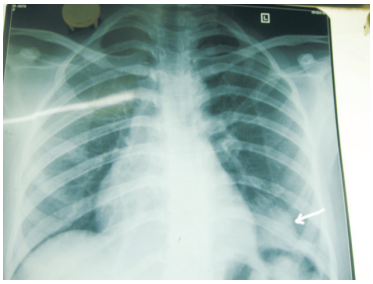
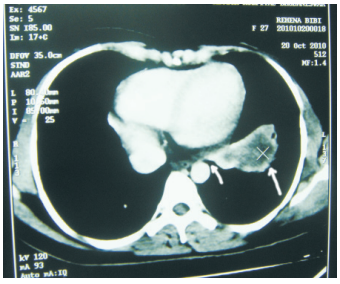
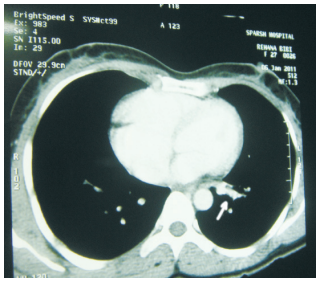



(X-ray chest PA view showing homogenous opacity in left lower lobe)

(CT angiography of chest showing opacity to have a separate blood supply from aorta)

congenital malformation characterised by presence of a segment of lung tissue that has absent or abnormal communication with tracheobronchial tree and arterial supply derived from systemic circulation [5] Frequency of this anomally varies between 0.15% and 1.7%[6]. It is classified into two types .Intralobar lung sequestration(ILS) and extralobar lung sequestration (ELS). In ILS the sequestrated tissue lies inside the visceral pleura with venous drainage to pulmonary circulation and accounts for 75%cases [6] whereas in ELS the tissue lies outside visceral pleura with venous drainage to systemic circulation. ILS are almost always located in lower lobes(98% cases) and most common in left (60%)[7]. In around 74% cases the arterial supply is from abdominal aorta[6]. Venous drainage may be variable. The calibre of anomalous vessels has been reported to vary between 1mm to 15mm [6]. Intralobar sequestration is located mostly in posterobasal segments. Upper lobe or bilateral involvement is rare and Sex distribution is equal.

In 15% cases anomaly is asymptomatic and normal longevity has been reported. Most cases present before 20yrs with recurrent chest infection [5,7] and minor hemoptysis is common. More severe hemoptysis, bleeding into pleural space, oesophagus or into sequestration itself has been reported[7]. Association of ILS with other congenital anomaly is uncommon [8].

The typical radiographic appearance of a bronchopulmonary sequestration is that of a soft tissue or cystic mass in lower lobes in association with systemic arterial feeder [9,10]. Definitive diagnosis of intralobar pulmonary sequestration requires the demonstration of abnormal arterial supply from systemic circulation mostly aorta by angiography or non invasive tests like CT angiography or MR angiography which also helps for surgical planning. Treatment for Intralobar pulmonary sequestration is surgical resection to avoid catastrophic hemoptysis.

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Case Report

UNUSUAL CAUSES OF GUILLAIN – BARRÉ SYNDROME

A.K. Sahu*, S. Dutta*, M.R. Naik, J.K. Panda*****

ABSTRACT

Guillain barre syndrome is an acute, frequently severe and fulminant polyradiculoneuropathy that is autoimmune in nature. It manifests as rapidly evolving areflexic motor paralysis with or without sensory disturbance. Most cases occur after an acute infectious process, usually respiratory or gastrointestinal. Frequently preceeded by an infection with C.Jejuni or Human herpes virus infection. Other antecedant events are CMV, EBV, M.pneumonia infection. Here we report 2 cases of GBS found to have unusual causes rarely reported before. ***Keywords*** *: Guillain-Barre Syndrome, Etiology, Complication.*

INTRODUCTION

Guillain–Barré syndrome (GBS) sometimes called Landry's paralysis, is named after the French physicians Georges Guillain and Jean Alexandre Barré, who described it in 1916. It is an acute inflammatory demyelinating polyneuropathy (AIDP), a disorder affecting the peripheral nervous system. In ascending paralysis weakness beginning in the feet and hands and migrating towards the trunk, is the most typical symptom. It can cause life-threatening complications like respiratory failure.

Six different subtypes of Guillain–Barré syndrome:-Acute inflammatory demyelinating polyneuropathy (AIDP) , Miller Fisher syndrome, Acute motor sensory neuropathy(AMAN), Acute motor sensory axonal neuropathy (AMSAN), Acute panautonomic neuropathy, Bickerstaff's brainstem encephalitis (BBE), All forms of Guillain–Barré syndrome are due to an immune response to foreign antigens that is mistargeted at gangliosides, naturally present in nerve tissues. The most common antecedent infection is *Campylobacter jejuni*.[1] However, 60% of cases do not have a known cause. One study suggests that a minority of cases may be triggered by the influenza virus, or by an immune reaction to the influenza virus[2]. Other rare organisms reported to be associated are Mycoplasma, EBV, CMV.[3]

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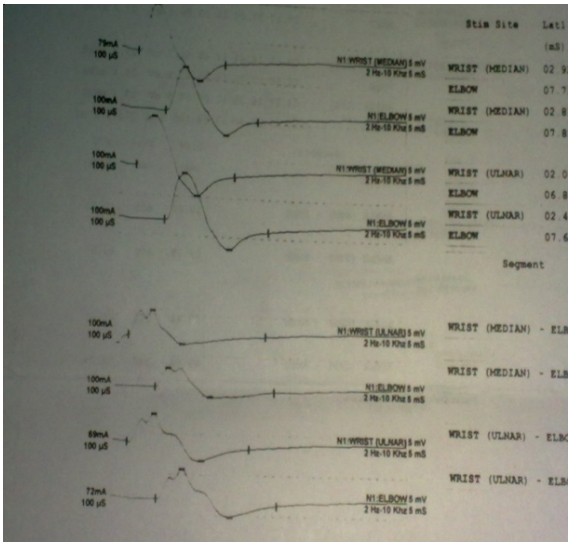
CASE REPORT

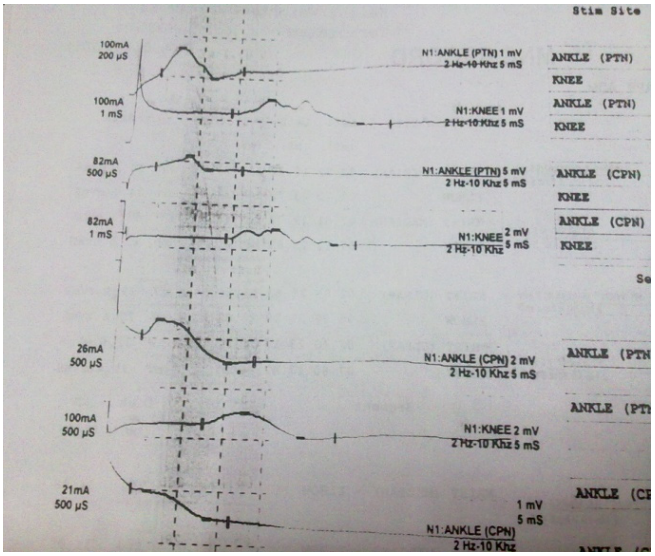
Here we present 2 cases of GBS found to have unusual causes rarely reported before.

CASE-1

37yr old male truck driver presented to Dept. of Medicine, SCB Medical College with complaints of



(NCV study showing prolonged latency & slowing of conduction velocity)



(NCV study showing prolonged latency & slowing of conduction velocity)

– weakness of both lower limbs for 4 days, weakness of both upper limbs for 2 days & breathlessness for 1 day. There was no history of fever, neck trauma, bladder bowel involvement. On detail neurological examination – bulk was normal in all 4 limbs, hypotonia in all 4 limbs, power in lower limbs around all the joints was 1/5, power in upper limbs around all the joints was 3/5, plantar reflexes were non responsive on both sides, deep tendon jerks were absent in all 4 limbs, but all modalities of sensations were intact. According to ASBURY CRITERIA he was diagnosed to have Guillain–Barré syndrome.

Laboratory investigations –Hb-9.6gm%, TLC - 8600/mm3, DC- N-71% L-27% E-1%, URINE-RBC-nil, pus cell-1-2/HPF, Epcell-2-3/HPF, FBS-95mg%, BUN-23mg/dl, serum creat-0.7 mg/dl, serum Na+ -139mEq/L, serum K+ - 4.4mEq/L, LFT showing Total Bilirubin 4.6mg/dl, Direct 2.8mg/dl, AST- 235 IU/L, ALT : 305 IU/L, ALP : 394 IU/L.

NERVE CONDUCTION STUDY showed features suggestive of AIDP i.e. prolonged latency in distal limbs & slowing of conduction velocity. Surprisingly he was found to be HCV Ag positive which was confirmed by ELISA.

CASE-2

27 yr old male presented to Dept. of Medicine, SCB Medical College with complaints of –yellowish discolouration of eyes for 15days, weakness of both lower limbs for 3 days, weakness of both upper limbs for 1day. There was history of fever for 2 days 20 days back. There was no history of breathlessness, neck trauma, bladder bowel involvement. On general examination he had icterus. Liver was palpable 2cm below right costal margin. On neurological examination –bulk was normal in all 4 limbs , hypotonia in all 4 limbs, power in lower limbs around all the joints was 1/5,power in upper limbs around all the joints was 2/5,plantar reflexes were flexor on both sides, deep tendon jerks were absent in all 4 limbs, but all modalities of sensations were intact..Provisional diagnosis of GBS was done.

Laboratory investigations –Hb-10.6gm%,TLC - 8800/mm3, DC- N-61% L-37% E-1%, Urine- RBC-nil, pus cell-1-2/HPF, Epithelial cells-2-3/HPF, FBS-65mg%,BUN-33mg/dl, serum creat-0.9 mg/dl,serum Na+ -135mEq/L, serum K+ - 4.0mEq/L. LFT-Total bil-6.4mg/dl, Direct bil-3.2mg/dl, AST-356 IU/L, ALT-415 IU/L, ALP-212 IU/L. Viral markers-HAV Ag –ve, HBs Ag –ve , HCV Ag –ve, HDV Ag –ve , HEV Ag +ve, Ig M anti HEV +ve. CSF study on 9th day of limb weakness showed-total cell-04/HPF, lymphocytes-100%, AFB -ve, sugar-65mg/dl, protein-130mg/dl, chloride-90mEq/L, ADA-5. i.e. typical albuminocytological dissociation characteristic of GBS

Nerve conduction study showed features suggestive of AIDP i.e. prolonged distal latency & slowing of conduction velocity.

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Case Report

SPLENIC INFARCTION IN MALARIA

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ABSTRACT

Splenic infarction is a very rare complication of malaria. Here we report a case of mixed Vivax and Falciparum malaria with splenic infarction with review of literature. ***Key words :*** *Malaria, Splenic Infarction, Complication.*

INTRODUCTION

Malaria is one of the most common infectious disease throughout India and it can manifest with various life threatening complications .Of all complications, splenic infarction is one of rare complication and only few such cases have been reported in literature[1,2,3,4].So far about 10 cases of splenic infarction have been reported in falciparum, vivax and ovale malaria. A case of malaria due to mixed infection with vivax and falciparum who presented with splenic infarction is reported here.

CASE REPORT

A 45 year old male presented with intermittent fever with rigor and chill, vomiting, headache for 8 days and pain over left hypochondrium for 2 days .There was history of repeated episodes of malaria during last two years. At the time of presentation his temperature was 104^0F ,pulse-134/min, regular, BP- 110/80mm of Hg, mild pallor and mild icterus. Abdominal examination revealed hepatomegaly (4 cm enlarged ,firm, non-tender, smooth) and splenomegaly (6 cm enlarged firm, tender).Investigation revealed Hb-9gm% ,TLC- 6000/ cmm,DC-$N_{60}L_{35}E_4M_1$,sr bilirubin 5mg% ,SGOT-80IU/ L, alkaline phosphatase-200IU/L, SGPT-100IU/L, sr. urea-36mg%, sr. creatinine-0.9mg%,sickling test negative, ring forms of plasmodium vivax and falciparum in peripheral blood smear,normal G6PD activity, and normal x-ray chest PA view. Ultrasonography of abdomen revealed hepatomegaly with echogenic parenchyma and splenomegaly (19 cm) with one large hypoechoeic lesion (Fig-A) and CT scan abdomen revealed an area of focal low attenuation in spleen(Fig-B) suggesting splenic infarction .Patient was treated with intravenous artesunate and oral doxycycline .He was also given NSAIDs for relief of pain. Subsequently he was also given primaquine 15gms/day for 2 weeks He recovered completely from fever and pain over right hypochondrium also subsided within one week. On 30th day of follow up he was asymptomatic and spleen size was only 2cms enlarged below the costal margin and on ultrasonography of abdomen there was no hypoechoic lesion in spleen suggesting a complete resolution of the infarction.

DISCUSSION

Malaria was confirmed in this case by demonstration of ring forms of both plasmodium vivax and falciparum. Tender splenomegaly with one hypoechoic lesion on abdominal ultrasonogram and complete clinical recovery with resolution of the infarct size after antimalarial treatment establishes the fact that splenic infarction was due to malaria .About 10 such cases due to both vivax and falciparum have been reported in the literature, but only one case due to ovale has been reported[5] implying thereby ,such complication can occur in malaria due to any species like falciparum ,vivax and ovale .In all these cases ,the course was benign and recovery was uneventful. CT scan of abdomen is the most sensitive tool for diagnosis

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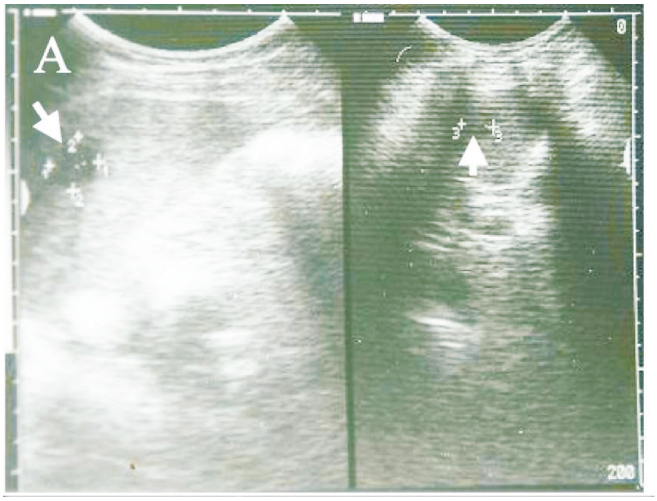
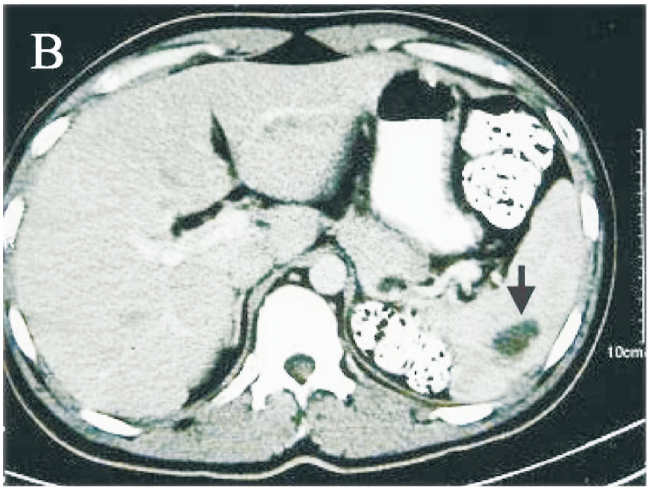


(USG of Abdomen showing hypoechoic lesion in spleen)



(CT Scan of abdomen showing an area of focal low attenuation in spleen.)

of splenic infarction though it can be diagnosed by ultrasonography of abdomen, early case may not be picked up by it .Splenic infarction can be segmental or global .It occurs as a result of arterial or venous occlusion .Spleen is supplied by splenic artery and the short gastric artery .Within the spleen arterial supply is segmental and occlusion of a secondary branch results in wedge shaped infarct .Splenic infarct can occur due to a number of cases like chronic myeloid leukemia, myelofibrosis, lymphoma , sickle cell disease ,various prothrombotic states and embolism due to infective endocarditis or atrial fibrillation . Approximately one third of patient of the splenic infarcts are clinically silent and most common symptom is pain over left hypochondrium which may be pleuritic and radiates to left shoulder .The main stay of therapy is the treatment of aetiology and analgesics.

Splenic infaction is a rare complication of malaria and it should be suspected in any malaria patient developing pain over left hypochondrium.

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Case Report

SELF LIMITING CEREBELLAR ATAXIA, DELAYED NEUROPATHY FOLLOWING ORGANOPHOSPHATE POISONING - A CASE REPORT

M. Samanta*, L.K. Meher**

ABSTRACT

A 30 year female of organophosphate poisoning (dimethoate) whose acute phase was uneventful, developed an unusual complication like self-limiting cerebellar ataxia and neuropathy afterwards.
Key words : *Organophosphorous poisoning, Neurological complications, Neuropathy, Cerebellar ataxia.*

INTRODUCTION

Organophosphate poisoning is the most common poisoning in India, accounting for almost half of the all hospital admissions due to poisoning.[1] This is due to easy availability of organophosphate compounds due to their common use in agriculture. Following exposure of organophosphate poison three well defined neurological syndromes, an initial life threatening acute cholinergic crisis which often requires intensive care and ventilatory support, an intermediate syndrome and a delayed organophosphate induced Polyneuropathy develops.[2] Only one case of cerebellar ataxia as a complication of acute organophosphate poisoning has been reported.[3] We here report a case of organophosphate compound (dimethoate) poisoning who developed self limiting cerebellar ataxia and delayed onset neuropathy.

CASE REPORT

A 30 Year married female in an attempt to commit suicide ingested around 150 cc of Dimethoate (Roger 30%). At time of hospitalization she had features of acute cholinergic crisis (Frothing from mouth, constricted pupil, bradycardia, acute pulmonary edema) for which she received gastric lavage, IV atropine, IV PAM, antibiotics and PPI. Patient recovered with above treatment. Her intermediate phase was uneventful. There was no history of any significant medical illness or drug intake. Her family history was not significant. She was a housewife by profession. However on 8th day of intake of the poison, she developed cerebellar dysarthria, paresthesia of distal part of all the four limbs. Next day she developed weakness of all the limbs simultaneously and was not able to walk. She had no dysphasia or dysphonia. On examination pulse rate was 90/mt regular, blood pressure was 122/70 mm of Hg. Neurological examination revealed patient was conscious, well oriented to time, place and person with other higher functions normal. There was horizontal gaze nystagmus grade III in both eye with other cranial nerves intact. Her power of muscles around all the joints of upper limbs were 4/5 and lower limbs were 3/5, ankle reflexes was diminished, plantar reflex was flexor both sides with no sensory deficit .Gait could not be tested because of weakness of both lower limbs. Finger nose test was positive on both sides.

Examinations of other systems like respiratory, cardiovascular and gastrointestinal were normal. Investigations like complete blood count, ESR were normal. Urine examination does not show any abnormality. Fasting blood sugar was 100 mg%. Renal function test (serum urea and creatinine) and liver function test were normal. HIV test was negative. Thyroid function does not show any abnormality. X ray cervical spine & lumbosacral spine revealed no abnormality. ECG, CSF study, CT scan brain and USG abdomen were normal. Antibody to Herpes simplex was not detected. Electrophysiological study showed markedly reduced amplitude of compound motor action

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potential (Tibial.N..0.4mv,.Peroneal.N..0.4mv, Median N.3.4mv, Ulnar N. 3.0mv) with decreased motor NCV in tibial (38.2m/s), peroneal Nerve(30m/s) of both lower limbs and mildly decreased in median(48.4m/s) and ulnar Nerve(50.6m/s) of both upper limbs. Sensory Nerve action potential was not markedly reduced in both upper and lower limbs (sural N. 5.2mv, ulnar N. 9mv, median N. 29mv). With conservative treatment patient gradually recovered over next 2 weeks and was discharged from hospital. Follow up at 6 weeks, she was completely asymptomatic.

DISCUSSION

Organophosphate poisoning is a common poisoning in India due to its ready availability and easy accessibility.[4] Three different types neurological presentations have been described. Type-I (Acute cholinergic crisis) developing within 24 hr and characterized by Sialorrhoea, Acute pulmonary edema, bradycardia, constricted pupil and twitching in leg. Type-II (Intermediate Syndrome) appearing in 24 - 96 hrs and presumed to be caused by down regulation of pre and post-synaptic nicotinic receptors due to release of excessive Ach and Ca^{2+} respectively.[5] Intermediate syndrome is characterized by predominant proximal muscle weakness, neck muscle weakness, ophthalmoplegia, loss of saccadic eye movement and respiratory paralysis. Type-III paralysis (Organophosphate Induced Delayed Neuropathy – OPIDN) which occurs 7-21 days after exposure and characterized by wrist drop or foot drop with minimal or no sensory loss.[5]

On 8th day of poisoning our patient developed clinical features of OPIDN, which was confirmed by nerve conduction study. The mechanism of OPIDN is presumed to be due to phosphorylation and aging of enzyme NTE(Neuropathic Target esterase) and neurotoxicesterase.[4] Although use of thiamin and high dose methylprednisolone found useful in experimental animals, Sena Nayak et al recommended only physiotherapy. Our patient improved considerably with physiotherapy.

Purkinje and granular cells of cerebellum have been recognized as important target for Organophosphate Poisoning.[2] In postmortem studies it has been demonstrated that highest reduction in ChE activity 60-85 % found in cerebellum which may lead to cerebellar dysfunction.[2] Foneska et al reported first case of self limiting cerebellar ataxia following Dimethoate poisoning.[2] Our patient developed features of cerebellar dysfunction (dysarthria , horizontal nystagmus and positive finger nose test of upper limbs) which recovered over a period of 1 week. As there was no cause found for cerebellar ataxia and delayed neuropathy, so it is ascribed to organophosphate (dimethoate) compound. To our knowledge this is 2nd case report of cerebellar ataxia following dimethoate poisoning. Cerebellar deficit was also described previously with same organophosphate compound (dimethoate). Subsequent similar report with this compound may suggest that this complication is specifically due to dimethoate.

CONCLUSION

Organophosphate poisoning can cause self limiting cerebellar ataxia.

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Case Report

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME IN A POSTPARTUM WOMAN WITHOUT ECLAMPSIA

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ABSTRACT

We report the case of a 26 year-old female patient who developed reversible posterior leukoencephalopathy syndrome (RPLS) in the puerperium, without evidence of preeclampsia-eclampsia or chronic arterial hypertension. RPLS is associated with diverse clinical entities including eclampsia. Seven days after giving birth to a baby, the patient presented with visual blurring,headache, elevated blood pressure and generalized tonic clonic seizure. Reversible vasogenic oedema affecting the white matter in the posterior regions of cerebral cortex was the characteristic finding in magnetic resonance imaging (MRI) of the brain. Her disease was successfully treated using antihypertensive, hyperosmolar agent, and anticonvulsants. Although the prognosis is favourable, treatment needs to be early and aggressive, with rapid control of convulsions and arterial hypertension, with the aim of preventing the development of ischemia and cerebral infarction. The physician needs to be highly alert and to consider the diagnosis of RPLS in women presenting with convulsions and other neurological symptoms in postpartum period. ***Key Words:*** *Reversible posterior leukoencephalopathy syndrome (RPLS), puerperium, postpartum, vasogenic oedema, magnetic resonance imaging(MRI).*

INTRODUCTION:

Reversible posterior leukoencephalopathy syndrome(RPLS) refers to a clinical and radiological entity presenting as headache, altered mental status such as confusion, lethargy, cortical visual disturbances,and seizures, with transient edematous changes of subcortical white matter on neuroimaging.Underlying clinical conditions predisposing to RPLS include chronic renal insufficiency, toxemia of pregnancy, pediatric post-streptococcal glomerulonephritis, thromboticthrombocytopenic purpura, autoimmune disorders alone or together with exposure to immunomodulating agents(cyclosporine, tacrolimus, interferon-alpha, cisplatin,cyclophosphamide etc.).

The well-known condition of eclampsia related RPLS can subside immediately after the delivery. We report here a case of postpartum RPLS without preceding eclampsia. These disorders have been believed to share similar pathophysiologic mechanisms with hypertensive encephalopathy.

Case Report:

A 26-year-old woman had a normal pregnancy and delivery at 40 weeks of gestation without proteinuria, peripheral edema, or neurological symptoms like seizure. There was no postpartum haemorrhage. She did not have any history of hypertension or epilepsy in the past and her blood pressure was consistently normal throughout her pregnancy; 110/72 mmHg at 32weeks,130/80 mmHg at 36 weeks of gestation and 130/80 mmHg at 39 weeks of gestation. She was also normotensive during her hospitalization from the day of delivery to the 6th postpartum day. Seven days after the delivery (day 1), she had sudden and severe headache in the morning and when she woke up from bed, she could not see anything. Her blood pressure was 182/104 mmHg then (measured by family physician).Immediately after this patient had one episode of classical generalized tonic clonic seizure.

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She was admitted to intensive care unit and antihypertensives and anticonvulsants were started. On arrival, she was disoriented. Her blood pressure was 220/110 mmHg, pulse rate was 86 bpm and regular, respiration rate was 20 per minute and her body temperature 99.2°F. On the very next day when she was out of post ictal phase her visual acuity was low without any evidence of papilloedema. She did not have any other neurological deficits. She did not have peripheral edema, anaemia, heart murmur or changes in retinal arteries and optic disc. Her urine analysis was normal. She had leukocytosis with neutrophillic dominance and raised CRP. The other biochemical and serological tests revealed no abnormalities. Hemostatic tests, endocrinologic tests, and tests for renin-aldosterone- angiotensin system were normal. MRI of brain (Fig. 1) demonstrated , hyperintense lesions expanded in bilateral parieto-occipital cortices. The site of parieto-occipital lesions did not correspond with arterial territories, and thus brain infarction was not a possible etiology.Because cerebral venous thrombosis sometimes occurs in puerperium and has predominant lesions in the posterior portions of the brain, we immediately evaluated the cerebral venous system by doing cerebral venography, which did not reveal any vascular disease including venous thrombosis or vasospasm. She was diagnosed as a case of RPLS. She was started intravenous infusion of nitroglycerin to lower the blood pressure to <140/90 mmHg and glycerol to attenuate mass effect. On the following day, she distinguished counting fingers, features, and large letters. On day4 , glycerol ,intravenous anticonvulsant and intravenous infusion of nitroglycerin were stopped and oral antihypertensive and anticonvulsants were started. By day 5, her visual function returned to normal. MRI-documented lesions disappeared on 30th day(Fig.2).The patient was discharged in a stable condition on 10th day and time to time follow up was done at regular interval which was incident free

DISCUSSION:

We report a case of RPLS in puerperium without history of preeclampsia or eclampsia or other triggering factors. An abrupt and severe increase in blood pressure, usually above the limit of diastolic pressure >130 mmHg, is the leading mechanism of RPLS due to hypertensive encephalopathy . [1,2] During this period there is no sufficient time for an upper shift in the autoregulatory curve of cerebral blood flow. In such a circumstance, RPLS may occur during relatively acute but a quantitatively modest elevation of arterial pressure .[3,4]Our patient had moderate hypertension and it might have augmented the progression of brain edema to some extent. The increase in blood pressure did not seem to result from the labor itself, because it was performed without antihypertensive agents and the delivery was uneventful.Our patient was normotensive for six days postpartum.

Reversible posterior leukoencephalopathy syndrome(RPLS) is a group of clinical disorders in which patients present with combinations of the following signs and symptoms: alterations in mental status, headache, occasional focal neurological signs, visual loss, seizure, and rarely, coma.[5] Hypertensive encephalopathy, renal failure, vasculitis, immunosuppressive treatment, and eclampsia have been reported to be major causes of this syndrome.[6] Computed tomography (CT) scans show vasogenic edema predominantly of the parietooccipital subcortical white matter, but involvement of the brain stem, cerebellum, frontal lobes, and basal ganglia are possible as well.[5] Recent advances in magnetic resonance imaging (MRI) and availability of fluid attenuated inversion recovery (FLAIR) sequences, diffusion-weighted imaging, and apparent diffusion coefficient (ADC) mapping have shown that edema occurs in both gray and white matter.[6]

The cause of RPLS is not clearly understood, but two main theories have been suggested regarding the mechanism of the disease process. One theory postulates a hypertension-induced autoregulatory failure. The failure causes vasodilation and subsequently increases capillary hydrostatic pressure, leading to vasogenic edema. A second theory is that excessive arteriolar vasoconstriction results in decreased blood flow, ischemia, and cytotoxic edema.[7]The preferential involvement of the parietal and occipital lobes is thought to be related to the relatively poor sympathetic innervation of the posterior circulation. One characteristic of this syndrome is that edema is present without infarction. Therefore, recognition and accurate treatment of the syndrome is imperative to halt progression, find and remove the cause, and prevent permanent damage or death.[6]

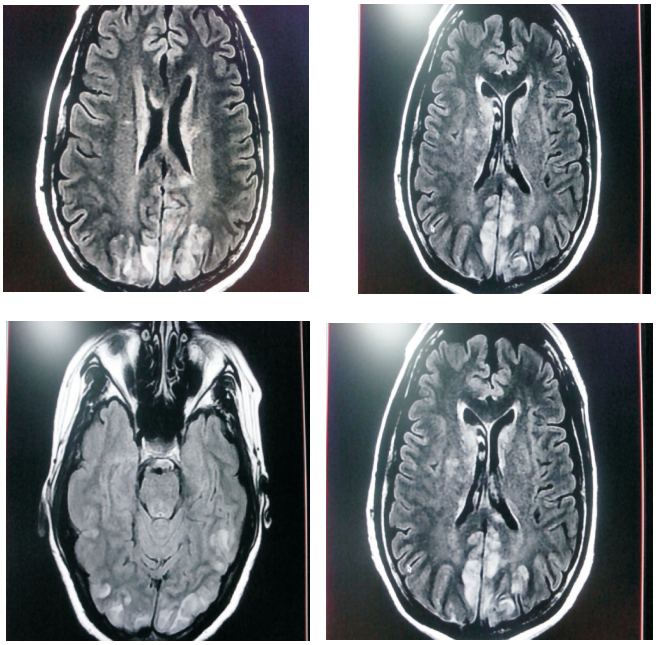

Figure 1. On day 1 MRI of brain demonstrating hyperintense lesions expanded in bilateral parieto-occipital cortices

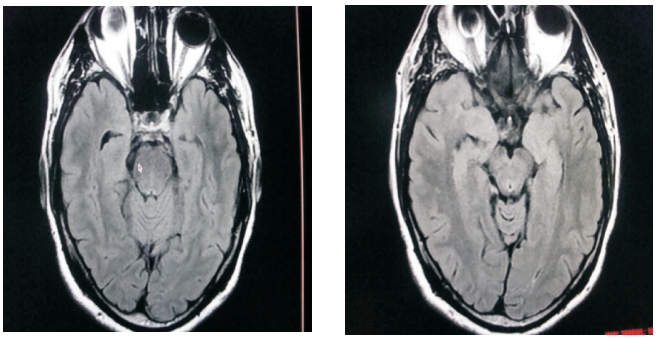

Figure 2 . On day 30 , MRI of brain - MRI-documented lesions disappeared.

Although she was not clinically preeclamptic, she might have had tendency toward endothelial dysfunction in cerebral blood vessels. Elevation of CRP, leukocytosis, and mild fever on admission suggested the existence of latent inflammation, and it might have triggered progression of endothelial dysfunction.

Regarding the therapeutic strategies, in addition to the basic therapy using antihypertensives and hyperosmolar agents ,anticonvulsants might be effective.[8]

CONCLUSION :

In conclusion, it can be highlighted that RPLS can develop in puerperium without preeclampsia-eclampsia or chronic hypertension as it can appear suddenly as bolt from the blue .This emphasizes the sincere follow up of the case in post partum period even if the patient had a normal blood pressure without preeclampsia or eclampsia.

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Case Reports

A RARE CASE OF TUBEROUS SCLEROSIS

S Mahata[*], S Kansurkar[**], J Narayan[**], M Mandal[**], P Panda[**], N Mohapatra[***], B L Parija[****]

ABSTRACT

Tuberous sclerosis is a rare disorder seen in 1 in 10,000 to 50,000 population. It is characterised by mental retardation, epilepsy and skin lesions like adenoma sebaceum, ash leaf spots and shagreen patches. A 16 yr boy presented to SCB Medical college with all these clinical features. On investigation he has also cortical tubers and subependymal calcifications in the brain. ***Key words:*** *tuberous Sclerosis, adenoma sebaceum, ash-leaf spot, epilepsy .*

INTRODUCTION:

Tuberous sclerosis is a rare disorder presenting with mental subnormality, epilepsy and skin lesions. It is characterised by hamartomatous lesions involving multiple organs of the body . Its transmission is autosomal dominant but sporadic cases are also frequent due to spontaneous mutations.

We report a case of tuberous sclerosis presenting at the age of 16 yrs, a case of sporadic spontaneous mutation.

Case Report:

History- A 16 yrs old boy presented to the Medicine OPD of SCB Medical college with h/o drowning after an episode of seizure. The boy has history of recurrent generalised tonic clonic seizures since childhood. He could not study after 3 months of school entry because of mental retardation. There is no history of similar disorder in the family.

On examination- the boy was of average body built. Ht 150 cm, Wt 48kgs. The boy had rash of reddish spots (adenoma sebaceum) over the nose and cheeks.He has raised, discolored areas on the forehead (Forehead plaques) .He had multiple hypomelanotic macules (ash leaf spots) over the back. There were areas of thick leathery skin (shagreen patches) over skin of lower back.There was burn scar over right thigh due to accidental burn injury sustained during seizure 7 yrs ago.Pulse and Blood pressure were normal. There was no pallor,icterus, cyanosis, clubbing, pedal edema or thyromegally. Respiratory and cardiovascular system examination was normal. Central nervous system examination revealed mental retardation.

On investigation: CT scan of brain showed Cortical tuber over left frontal lobe. He had also subependymal calcific nodules.X ray chest was normal. Ultrasonography of abdomen did not reveal any abnormal finding.Echocardiography of heart was normal. Fundoscopy did not reveal any abnormality.

Diagnosis of tuberous sclerosis was done based on clinical features and results of investigation and the patient was given Phenytoin for control of seizures.

DISCUSSION:

The incidence of tuberous sclerosis is 1 in 10,000 to 50,000. Tuberous sclerosis is caused by a mutation of either of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin respectively. These proteins act as tumor growth suppressors. Tuberous sclerosis is transmitted as an autosomal dominant trait. Sporadic cases are also frequent due to spontaneous mutations.

Cases of tuberous sclerosis have developmental delay, there is mental retardation and seizures since

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Fig.1

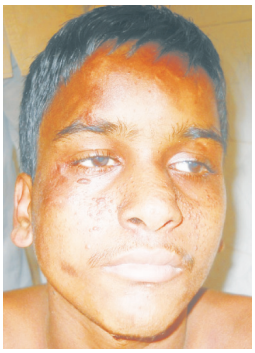


Fig.2

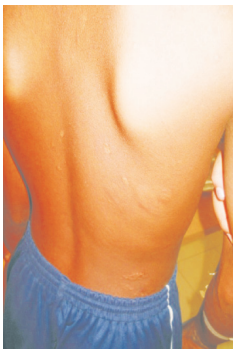


Fig.2

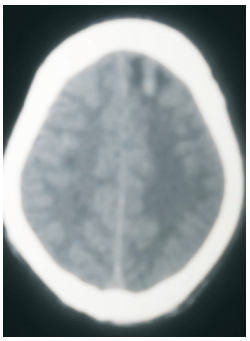
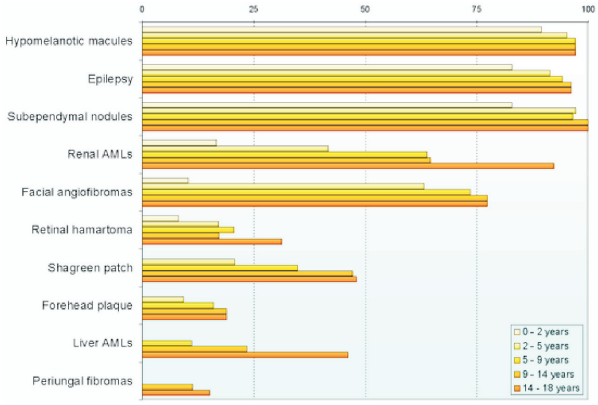


Figure 1: Adenoma Sebaceum on face
Figure2: Ash Leaf Macules(Grey arrow) and Shagreen Patches (Black arrow) Figure 3: Cortical Tuber (encircled)

Picture-1



The frequency of clinical signs in tuberous sclerosis, grouped by age

childhood. Three types of brain tumours may be associated with Tuberous sclerosis like Giant cell astrocytoma, Cortical tubers and Sub-ependymal nodules.The subependymal nodules may calcify to give rise to subependymal calcification in CT scan of brain. In heart rhabdomyomas are found. These are found during intrauterine life or within 1st year of life. In upto 60% of cases there are angiomyolipomas of kidney. 20-30% cases have renal cysts. No abnormality of kidney was detected in our case. In lungs, patient can have multiple cysts. X- ray chest was normal in this case.In eyes, retinal lesions called astrocytic hamartomas(phakomas) are found. They are yellowish to greyish white lesions on retina. Other features like coloboma, angiofibroma of eyelids may be seen. There may be papilloedema. These were absent in our case.

Prognosis :Children with mild tuberous sclerosis usually lead a normal life. However, children with severe mental retardation or uncontrollable seizures usually have bad prognosis. The tumors in this disease tend to be noncancerous (benign). However, some tumors (such as kidney or brain tumors) can become cancerous.

CONCLUSION :

Tuberous sclerosis is a rare disease involving multiple systems. In this case most of the skin and CNS features were present, but solid organ tumors were absent.

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Case Report

POLYCYTHEMIA VERA PRESENTING AS STROKE & UROLITHIASIS

S. Sahu*, B.K. Barik, S. Roy***, P. Das****,
S.S. Mahapatra*****, S. Das******

ABSTRACT

Polycythemia vera is a rare disease belonging to the group of myeloproliferative disorders. The commonest complication of PV is thrombosis of the arteries and veins leading to cerebrovascular accidents, myocardial infarction, peripheral vascular thrombosis etc. Kidney stones though lesser in frequency is an established complication. ***Key words*** *- Poycythemia vera(PV), erythropoietin, infarction, urolithiasis.*

CASE REPORT

A 42 years old(M.R.) from Balugaon was admitted to this hospital on 16-03-2011 with complains of sudden weakness of left half of the body over last 12 hours with deviation of mouth to the right.

On examination he was conscious. There was no pallor, cyanosis, icterus, clubbing, edema or thyroid enlargement. Pulse was 96/minute regular & all peripheral pulses were felt. BP-160/100 mm of Hg in both upper limbs. Respiration rate-20/minute & abdominothoracic.

Neurological examination revealed normal higher intellectual functions. There was left 7th Cranial nerve palsy (UMN type). Motor examination showed normal bulk & tone of all muscles in upper & lower limbs. Power in left upper limb was 3/5 grade in both proximal & distal groups including handgrip. Power in left lower limb was 4/5 grade in both proximal & distal groups. Power of right upper & lower limbs were normal. Bowel & bladder were not involved. There was no involuntary movements. DTJ were absent in left upper & lower limbs but normal on right half. Plantar was extensor on left side. Sensory system was normal. Funduscopy was normal. There was no other neurologic deficit.

Abdominal examination showed splenomegaly (3 cm below costal margin).Respiratory, CVS & Other systems were normal.

He had history of hypertension in past but taken irregular treatment. Occasional smoker & alcoholic. No history of DM. There was no such similar attack. No history of headache or blurred vision.

INVESTIGATIONS

Routine tests were done that revealed-

Hb-21.2gm% TLC-16,700/mm^3 DC—N-69 L-29 E-02 M-0 B-0, TRBC-6.8 million/mm^3 , PCV-57.1%, MCV-84.9fl, MCH-30.3pg , MCHC-35.7gm/dl. PS Comment-RBC- normochromic normocytic, WBC-Increased, no abnormal cell, Platelet- Adequate, MP-not found. TPC-2.90lakhs/mm^3 FBS -90mg% PPBS(2 hrs)-100mg%

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ESR-10mm/1st hour. S.Urea-17mg%. S.Creatinine-0.9mg%. S.Ca-10.0mg%. S.Phosphrous-4mg%. S.Uric acid-8mg%. Lipid profile-TG-170mg/dl, TCH-220mg/dl, HDL-42mg/dl, LDL-144mg/dl, VLDL-34mg/dl. S.Na+ - 136mEq/L. S.K+ - 4.3mEq/L.

LFT-—S.Bilirubin-1.6mg%(total), 0.8mg%(direct), SGOT-45IU/L, SGPT-41IU/L, Alk.Phos-96IU/L

S.Protein-6.3gm% ECG & ECHO – normal study. USG of abdomen & pelvis-Splenomegaly with left renal calculus of 16mm size with Hydronephrosis X-ray KUB showing left renal calculus (Fig.-1). CT Scan of brain-Normal on day of admission but revealed infarction in right paraventricular region on 3rd day.(Fig.-2)

S.Erythropoetin-3 U/L Chest x-ray-normal, CSF study - Normal, Urine - R/M-Normal

On the basis of clinical & laboratory findings the patient was diagnosed to be a case of Polycythemia vera complicating with acute stroke(cerebral infarct),urolithiasis and hydronephrosis. There was gradual recovery from stroke with I/V Mannitol, Clopidogrel+Aspirin, amlodipine,physiotherapy. For polycythemia he was treated with phlebotomy(draining 250ml of blood on alternate days for 6 sittings after which the patient refused).He was referred to Urologist for renal stone. The patient was discharged on 14th day with follow up advice after 2 weeks.

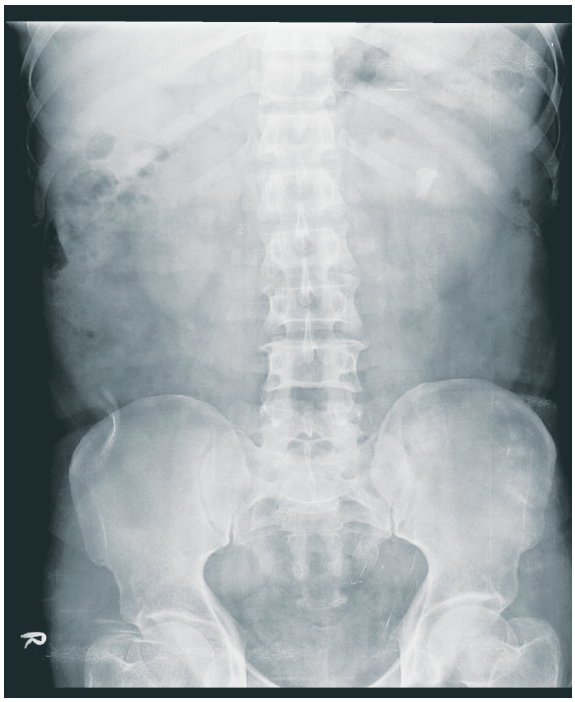

Figure -1.
Radiopaque shadow in the left renal midpole region suggestive of calculus

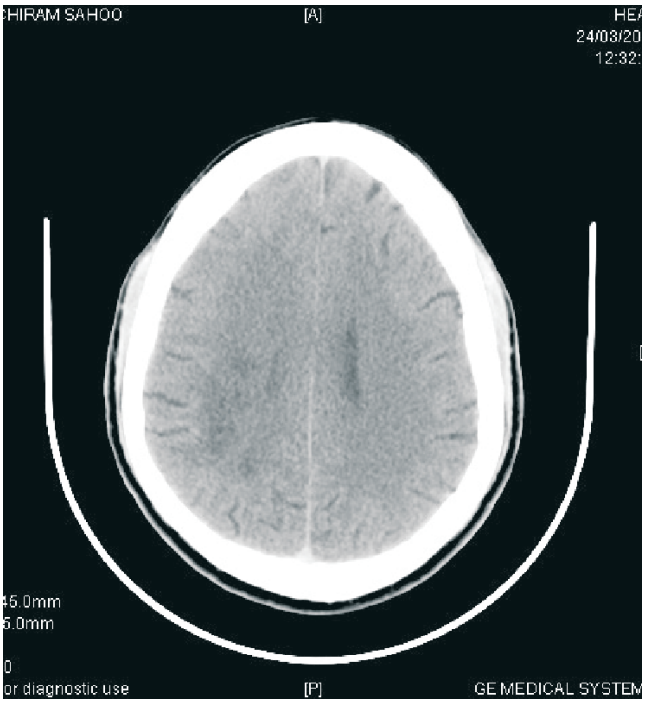

Figure – 2.
Illdefined patchy ovoid hypodensities in right paraventricular / corona radiate region suggestive of acute small vessel infarct

DISCUSSION

PV is a Stem Cell Disorder characterized as a panhyperplastic, malignant and neoplastic marrow disorder .The most prominent feature of this disease is an elevated absolute red blood cell mass of uncontrolled RBC production. This is accompanied by increased WBC(Myeloid) and platelets (megakaryocytes) production due to an abnormal clone of the hematopoietic stem cell with increased sensitivity to the different growth factors for nucleus. [1, 2,3]

PV occurs in all age groups(including children) although the incidence increases with age. The peak incidence is between 50-70 years. Over all incidence is 1-9 per 100,000 person years.

Several reasons suggest that a mutation of the Janus kinase-2 (JAK-2) gene is most likely candidate gene involved in PV. Pathogenesis as JAK-2 is directly involved in the intracellular signaling following exposure to cytokines to which polycythemia vera progenitor cells display hypersensitivity.[4]

Uncontrolled erythrocytosis causes hyperviscosity, which impair micro circulation, leading to neurologic symptoms such as vertigo, tinnitus, headache, dizziness paresthesia and visual disturbances.[4]With the exception of aquagenic pruritus, no symptoms distinguish PV from other causes of erythrocytosis. [4]

PV can cause arterial and venous cerebral thrombosis which may result in TIA(19.5%), ischemic stroke (9.5%), cerebral venous sinus thrombosis(1%). Here also the mechanism is hyper viscosity of blood and impaired cerebral blood flow. The Framingham study includes that the risk of stroke and the hemoglobin level are directly related.(Kannel et al 1972). Moreover an increased haematocrit has been associated with decreased reperfusion and increased infarct size following an acute ischemic stroke.

When PV presents with erythrocytosis in combination with leukocytosis, thrombocytosis, or both the diagnosis is apparent. [4]

Hyperuricemia and hyperuricosuria may result from an increase in cellular nucleic acid metabolism by execessive production of cells in PV which leads to formation of uric acid stones in kidney.[5]

Proposed diagnostic criteria for polycythemia vera (PV). [6]

A1. Raised red cell mass (> 25% above predicted, or hematocrit ³ 0.60 in males or > 0.56 in females)

A2. Absence of causes of secondary erythrocytosis (normal arterial oxygen saturation and no elevation of serum erythropoietin.)

A3. Palpable splenomegaly.

A4. Presence of JAK2 V617F mutation or other cytogenetic abnormality (excluding BCR-ABL) in hemopoietic cells.

B1. Thrombocytosis (platelets > 400 x 10^9/L)

B2. Neutrophilia (neutrophils > 10 x 10^9/L; > 12.5 x 10^9/L in smokers)

B3. Radiological splenomegaly.

B4. Endogenous erythroid colonies or low serum erythropoietin

A1 + A2 + either another A or two B criteria is required for a diagnosis of PV

Recommendations for management of patients with polycythemia vera (PV). [6]

1. Venesection to maintain hematocrit < 0.45
2. Low-dose aspirin (unless contraindicated)a
3. Manage reversible thrombotic risk factors aggressively (e.g., smoking, hypertension, hypercholesterolemia, obesity)
4. Consider cytoreduction if

   (i) patient intolerant of venesection

(ii) thrombocytosis develops

(iii) symptomatic or progressive splenomegaly

5. Choice of cytoreductive therapy:

(i) < 40 years – interferon-áb

(ii) > 40 years – hydroxyureab,c

CONCLUSION

Though polycythemia vera is an uncommon cause of cerebrovascular accident, still stroke is one of its most significant complication which can be prevented to a great degree by maintaining haematocrit at <45%. The patients present with urolithiasis as we report a case here.

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Articles, preferably original articles and case reports are invited from honourable members of API, Orissa State Branch to be published in the ORISSA PHYSICIANS' JOURNAL, volume VIII, in the month of November 2011. The last date for submission of articles is September 15, 2011.

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