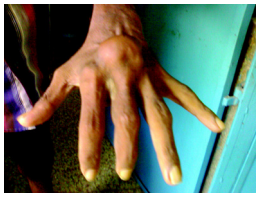
ORISSA PHYSICIANS JOURNAL

ESTABLISHED IN 2005 Vol. 5 2009 www.apiorissa.org

ISSN 0973-2853

SELECTED HIGHLIGHTS



ORISSA PHYSICIANS JOURNAL

ESTABLISHED IN 2005 Vol. 5 2009 www.apiorissa.org

ISSN 0973-2853

ORISSA PHYSICIANS JOURNAL
Official Journal of API, Orissa Chapter

Subscription information

Orissa Physicians Journal is published annually. The annual subscription is Rs.100.00. The journal is despatched within India by surface mail.

Edited, Printed & Published by

Dr. Bijayalaxmi Parija
for the Association of Physicians of India,
Orissa State Branch,
Department of Medicine, S.C.B. Medical College, Cuttack-753007, Orissa, India.

Advertorial enquiry

Dr. B.L. Parija, Hon Editor, OPJ
Dept. of Medicine
SCB Medical College, Cuttack

Printed at

Graphic Art Offset Press, Nuapatna, Cuttack-1.
Website : www.apiorissa.org

OPJ Vol.5 * 2009

CONTENTS

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Editorial

C-REACTIVE PROTEIN AS A PROGNOSTIC INDICATOR IN ACS

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

Cardiovascular disease continues to be the major cause of death worldwide including India. Despite the use of new pharmacological strategies to lower blood lipids, more aggressive therapy for hypertension control and lifestyle modification the morbidity and mortality still remains high.Atherosclerosis and its sequelae once considered solely a problem of hypercholesterolemia is now known to be a more complex process.

Though hyperlipidemia is a critical factor in 50% of patients with atherosclerotic cardiovascular disease yet various novel factors like inflammatory and neurohormonal have been identified.Atherosclerosis is not simply the accumulation of lipid but involves modification by a conglomeration of inflammatory,metabolic and degenerative process.Chronic vascular inflammation is a dynamic process of the arterial wall where inflammatory and thrombotic activity play a critical role in development of atherothrombosis resulting in the acute coronary syndrome. Inflammation of the vessel wall is considered to play an essential role in the initiation and progression of atherosclerosis and also in its final steps that is plaque erosion or fissuring and eventually plaque rupture.

In the process of inflammation various acute phase reactants and cytokines play important role. hs-CRP has been shown to be increased in the process of inflammation associated with atherosclerosis. There are many publications showing the increase in hs-CRP in atherosclerotic complications and its correlation with morbidity and mortality.

CRP,a major acute phase response protein synthesised in the liver in response to the acute phase cytokines such as IL-1,IL-6,&TNF-α. Inflammation may determine plaque stability. Unstable plaques have increased leukocyte infiltration. T-cells and macrophages predominate rupture sites. Cytokines and metalloproteinases influences both stability and degradation of plaques. The normal serum concentration of CRP ranges from 3mg/dl to more than 200 mg/dl.hs-CRP levels correlate more accurately with the clinical severity of coronary artery disease.Patients with raised CRP levels have significantly more ischemic episodes than patients with lower CRP levels.

A recent study from Zairis et al reported that hs-CRP concentration correlate with stenosis complexity in patients with Acute coronary syndrome.Ghazala Irfan et al in 2008 showed that CRP is not only a marker of vascular inflammation but also plays a key role in plaque disruption leading to STEMI and NON –STEMI.

Thus inflammation can be implicated in transformation of stable coronary plaque to unstable plaque rupture and thrombus formation. Identification of markers indicating propensity of plaque rupture and prognosis of the disease is of clinical importance and CRP may be simple and useful in this regard.However hs-CRP is a better prognostic indicator and less likely to be influenced by physiological processes and should be used as a marker of ACS.

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Original Article

CORRELATION OF HAEMORRHEOLOGICAL ABNORMALITIES WITH HEPATIC AND RENAL DYSFUNCTION IN PATIENTS OF *Plasmodium falciparum* MALARIA

D P Misra[*****] , S Das[*], R K Jena[**], S N Das[***], N T Minz[****], M Pattnaik[****]

ABSTRACT

41 consecutive patients of slide / ICT positive Plasmodium falciparum malaria were studied. Mean age was 33.82 (± 12.43) years, 83% were males. All presented with rigor and chill, icterus, 59% had oliguria, 51% hepatomegaly, 42% splenomegaly, with less than 3 % having overt bleeding diathesis. On evaluation, 83 % had acute renal failure, mean values of bilirubin 13.47(± 12.59) mg/dL, ALT 76.29 (± 40.44) IU/ml, AST 137.66 (±106.38) IU/ml while mean PT was 12.85 (± 2.22) seconds, mean APTT was 33.6 ± 7.69 seconds and FDP by D-dimer was raised in 48% cases respectively. Clot retraction test was abnormal in 12.5% cases and thrombocytopenia was seen in 22% cases. Serum LDH was raised in 48% cases. On analysis, bleeding time had statistically significant correlation with serum AST (r = +0.471, p = 0.010, n = 29), serum ALT (r = + 0.373, p = 0.046, n = 29), serum urea (r = + 0.418, p = 0.024, n = 29) and serum creatinine (r = +0.369, p = 0.049, n = 29). Prothrombin time had statistically significant correlation with serum urea (r = + 0.570, p = 0.001, n = 32) and serum creatinine (r = +0.553, p = 0.001, n = 32). Serum FDP significantly correlated with serum urea (r = +0.414, p = 0.021, n = 31) and serum creatinine (r = + 0.411, p = 0.022, n = 31). Serum bilirubin had significant correlation with serum urea (r = + 0.397, p = 0.027, n = 41) and serum creatinine (r = +0.583. p = 0.000, n = 41). Raised FDP (48 %), prolonged APTT(34%), low total platelet count(22%) and anemia (68%) are markers of DIC, and anemia(68%), raised LDH(48%) and hyperbilirubinemia are markers of intravascular hemolysis. Therefore patients with Plasmodium falciparum malaria have significant subclinical haemorrheological disorders which do not amount to DIC but adversely affect renal function leading to acute renal failure.

INTRODUCTION

Malaria continues to be a major public health problem in South East Asia Region with nearly 290 million people estimated to be at high risk[1]. Of the reported cases of malaria, India accounts for 77 % of the regional total[1]. As reported in 2006, Orissa accounts for the second highest number of malaria cases in the country (17.86%), with 86.92 % of these being *Plasmodium falciparum* malaria, which constitute 29.63% of total number of *Plasmodium falciparum* malaria cases in the country[1]. The most frequent presentation of malaria is that of a pronounced febrile illness with rigors[2]. Severe malaria is principally a result of *Plasmodium falciparum* infection because this species uniquely infects erythrocytes of all ages and mediates the sequestration of infected erythrocytes in small blood vessels, thereby evading clearance of infected erythrocytes by spleen[3]. The clinical pattern of malaria has changed worldwide including India in last decade[4]. Earlier cerebral malaria was the predominant manifestation of severe malaria, whereas now the combination of jaundice and renal failure are more common[4]. Studies on renal and hepatic dysfunction in *Plasmodium falciparum* malaria are

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aplenty, but there is a paucity of studies correlating haemorrheological abnormalities with hepatic and renal dysfunction in *Plasmodium falciparum* malaria. The present study was designed to assess hepatic and renal dysfunction in *Plasmodium falciparum* malaria, and evaluate if such abnormalities had any bearing with the hemorrheological dysfunction .

MATERIALS AND METHODS

The present study was done on 41 consecutive patients of either slide or ICT positive *Plasmodium falciparum* malaria admitted to the Medicine wards of S.C.B. Medical College and Hospital , Cuttack during the period 2008 – 2009. It included adult patients of all age groups and both genders who were slide / ICT proven cases of *Plasmodium falciparum* malaria, and had jaundice or renal failure or both at the time of admission. All these patients were evaluated for history of fever with chill and rigor, yellow discolouration of eyes, decreased urination, altered sensorium, convulsions, respiratory difficulty, clinically overt bleeding diathesis, and hepatosplenomegaly. Patients with past history of alcoholism, jaundice, chronic renal failure , bleeding diathesis or coagulopathy were excluded from the study. Laboratory investigations done were routine hemogram, bleeding time(BT), clotting time(CT), prothrombin time(PT) with INR, activated thromboplastin time(APTT), FDP by d-Dimer, liver function tests (LFT), serum urea, serum creatinine, serum sodium, serum potassium, random plasma glucose, serum lactate dehydrogenase(LDH), blood glucose-6-phosphate dehydrogenase activity, clot retraction test and ultrasound abdomen were done. The data collected was tabulated and analysed using SPSS software (Version 16).

OBSERVATIONS

The age of the patients studied ranged between 15-70 years, with a mean age of 33.82 ± 12.43 years. 83 % patients were males. Malarial parasite ICT positivity for *Plasmodium falciparum* was seen in 98 % cases, with concomitant positivity for *Plasmodium vivax* seen in 88 % cases suggesting mixed infection. Clinical presentations encountered are Fever with chills and rigor in all cases, icterus in all cases, oliguria in 59%, hepatomegaly in 51%, splenomegaly in 42%, disorientation in 29%, respiratory difficulty in 12%, bleeding from mouth and gums in 2.5% of cases. Laboratory parameters assessed including haemorrheological parameters are summarized in Table No. 1 and 2. Ultrasonography reveals splenomegaly in 68% of cases, hepatomegaly in 57% of cases, hepatosplenomegaly in 43% & normal ultrasound of abdomen in 14% of cases.

TABLE NO. 1 – RENAL AND LIVER FUNCTION TESTS

S.No.	Parameter	Mean	Range	Comments
1	Serum urea (mg/dL)	127.32 ± 97.44	28 - 405	Raised in 83 % cases
2	Serum creatinine (mg/dL)	3.50 ± 3.67	0.8 - 20.9	Raised in 61 % cases
3	Random plasma glucose(mg/dL)	131.38 ± 55.26	50 - 257	
4	Total bilirubin(mg/dL)	13.47 ± 12.59	2.0 - 50	Conjugated pattern in 79 % cases
5	Serum AST (IU/ml)	137.66 ± 106.38	24 - 496	Raised in 95 % , greater than 3 fold in 44 % cases
6	Serum ALT (IU/ml)	76.29 ± 40.44	20 - 181	Raised in 83 % , greater than 3 fold in 17 % cases
7	Serum ALP (IU/ml)	179.2 ± 92.16	71 - 521	Raised in 32% cases

TABLE NO. 2 - HAEMORRHEOLOGICAL ABNORMALITIES

S.No	Parameter	Mean	Range	Comments
1	Hemoglobin (gram%)	10.29 ± 1.96	6.6 - 15	68% had anemia, Normocytic normochromic 62%, microcytic hypochromic 38%
2	Total platelet count count(/mm3)	1,99,740 ± 79,775	48000 - 396000	Thrombocytopenia in 22 % cases
3	Reticulocyte count(%)	1.53 ± 0.82	0.5 - 4	
4	Bleeding time	1min 36 sec ± 20sec	1min - 2min 16sec	
5	Clotting time	8min 31 sec ± 3min 17sec	3min 25 sec - 16 min 20 sec	
6	Prothrombin Time (sec)	12.85 ± 2.22	9.7 - 19.8	
7	INR	1.19 ± 0.21	1 -1.7	Greater than 1.4 in 22 % cases
8	APTT (sec)	33.6 ± 7.69	25.7 - 60.13	Raised in 34 % cases
9	FDP by d-Dimer (ng/ml)	453.39 ± 384.19	200 - 1925	Raised in 48 % cases
10	Serum LDH (IU/ml)	667.7 ± 649.41	82 -2431	Raised in 48 % cases
11	Clot retraction test			Abnormal in 12.5 % cases , 50% had concurrent thrombocytopenia

Statistical analysis to deduce Pearson's correlation coefficient (2 – tailed) revealed bleeding time to have statistically significant correlation with serum AST ($r = + 0.471$, $p = 0.010$, $n = 29$), serum ALT ($r = + 0.373$, $p = 0.046$, $n = 29$), serum urea ($r = + 0.418$, $p = 0.024$, $n = 29$) and serum creatinine ($r = + 0.369$, $p = 0.049$, $n = 29$). Prothrombin time had statistically significant correlation with serum urea($r = + 0.570$, $p = 0.001$, $n = 32$) and serum creatinine ($r= + 0.553$, $p = 0.001$, $n = 32$). Serum FDP correlated significantly with serum urea ($r = + 0.414$, $p = 0.021$, $n = 31$) and serum creatinine ($r = + 0.411$, $p = 0.022$, $n = 31$). (Table-3 & 4) Serum bilirubin had significant correlation with serum urea ($r = + 0.397$, $p = 0.027$, $n = 41$) and serum creatinine ($r = + 0.583$, $p = 0.000$, $n = 41$) Table-5.

DISCUSSION

Liver is the first organ to be involved in malarial parasite replication[5]. Jaundice in malaria appears to have hemolytic, hepatic and cholestatic components[6]. Jaundice in *Plasmodium falciparum* malaria is due to malarial hepatitis, intravascular hemolysis and disseminated intravascular coagulation[5] . Mild jaundice may be due to hemolysis with serum bilirubin upto 5 – 6 mg/dL, but very high levels can occur only due to associated hepatocyte dysfunction[7]. The evidence of predominant conjugated hyperbilirubinemia, increased levels of AST and ALT alongwith evidence of hepatocellular necrosis in histopathological examination were taken as strong evidence of gross hepatocyte dysfunction and the term malarial hepatitis was justified[8].

The renal injury in severe malaria results from acute tubular necrosis[6]. Acute tubular necrosis presumably results from renal microvascular obstruction and cellular injury consequent upon sequestration in the kidney and the filtration of free hemoglobin, myoglobin and other cellular material[6].

In acute malaria , coagulation cascade activity is accelerated with accelerated fibrinogen turnover, consumption of antithrombin III, reduced Factor XIII activity and increased concentration of fibrin degradation products in acute malaria[6]. In severe infections, the prothrombin and partial thromboplastin times may be prolonged, and in the occasional patient (<5%) bleeding may be significant, and lethal hemorrhage (usually gastrointestinal) is quite unusual [6,9]. Severe anemia (PCV <15 or Hb <5 g%) can develop rapidly in non-immune person and in unstable malaria transmission zone[7]. It is usually normochromic normocytic[7]. Severe bleeding from gums, nose or gastrointestinal tract occur in <5% of

TABLE NO. 3 – CORRELATION BETWEEN HAEMORRHEOLOGICAL ABNORMALITIES AND LFT

Correlations

		Totalplatelet count	BT	CT	PTT est	INR	APTTT EST	APTTR atio	FDPbyDdi mer	Serumbilirubinatad mission	AS T	AL T
Totalplateletcount	Pearson Correlation	1	-.132	-.043	-.155	.041	-.064	-.043	-.315	-.284	.119	**.397***
	Sig. (2-tailed)		.495	.827	.405	.827	.732	.820	.084	.121	.525	**.027**
	N	31	29	29	31	31	31	31	31	31	31	**31**
BT	Pearson Correlation	-.132	1	-.140	.278	.145	.207	.204	.446*	.079	**.471****	**.373***
	Sig. (2-tailed)	.495		.470	.144	.453	.280	.289	.015	.685	**.010**	**.046**
	N	29	29	29	29	29	29	29	29	29	**29**	**29**
CT	Pearson Correlation	-.043	-.140	1	-.169	.297	.143	.175	-.465*	.074	.014	-.081
	Sig. (2-tailed)	.827	.470		.382	.118	.460	.364	.011	.704	.941	.676
	N	29	29	29	29	29	29	29	29	29	29	29
PTTest	Pearson Correlation	-.155	.278	-.169	1	.626**	.110	.061	.359*	.295	-.181	-.112
	Sig. (2-tailed)	.405	.144	.382		.000	.555	.743	.047	.102	.323	.541
	N	31	29	29	32	32	31	31	31	32	32	32
INR	Pearson Correlation	.041	.145	.297	.626**	1	.375*	.380*	-.215	.089	-.133	.011
	Sig. (2-tailed)	.827	.453	.118	.000		.037	.035	.246	.629	.466	.950
	N	31	29	29	32	32	31	31	31	32	32	32

APTTTEST	Pearson Correlation	-.064	.207	.143	.110	.375*	1	.996**	-.097	.324	-.029	.119
	Sig. (2-tailed)	.732	.280	.460	.555	.037		.000	.603	.075	.876	.523
	N	31	29	29	31	31	31	31	31	31	31	31
APTTRatio	Pearson Correlation	-.043	.204	.175	.061	.380*	.996**	1	-.139	.297	-.019	.145
	Sig. (2-tailed)	.820	.289	.364	.743	.035	.000		.456	.104	.920	.436
	N	31	29	29	31	31	31	31	31	31	31	31
FDPbyDdimer	Pearson Correlation	-.315	.446*	-.465*	.359*	-.215	-.097	-.139	1	.339	.212	.023
	Sig. (2-tailed)	.084	.015	.011	.047	.246	.603	.456		.062	.251	.902
	N	31	29	29	31	31	31	31	31	31	31	31
Serumbilirubinat admission	Pearson Correlation	-.284	.079	.074	.295	.089	.324	.297	.339	1	.189	.157
	Sig. (2-tailed)	.121	.685	.704	.102	.629	.075	.104	.062		.236	.326
	N	31	29	29	32	32	31	31	31	41	41	41
AST	Pearson Correlation	.119	**.471****	.014	-.181	-.133	-.029	-.019	.212	.189	1	.535**
	Sig. (2-tailed)	.525	**.010**	.941	.323	.466	.876	.920	.251	.236		.000
	N	31	**29**	29	32	32	31	31	31	41	41	41
ALT	Pearson Correlation	**.397***	**.373***	-.081	-.112	.011	.119	.145	.023	.157	.535**	1
	Sig.(2-tailed)	**.027**	**.046**	.676	.541	.950	.523	.436	.902	.326	.000	
	N	**31**	**29**	29	32	32	31	31	31	41	41	41

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

TABLE NO. 4 - CORRELATION BETWEEN COAGULATION PARAMETERS AND RENAL FUNCTION TESTS

Totalplateletcount	Pearson Correlation	1	-.132	-.043	-.155	.041	-.064	-.043	-.315	-.092	-.227
	Sig. (2-tailed)		.495	.827	.405	.827	.732	.820	.084	.621	.219
	N	31	29	29	31	31	31	31	31	31	31
BT	Pearson Correlation	-.132	1	-.140	.278	.145	.207	.204	.446*	**.418***	**.369***
	Sig. (2-tailed)	.495		.470	.144	.453	.280	.289	.015	**.024**	**.049**
	N	29	29	29	29	29	29	29	29	**29**	**29**
CT	Pearson Correlation	-.043	-.140	1	-.169	.297	.143	.175	-.465*	-.135	-.239
	Sig. (2-tailed)	.827	.470		.382	.118	.460	.364	.011	.487	.211
	N	29	29	29	29	29	29	29	29	29	29
PTTest	Pearson Correlation	-.155	.278	-.169	1	.626**	.110	.061	.359*	**.570****	**.553****
	Sig. (2-tailed)	.405	.144	.382		.000	.555	.743	.047	**.001**	**.001**
	N	31	29	29	32	32	31	31	31	**32**	**32**
INR	Pearson Correlation	.041	.145	.297	.626**	1	.375*	.380*	-.215	**.500****	.345
	Sig. (2-tailed)	.827	.453	.118	.000		.037	.035	.246	**.004**	.053
	N	31	29	29	32	32	31	31	31	**32**	32
APTTTEST	Pearson Correlation	-.064	.207	.143	.110	.375*	1	.996**	-.097	.212	.053
	Sig. (2-tailed)	.732	.280	.460	.555	.037		.000	.603	.252	.778
	N	31	29	29	31	31	31	31	31	31	31
APTTRatio	Pearson Correlation	-.043	.204	.175	.061	.380*	.996**	1	-.139	.202	.033
	Sig. (2-tailed)	.820	.289	.364	.743	.035	.000		.456	.276	.860
	N	31	29	29	31	31	31	31	31	31	31

FDPbyDdimer	Pearson Correlation	-.315	.446*	-.465*	.359*	-.215	-.097	-.139	1	**.414***	**.411***
	Sig. (2-tailed)	.084	.015	.011	.047	.246	.603	.456		**.021**	**.022**
	N	31	29	29	31	31	31	31	31	**31**	**31**
Urea	Pearson Correlation	-.092	**.418***	-.135	**.570****	**.500****	.212	.202	**.414***	1	.893**
	Sig. (2-tailed)	.621	**.024**	.487	**.001**	**.004**	.252	.276	**.021**		.000
	N	31	29	29	32	32	31	31	**31**	41	41
Creatinine	Pearson Correlation	-.227	**.369***	-.239	**.553****	.345	.053	.033	**.411***	.893**	1
	Sig. (2-tailed)	.219	**.049**	.211	**.001**	.053	.778	.860	**.022**	.000	
	N	31	**29**	29	**32**	32	31	31	**31**	41	41

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

TABLE NO. 5 - CORRELATION BETWEEN LFTS AND RENAL FUNCTION TESTS

Correlations

		Serumbilirubinatadmission	AST	ALT	Urea	Creatinine
Serumbilirubinatadmission	Pearson Correlation	1	.189	.157	**.596****	**.583****
	Sig. (2-tailed)		.236	.326	**.000**	**.000**
	N	41	41	41	**41**	**41**
AST	*Pearson Correlation*	*.189*	*1*	*.535***	*.296*	*.264*
	Sig. (2-tailed)	.236		.000	.060	.096
	N	41	41	41	41	41
ALT	Pearson Correlation	.157	.535**	1	.192	.150
	Sig. (2-tailed)	.326	.000		.229	.349
	N	41	41	41	41	41
Urea	Pearson Correlation	**.596****	.296	.192	1	.893**
	Sig. (2-tailed)	**.000**	.060	.229		.000
	N	**41**	41	41	41	41
Creatinine	Pearson Correlation	**.583****	.264	.150	.893**	1
	Sig. (2-tailed)	**.000**	.096	.349	.000	
	N	**41**	41	41	41	41

**. Correlation is significant at the 0.01 level (2-tailed).

patients[7]. Hematemesis may also occur from stress ulcer or from acute gastric erosion[7]. Thrombocytopenia is common to all the four human malarias and is caused by increased splenic parasitic clearance[6]. Thrombocytopenia may be a cause of severe bleeding from different parts of body[7].

Our study revealed significant burden of subclinical haemorrheological dysfunction in population of patients with *Plasmodium falciparum* malaria complicated by renal and hepatic dysfunction, even though less than 3% of patients studied had clinically overt bleeding manifestations. The parameters of haemorrheological dysfunction (BT, PT, FDP) all correlated significantly with parameters of renal dysfunction (serum urea and serum creatinine), whereas only BT correlated significantly with serum AST and serum ALT.

CONCLUSION

Anemia (68%), raised LDH (48%) and hyperbilirubinemia (100%) are markers of intravascular hemolysis in patients with *Plasmodium falciparum* malaria. Similarly, raised FDP (48%), prolonged APTT (34%), low platelet count (22%) and anemia (68%) are markers of coagulation disorder. Therefore, as revealed in our study, patients of complicated *Plasmodium falciparum* malaria have significant subclinical haemorrheological disorders which do not amount to clinically overt DIC. However keeping in mind a significant number of such patients having renal failure these subclinincal haemorrheological disorders which also correlate directly with renal dysfunction, can adversely affect renal function leading to acute renal failure.

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Original Article

PROLONGED FEBRILE ILLNESS IN THE ELDERLY

S. N. Das*, A. Maitra, K. Chakravarty*****

ABSTRACT

Fever is one of the primary manifestation of disease. Despite a substantial percentage of elderly patients presenting with diminished febrile responses, the majority (70-80%) will have fever. Compared to the young, in whom febrile responses are often caused by benign illnesses; fever in elderly patients is usually caused by a serious infection or disease. Thus any elderly person presenting with a fever must always be thoroughly evaluated.[1]

AIM OF THE STUDY : To evaluate clinical & etiological profile of prolonged febrile illness in elderly patients.

MATERIALS & METHODS: Elderly patients (>60yr) presenting to S.C.B. Medical college with fever for >3 weeks without a diagnosis at presentation were taken up for study. A diagnostic workup included detailed clinical work up, lab.tests , cultures, serology, chest x-rays and ultrasound . In non-revealing cases based on potential diagnostic clues special diagnostic tests were taken up. Only diagnoses that were evidence based or clinically nearest was retained. Patients were categorized into 4 groups based on the timing of presentation to diagnosis. Viz, Early Diagnosis (within 3 days),Intermediate Diagnosis (between Days 4 & 7),Late Diagnosis (after day 7), and No Diagnosis. The etiologies were classified into 5 diagnostic categories 1.Infections 2.Malignancies 3.Noninfectious Inflammatory diseases (NIID) 4.Miscellaneous cause 5.No diagnosis.

OBSERVATION: After exclusion 50 elderly pts were selected for study. Elderly male cases predominated (72%) with mean age 65.5yr v/s elderly female (28%) at 64.5yr.Mean duration of fever at presentation was 42±26 days. Commonest accompaniment to fever was pallor, chest signs, hepato-splenomegaly and lymphadenopathy.60% were diagnosed to have infection as cause of fever, the commonest being tuberculosis (TB). Malignancies accounted for 30% cases, commonest being NHL. On follow up 42%were cured,34% are on follow up,16% lost to follow up and 8% died.

INTRODUCTION

WHO defines people aged 60-74 yr as elderly, between 75-84 as old, and 85 plus as old old.[2] The elderly population of Orissa is rising rapidly. It was 22.81 lakh in 1991, grew to 30.39 lakh in 2001 and majority of them (88%) live in rural areas. Elderly persons constitute 8.26% of total population of the state. As per population projections, the number of elderly in Orissa was likely to be around 62.69 lakh in 2006 and share of elderly was expected to be 13.8% of the total population.[3]

Past studies of fever on unknown origin (FUO) in elderly have revealed that unlike in the young ,a precise diagnosis can be made 87-95% of the time. In many cases, FUO is due to atypical presentations of common disease. Infection is the etiology in 25-35% of cases, with tuberculosis being commonest. Connective tissue diseases such as temporal arteritis, Rh arthritis and polymyalgia rheumatica are causes in 25-31% cases and malignancies accounted for 12-23%.Since many of these diseases are treatable, it is well worth to describe the etiology of FUO in the elderly.[4,6]

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There are only few studies on prolonged febrile illness and fever of unknown origin in the elderly world wide. Gerontological literature is scarce in this field, there is also no published study from India, with an elderly population of 76.62 million(7.7% of total population)which is more than the total population of UK(60.77million)& Australia(20.43 million).

DEFINITIONS

1. PROLONGED FEBRILE ILLNESS (Vanderschueren S, et al 2003)[7]

   (i) An illness of at least 3 Wks duration before diagnosis (ii) Temperature exceeding 101ºF (38.3ºC) on > 3 occasions. (iii) No Diagnosis at referral.

2. FEVER OF UNKNOWN ORIGIN :

   (Petersdof & Beeson 1961)[8]

   (i) An illness of at least 3 weeks duration. (ii) Temperatures of > 38.30C (1010F) on several occasions. (iii) Failure to reach a diagnosis despite 1 Wk of inpatient investigation.

3. CLASSICAL FUO(Durack and Street 1991)[9]

   First 2 criteria of Petersdorf and Beeson **plus** Uncertain diagnosis after appropriate investigations after at least 3 OPD visits or 3 days in hospital or 1 Wk of "Intelligent and Invasive" ambulatory investigation.

AIM OF THE STUDY

(i) To evaluate clinical & etiological profile of prolonged febrile illness in elderly patients.

(ii) To arrive at a correct final diagnosis.

(iii) To treat the patients and follow up to record cure, mortality or morbidity.

INCLUSION CRITERIA

(i) Elderly patients (Age ≥ 60 Years) presenting with febrile illness of more than 3 weeks were taken up for the study.

(ii) Patients had documented temperature exceeding 101ºF (38.3ºC) on more than 3 occasions. (iii) No diagnosis at presentation.

EXCLUSION CRITERIA

(i) Correct diagnosis already established by referring physician/institute. (ii) Nosocomial fever / Known/diagnosed HIV Infection.

MATERIALS & METHODS

(i) After inclusion of patients oral temperature was recorded 6 hrly. (ii) A diagnostic workup including detailed history (including Drug Intake), Clinical examination, routine laboratory tests, urinalysis, cultures, serology, chest radiography and abdominal ultrasound was done. (iii) In non-revealing cases based on potential diagnostic clues special diagnostic tests was taken up. Only diagnoses that are evidence based or clinically nearest were retained.

According to the timing of Diagnosis patients were categorized into 4 groups :

1. Early Diagnosis (within 3 days)
2. Intermediate Diagnosis (between Days 4&7)
3. Late Diagnosis (after day 7)
4. Non Diagnosis.

(2), (3), (4) were taken as classical FUO as defined by Durack & Street.

(3), (4) were taken as FUO as defined by Petersdorf & Beeson.

The etiologies were classified into 5 diagnostic categories.

1. Infections 2. Malignancies 3. Non infectious Inflammatory diseases(NIID) 4. Miscellaneous causes 5.No diagnosis.

INVESTIGATIONS

ROUTINE : Complete haemogram including ESR,urine analysis, LFT, serum urea&creatinine, PPD skin test, HIV Elisa, different body fluid cultures, occult blood test, chest X-rays and ultrasound were done.

SPECIAL :

Transthoracic & Transesophageal Echocardiography., CT Scan of Abdomen/Chest/ Pelvis, FNAC/Biopsy of suspected lymphnode/mass, Bone marrow examination, Serum protein

electrophoresis, Serological tests (ANA, RF, Serum ACE Level etc.), Upper G.I. Endoscopy/Colonoscopy.

Any other specialized Lab/Imaging procedure as applicable based on clinical clues (eg.CSF study, PCR) were done.

OBSERVATION:

Total No. of patients studied were 50, male were 36, (72%), Female were 14 (28%). Mean age was65.55 years. Age Group Distribution is shown in Table -1.

TABLE -1 : Age Group Distribution

Age in yrs	Male		Female		Total	
	No	%	No	%	No	%
60-64	10	20	4	8	14	28
65-69	19	38	10	20	29	58
70-74	2	4	0	0	2	4
75-79	4	8	0	0	4	8
>80	1	2	0	0	1	2

ASSOCIATED SYMPTOMS : Commonest symptoms in the study apart from fever were weakness, weight loss, cough with expectoration, headache, drowsiness (8%each) followed by non productive cough (6%), joint pain(6%), dyspnoea(6%). Mean duration of faver was 42.50±26.43 day

Clinical features : Are shown in Table-2

TABLE -2 : Clinical features

Sl. No	Signs	No.	%
1	Pallor	31	62
2	Chest examination abnormality	11	22
3	Splenomegaly	9	18
4	Hepatomegaly	7	14
5	Lymphadenopathy	7	14
6	Neck rigidity	4	8
7	Arthritis	4	8
8	Gallop rhythm	3	6
9	Icterus	2	4
10	Edema	2	4
11	Clubbing	2	4
12	B/L thickened nerves	2	4
13	Sternal tenderness	1	2
14	Gum hyperplasia	1	2
15	Sclerodactyly	1	2
16	Raynaud's phenomenon	1	2
17	Pericardial rub	1	2
18	Petechiae	1	2
19	Erythematous Rash	1	2
20	Paraplegia	1	2
21	Hemiparesis	1	2
22	Cranial nerve palsy	1	2
23	B/L renal mass	1	2

Mean haemoglobin was 9.20 ± 2.39 gm/dl,

Mean TLC count was 11020.48±12517/m^3

Minimum TLC count was 800/cumm, maximum value was 90700/cumm, median was 8750/cumm.

Peripheral smear comment is shown in Table-3. The gender distribution of various disease groups is shown in Table-4.

TABLE -3 : Peripheral smear comment

Sl. No	Comment	No.	%
1	Normocytic normochromic	21	42
2	Normocytic hypochromic	21	42
3	Microcytic hypochromic	2	4
4	Anisocytosis	3	6
5	Myeloblast	2	4
6	Dimorphic anemia	1	2
7	Atypical blast	1	2

TABLE -4 : Diagnostic groups

	Male		**Female**		**Total**	
	No	%	No	%	No	%
Infections	21	42	9	18	30	60
Malignancies	12	24	3	6	15	30
NIID	0	0	2	4	2	4
Miscellaneous	2	4	0	0	2	4
No diagnosis	1	2	0	0	1	2

TABLE -5 : Infection categories : (n-30)

Infection categories (n = 30)		Male		Female		Total	
		No	%	No	%	No	%
Tuberculosis	PTB	4	13.33	2	6.66	6	20
	ETB	6	20	2	6.66	8	26.66
Infective Endocarditis		2	6.66	0	0	2	6.66
ENL		2	6.66	0	0	2	6.66
Enteric Fever		2	6.66	1	3.33	3	10
UTI		1	3.33	0	0	1	3.33
Respiratory infection		1	3.33	0	0	1	3.33
Vivax malaria		0	0	1	3.33	1	3.33
Falciparum malaria		1	3.33	0	0	1	3.33
Liver abscesses		2	6.66	0	0	2	6.66
Splenic abscesses		1	3.33	0	0	1	3.33
Infection unknown focus		2	6.66	0	0	2	6.66

TABLE - 6 : Malignancy (n-15)

	Male		Female		Total	
	No	%	No	%	No	%
NHL	5	33.33	0	0	5	33.33
MM	2	13.33	1	6.66	3	20
AML	2	13.33	0	0	2	13.33
CLL	1	6.66	0	0	1	6.66
Lung Cancer	1	6.66	0	0	1	6.66
Atrial Myxoma	0	0	1	6.66	1	6.66
GastricLymphoma	0	0	1	6.66	1	6.66
Ca stomach	1	6.66	0	0	1	6.66

DISCUSSION

TABLE -7

Comparison with other studies[4,6,10-14]

	Esposito & Gleckman (1978, n = 111)	Iikuni (1983, n=14)	Knockaert (1993, n = 201)	Iikuni (1994, n=31)	Saxena (2005, n = 67)	Onal (2006, n=22)	Chen (2008, n=87)	Present study (2008, n=50)
Infection	36%	43%	35%	26%	40.29%	45.5%	50.6%	60%
Malignancy	24%	21%	19%	29%DISCUSSION: Comparison with other studies[4,6,10-14]	29.85%	4.5%	4.6%	30%
NIID	26%	7%	28%	23%	1.49%	4.5%	4.6%	4%
Miscellaneous	9%	7%	8%	10%	14%	NA	5.7%	4%
No diagnosis	5%	21%	9%	13%	13.48%	NA	28.7%	2%

In this study among the 50 elderly patients 30 (60%) were diagnosed to have infectious etiology – male 21 (42%) patients, female 9 (18%) patients. (Table-5) 15 patients diagnosed to have malignancies – male 12 (24%), female 3 (6%) patients(Table-6). Noninfectious inflammatory disease comprised 2 cases (4%), all being female. Miscellaneous cause was found in 2 cases (4%), all being males. Diagnosis could not be made in one case (2%).

In the current study tuberculosis (TB) was the commonest infection found in 14 patients (28%), comprised 46.66% of infections. In the present study among TB commonest was pulmonary TB (35.71%), followed by TB meningitis (28.57%), TB of undetermined site (14.23%). While miliary, TB pericardial effusion & adrenal TB was found in one case each (7.14%).

Other causes among infectious etiology in current study are enteric fever (10%) infective endocarditis (6.6%) Erythema Nodosum Leprosum (6.6%), Malaria (6.66%), urinary tract infection (3.33%), respiratory infection (3.33%) while no focus could be found in 6.66%.

In the present study malignancies account for 30% cases (n = 15). Among the malignancies most common was NHL 33.33% of cases (n = 5), next common was multiple myeloma 20% of cases (n = 3). Other malignancies were AML (6.6%), CLL(6.6%), lung cancer, brain & spinal metastasis (6.6%), atrial myxoma (6.6%), gastric lymphoma (6.6%) and ca.of stomach (6.6%). In the study hematologic malignancies accounted 73.33% of cases (n = 11). Miscellaneous cause found in 2 cases (4%) in the present study. One was hypoplastic anaemia and for other was myelodysplastic syndrome (Refractory cytopenia with multilineage dysplasia).

In the present study 18 cases (36%) had early diagnosis (≤3days), 26cases (52%) had intermediate diagnosis (4-7days) and 6 cases (12%) late diagnosis (>7days).

On the follow up for 6 months, 21 patients (42%) were cured (all of them having infectious etiology), 8 patients (16%) were lost to follow up, 7 patients (14%) are still on treatment, 4 patients (8%) died.

CONCLUSION

The prolonged febrile illness in the elderly is a major diagnostic challenge and dilemma to the physician. Current studies show that most of the cases of prolonged fever in the elderly can be diagnosed with meticulous history taking, detailed clinical examinations and investigations based on the potential diagnostic clues. Infection is the predominant cause followed by malignancy. The incidence of tuberculosis is much more common in the elderly than their younger counterparts. Prolonged pyrexia due to connective tissue disorders in the elderly in the present study is much less common when compared to the data in western literature (Table-7). The percentage of cases for which a cause is never identified in the elderly patients is significant lower than it is in the younger patients.

The elderly have increased susceptibility to many diseases usually not encountered in the younger age group and are at significantly increased risk for morbidity and mortality due to delays in diagnosis and management. Early recognition and prompt clue related investigations of the prolonged febrile illness in the elderly are the cornerstones to make an early diagnosis whenever possible, thus reducing sufferings in the elderly who are already compromised with low physiological reserves due to the process of ageing and frequent presence of comorbid illnesses.

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Original Article

EFFECT OF *Low Molecular Weight HEPARIN* IN VASCULOTOXIC SNAKE BITE

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ABSTRACT

Aim of the Study : *To study the efficacy of low molecular weight heparin (LMWH) in the treatment of viper envenomation, to combat haematotoxicity and disseminated intravascular coagulation (DIC).* ***Methodology :*** *100 patients with viper bite with clot retraction test negative were randomised into two groups of 50 each. One group (Test group) received LMWH in addition to the antisnake venom (ASV) and other supportive measures. Another group (control group) received only ASV with supportive measures. Efficacy was assessed by monitoring the bleeding time, clotting time, prothrombin time, fibrinogen degradation products, total platelet count, Blood Urea, Serum creatinine, development of complications like renal failure and over all outcome.* ***Results :*** *LMWH group showed favourable outcome in the form of decreased incidence of renal failure, less number of haemodialysis requirement and less number of deaths and decreased number of hospital stay.* ***Conclusion :*** *LMWH seems to have a beneficial role in the treatment of viper bites to prevent DIC and renal failure, but this needs to be confirmed by a larger study.*

INTRODUCTION

There are about 216 species of snakes identifiable in India, of which 52 are known to be poisonous. All venomous species belongs to one of the following families – Elapidae, Viperidae, and Hydrophidae. Global incidence of poisonous snake bite is 2.5 million/yr with 1.25 lac deaths per year. In India 35000-50000 die of snake bite each year. Viper snake bite is very common during rainy and Summer Season in our State and majority of the patients present with Coagulopathy and Acute renal failure. Till date no specific treatment is available for coagulopathy except Anti Snake Venom therapy (ASV). In spite of early Anti Snake Venom therapy quite a good number of patients develop Acute renal failure leading to mortality and morbidity. Heparin is known to inactivate factors involved in coagulation cascade. So, use of heparin provides a rational therapy to inhibit Disseminated intravascular coagulation after viper envenomation.

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Pathogenesis of ARF in Vasculotoxic Snake bite

- Hypotension due to bleeding, increased vascular permeability and vasodilation, myocardial depression.
- Intravascular haemolysis either directly by Phospholipase A2, or indirectly by haemolytic Lysolecithin.
- Direct Nephrotoxicity.
- Disseminated Intravascular coagulation (DIC)
  - Viper venom contains proteins that interact with members of coagulation cascade and fibrinolytic pathway
  - They are mainly pro-coagulant and some are anticoagulants & direct acting fibrinolytic enzymes
  - Occurrence of DIC as a major hemostatic abnormality is well documented experimentally with Rhesus monkey
  - Presence of fibrin thrombi in the renal microvasculature and glomerular capillaries & finding of microangiopathic haemolytic anaemia with thrombocytopenia strongly suggest that DIC plays a major pathogenetic role in viper bite induced cortical necrosis and renal failure

- Intra glomerular fibrin deposition of lesser degree has been suspected as causing acute tubular necrosis via a temporary haemodynamic alteration
- Out of above mechanisms of renal failure in Viper bite, DIC is thought to be the major one

Previous studies

Shah et al[3] (1986) in their study of *Echis carinatus* bite found that combined therapy with Anti snake venom and Unfractionated Heparin normalised laboratory parameters compared to ASV alone. V Paul et al (2007) studied 80 patients in Thrissur, Kerala and found that Low Molecular Weight Heparin (LMWH) seems to have a beneficial role in the treatment of Viper bites. Several studies showed the beneficial role of LMWH having less side effects in comparision to Unfractionated Heparin (UFH) in the management of DIC. So with this background knowledge we have conducted the study of LMWH in treatment of DIC induced by Viper envenomation to find out its beneficial role in improving Clotting time,Bleeding time, TPC and Renal failure.

MATERIALS AND METHODS

100 patients of Viper bite with in-coagulable (by 20 min clotting test) blood admitted to Medicine dept. of S.C.B MCH from March 2008 to March 2009 were included for study. They were randomised into 2 groups in 1:1 manner on alternate basis. One group received LMWH @ Dose of 40 mg SC OD for 5 days along with ASV & the other group received only ASV. Patients of known renal disease, bleeding disorders were excluded from the study. Efficacy of LMWH was assessed by monitoring BT, CT, PT, TPC, Fibrin Degradation Products, Blood Urea and Sr. Creatinine and development of overall complications. Estimation of BT, CT, PT, TPC, FDP, Blood Urea and Sr. Creatinine were done on 1st, and 5th day of admission both for case and control. Clinical outcome was assessed in terms of development of complications like ARF, signs of bleeding and need for Dialysis**.**

Base line characteristics of case and control group (Clinical)

Variable	Case (n-50)	Control (n-50)
AGE (avg. yrs)	35.2	37.05
Male : Female	2 : 1	1.6 : 1
Bleeding manifestation	13 (32.5%)	16(40%)
Local Cellulitis	18(45%)	14 (35%)
Decreased urination	13 (32.5%)	17 (42.5%)

Comparison of laboratory findings in case group on the 1st and 5th day

Variables	Day 1	day 5	P value
Bleeding Time (BT) (secs)	118.1+/-139.8	97.0+/-31.43	.319
Clotting Time (CT) (secs)	476.9+/-674.5	246.6+/-100.7	.021
Prothrombin time (PT) (secs)	40.0+/-5.0	17.0+/-4.83	.037
Total Platelet count (TPC) (lac/cmm)	1.46+/-0.61	1.73+/-0.5 .004	
Fibrin Degradation Products (FDP) (ng/ml)	1015.4+/-908.2	191.8+/-28.1	.001
Serum Urea (mg/dl)	54.6+/-41.2	33.62+/-8.5	.002
Serum Creatinine (mg/dl)	2.77+/-1.37	1.03+/-0.36	.002

Comparison of laboratory findings in control group on the 1st and 5th day

Variables	Day 1	Day 5	P value
Bleeding Time (BT) (secs)	118.6+/-61.65	137.0+/-62.7	.16
Clotting Time (CT) (secs)	272.1+/-134.9	275.7+/-133.7	.29
Prothrombin time (PT) (secs)	26.52+/-2.0	25.28+/-1.9	.108
Total Platelet count (TPC) (lac/cmm)	1.50+/-0.48	1.48+/-0.41	.728
Fibrin Degradation Products (FDP) (ng/ml)	810.2+/-765.9	827.4+/-786.8	.282
Serum Urea (mg/dl)	70.8+/-49.3	71.6+/-47.3	.809
Serum Creatinine (mg/dl)	2.65+/-2.39	2.67+/-2.45	.785

FINAL OUTCOME

	CASE(n-40)	CONTROL (n-40)
Duration of hospital stay (Avg. days)	**5.3**	**6.5**
No. of ASV vials required (Avg. / patient)	**18.72**	**19.8**
Renal Failure during treatment	**4 (10%)**	**14 (35%)**
No. of Haemodialysis required	**6**	**27**
Death	**Nil**	**4 (10%)**

DISCUSSION

The common causes for morbidity and mortality in viper bite are hypotension and acute renal failure (ARF). DIC plays a major role in causing these complications. LMWH is used more and more these days in cardiovascular diseases, pulmonary embolism, deep vein thrombosis and a host of other conditions, as the side effects like serious bleeding are less as compared to UFH. It is easier to monitor the dosage of LMWH without estimations of CT and APTT. LMWH is more effective than UFH in the treatment of DIC.

CONCLUSION

LMWH has a beneficial role in the treatment of viper bite in the form of decreased incidence of renal failure, less no.of haemodialysis requirement, less duration of hospitalisation and less no. of deaths All the clotting parameters were better in the treatment (case) group as compared to the control But this conclusion has to be confirmed by a larger trial.

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Original Article

INTRAVENOUS LEVETIRACETAM IN STATUS EPILEPTICUS

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ABSTRACT

Purpose & Background : *Clinical experience with intravenous levetiracetam is very limited especially in status epilepticus. The main objective of this study is to asses the efficacy & tolerability of IV Levetiracetam in patients presenting with status epilepticus.* ***Patients & Methods :*** *Patients presenting with status epilepticus & not responding to conventional AED were included in the study. Twelve patients of status in between October 2007 to June 2009 were included.* ***Result :*** *Age range 18-80 years, dosage range of IV Levetiracetam 500-1500mg. Seizure control could be achieved in 9 out of 12 patients. No significant adverse effects were observed.* ***Conclusion :*** *IV Levetiracetam was effective & well tolerated in patients who failed to respond to conventional AED. It seems to be a reasonable & practical alternative/add on drug for management of status epilepticus.*

Key words : *Status epilepticus, epilepsy, Intravenous Levetiracetam, seizure*

INTRODUCTION

Status epilepticus (SE) is a neurological emergency with high morbidity & mortality. For first line treatment benzodiazipines, Phenytoin & barbiturates are used based on randomized controlled trials. Other anti epileptic drugs such as valproate have been used on the basis of uncontrolled trials. Aproximately 15% of patients don't respond to standard treatment, who eventually require admission to ICU with all the inherent risk of mechanical ventilation.Adminstration of traditional AED is often complicated by side effects such as respiratory depression, hypoxia or cardiac arrhythmia.

Levetiracetam is one of the most recently introduced AED, approved in 1999 as add on treatment for partial onset seizure with or without secondary generalization & as add on therapy for myoclonic & primary generalized tonic clonic seizures. Intravenous formulation was approved in 2006 for the treatment of patients with epileptic seizure who are temporarily unable to swallow. Although presently not approved for treatment of SE results from retrospective & uncontrolled studies suggest that IV Levetiracetam may be a useful alternative treatment option in patients with various forms of SE. Further more its favourable pharmacokinetic & side effect profile makes it an ideal agent for use in the management of status epilepticus.[2,3,6]

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Patients & Methods

All 12 patients (8 male & 4 female) were admitted to the Department of Neurology, S.C.B Medical College, Cuttack during the period October 2007 to June 2009.The reason for admittance to the hospital was a generalized tonic clonic seizure & status epilepticus. The patients not responding to conventional AED (Lorazepam & loading dose of phenytoin) were included in the study.A detail clinical examination of the patient was done. Routine investigation like CBC, FBS, Blood urea, S. Creatinine, LFT, Na+, K+ were done. These investigations were repeated at 4 days interval till discharge. C.S.F study was done in selected cases where intracranial infection was suspected. EEG study was done in all cases particulary after clinical cessation of seizures to rule out electrographic seizure(non convulsive status epilepticus).

Treatment protocol

Inj. Lorazepam 0.1 to 0.15mg /kg IV over 1-2min given.It was repeated in same dose if there was no response after 5 mins.Loading dose of pheynetoin sodium(20mg/kg) dissolved in 100ml normal saline was given rapidly not exceeding 50mg/min. A repeat bolus dose of 10mg/kg given if seizure not controlled. Cases not responding to above therapy were given IV Levetiracetam 20-30mg/kg in 100ml normal saline over 30 mins & it was repeated 8-12 hourly depending on the response. Intravenous Levetiracetam was continued till clinical seizure was controlled & patients became conscious. EEG was done in patient who remained unconscious after control of clinical seizure to rule out electrographic status epilepticus.

IV Levetiracetam was continued till electrographic status was controlled. Patients were followed up to 14 days. Adverse effects-clinical, biochemical, hematological were recorded.

RESULTS

The clinical characteristics of patients treated with LEV IV are shown in table 1.Total number of patients were 12 out of which 8 were male & 4 were female. Most common underlying pathology was Cerebrovascular disease. Age range was 18-80years.Complete seizure control was achieved in 9 out of 12 patients as documented by termination of clinical &/or electrographic seizure activity. Overall, the tolerability of LEV IV was excellent. Vomiting was present in two cases. No serious side effects were observed. No significant changes in laboratory values were observed which could have been attributed to LEV use. In one patient of encephalitis seizure was not controlled & the patient died. (Table-1)

DISCUSSION

The main findings of the present study are that LEV IV may be an excellent & well tolerated practical alternative IV AED in seizure emergencies.

CLINICAL CHARACTERSTICS- (table-1)

Sl. No.	Age/Sex	Type/Course	Dose of Lev(BD)	Duration of IV(Days)	Side Effect	Outcome (14 days follow up)
1	M/18	GTCS/ANOXIC ENCEPHALOPATHY (HANGING)	1000mg	4	Well tolerated	Seizure not Controlled
2	M/45	GTCS / ICH	1500mg	3	Well tolerated	Seizure not Controlled
3	F/68	EPC/DM HYPERGLYCEMIA	1250mg	2	Vomiting	Seizure Controlled
4	M/56	GTCS/DRUG DEFAULT	1000mg	3	Well tolerated	Seizure Controlled
5	M/25	GTCS/ALCOHOL WITHDRAWAL	1000mg	2	Well tolerated	Seizure Controlled
6	M/65	GTCS/ INFARCTION	1500mg	3	Well tolerated	Seizure Controlled
7	F/53	GTCS/ HYPONATRAEMIA	1000mg	4	Sedation	Seizure Controlled
8	F/46	GTCS/INF GRANULOMA	1000mg	3	Well tolerated	Seizure Controlled
9	M/33	GTCS/ICH	1000mg	4	Well tolerated	Seizure Controlled
10	M/70	GTCS/ Left MCA STROKE	1000mg	2	Well tolerated	Seizure Controlled
11	F/80	GTCS / LATE ONSET SEIZURE IDIOPATHIC	500mg	3	Vomiting	Seizure Controlled
12	M/28	GTCS / ENCEPHALITIS	1000mg	4	Well tolerated	Seizure not Controlled(Died)

LEV has become a widely used drug in patient with different epileptic syndrome.Previous reports have suggested that oral LEV is effective as treatment for SE.LEV IV is used off level in patient with status epilepticus.However experiences with IV treatment with LEV in seizure emergencies is limited. Schulge Bonhage & Knake etal reported an 19episodes of focal SE refractory to first line treatment ,17 of which were terminated by LEV IV.

10 published papers (6 retrospective case series& 4 case reports) documented. They reported an overall success rate of 81.6%.Latest papers published in 2009 by Nicholas S.Abend et al on critically ill children & by Moddel et al in refractory SE in adult & geriatric population reported a success rate of 100 & 69% respectively. No major adverse events were reported.[1,2,4,5,7,8,9].

LEV has a valuable pharmaco kinetic profile with lack of significant interaction & lack of hepatic metabolism.

CONCLUSION

In conclusion the present study is limited by its small size,a patient profile with different co-morbidities; more over the majority of patient were given LEV IV as co-medication restricting our ability to evaluate adverse events & effectiveness of the drug.Despite these limitation, our findings extend the knowledge about the usefulness of LEV IV & suggest that this treatment is well tolerated, lacking major adverse effects & effective in varied age group with seizure emergencies .Because the choice of IV formulation of AED is still limited LEV IV appears to be a reasonable alternative treatment option. Further prospective study are needed to establish it's role in the setting of seizure emergencies.

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Original Article

ROLE OF C-REACTIVE PROTEIN AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROME

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ABSTRACT

C-Reactive protein (CRP), a novel biomarker has now emerged as a major cardiovascular risk factor. In the present study , we sought to ascertain if level of CRP could influence short term prognosis in acute coronary syndrome (ACS). A total of 52 cases of acute coronary syndrome taken for the study were divided into 3 groups : 1. ST elevated MI (STEMI), 2. Non ST elevated MI (NSTEMI) and 3. Unstable Angina (UA). Serial determination of CRP was done and level of CRP were correlated with severity of ACS basing on primary and secondary end points. All the relevant data were statistically analyzed. CRP level was found to be significantly elevated in ACS. Among the ACS patients maximum elevation was observed in STEMI and NSTEMI compared to unstable angina. Patients who developed primary end points of death and heart failure had higher CRP than those who did not develop these end points. There was an inverse relationship between raised CRP and secondary end points of ejection fraction. Therefore, CRP level proves to be an important determinant of severity and short term outcome of ACS.

INTRODUCTION

Cardiovascular disease has emerged as a major health burden worldwide and in India its prevalence is increasing with Indians supposed to be at twice the risk of white populations for development of coronary heart disease (CHD). Recent data from the Jaipur heart watch-2, on 1800 subjects based on a stratified sampling technique reported an escalation in the prevalence rates of conventional risk factors like obesity, diabetes and dyslipidemia among North Indians compared to figures noted in 1990[1].

Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiological link between plaque formation and acute rupture, leading to occlusion and infarction[2]. The acute phase reactant, CRP, a simple downstream marker of inflammation has now emerged as a major cardiovascular risk factor[3]. CRP is a circulating member of the pentraxin family that plays a major role in the human innate response. Although derived from the liver, studies have found that cells within human coronary arteries, particularly in the atherosclerotic intima can also elaborate CRP. We sought to ascertain if levels of CRP in a situation of acute coronary syndrome (ACS) could influence the short term outcome i.e. during hospitalization.

METHODS

The study consisted of 52 cases of acute coronary syndrome admitted to the Medicine Department of S.C.B. Medical College, Cuttack over a period of 3 years. ACS included acute myocardial infarction (both ST elevated and non ST elevated) and cases of unstable angina. ECG, lipid profile, serum urea and creatinine, FBS and echocardiography were done in all cases. CRP was measured at admission and on the 3rd and 7th days of hospital stay. In addition CKMB estimation was done in all patients. Primary end points were, incidence of death and heart failure while secondary end point was left ventricular ejection fraction at the end of hospital stay (7th day post ACS).

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RESULTS

The incidence of the various types of acute coronary syndrome as per gender distribution are shown in Table-1.

As expected the number of patients presenting with STEMI were higher in both sexes with NSTEMI the next most common mode of presentation.

The CRP values showed a maximum level at the 3rd day when compared to days one and seven (P<0.03). (Table-2). The CRP values were significantly higher in STEMI and NSTEMI compared to those in unstable angina (Table-3). The primary end points of death and heart failure were seen in 30 (57.7%) cases. It is seen that patients who developed primary end points had a higher CRP value than patients who did not develop these end points (Table-4,5). There was an inverse relationship with raised CRP levels and secondary end point of ejection fraction. The higher the CRP levels the lower was the ejection fraction (Fig.1). Moreover, patients of unstable angina had lower CRP levels compared to patients who presented with myocardial infarction (Table-6).

RELATIONSHIP OF CRP (3RD DAY) WITH EJECTION FRACTION IN PATIENTS OF HEART FAILURE

Fig - 1

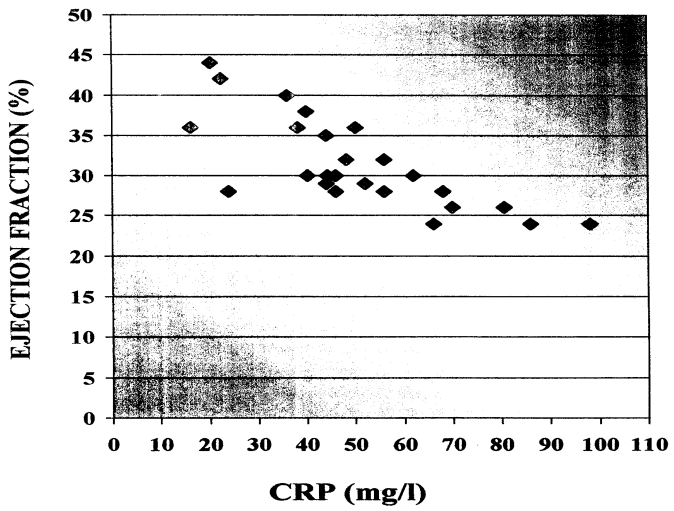

TABLE-1

Incidence of Different Types of Acute Coronary Syndrome

Types	Male (n=39)	Female (n-13)	Total (n=52)
STEMI	15 (28.84%)	5(9.6%)	20 (38.46%)
NSTEMI	10 (19.23%)	6 (11.5%)	16 (30.77%)
UA	14 (26.9%)	2 (3.84%)	16 (30.77%)

TABLE-2

Comparison of Serial CRP Values in Patients of ACS

Day	Males CRP Value	Females CRP Value	Total Patients CRP Value
1st day	32.26±22.29 mg/l	36.83±25.69 mg/l	38.74±23.46 mg/l
3rd day	34.87±23.77 mg/l	39.76±25.69 mg/	38.74±23.46 mg/l
7th day	34.68±22.71 mg/l	39.60±28.02 mg/l	38.01±24.12 mg/l

TABLE-3

Comparison of CRP Values (3rd Day) in Cases in various types of ACS Mean + SD mgl

Types of ACS	Males	Females	Total Patients
STEMI	44.38±27.75 mg/l (n=15)	57.2±28.17mg/l (n=5)	51.68±28.45 mg/l (n=20)
NSTEMI	37.54±31.07 mg/l (n=10)	40.10±26.26 mg/l (n=6)	38.56±29.01 mg/l (n=16)
UA	20.2±12.42 mg/l (n=14)	14±2.82 mg/l (n=2)	18.34±8.13 mg/l (n=16)

TABLE-4

Comparison of Mean CRP value (3rd Day) among patients with or without heart failure Mean ± SD mg/l

Sex	Cases without HF CRP value	Cases with HF CRP value	P Value
Males	21.99±19.6 mg/l (n=21)	50.13±19.95 mg/l (n=18)	P < 0.001
Females	28.73±26.39 mg/l (n=6)	50.37±22.7 mg/l (n=7)	P < 0.05
Total patients	24.42±22.34 mg/l (n=27)	50.16±20.86 mg/l (n=25)	P < 0.001

TABLE-5

Relationship of CRP Values with Mortality

Types of ACS	CRP value ± SD (mg/l)	Mortality (%)
STEMI (n=20)	87.10 ± 15.69	2 (10%)
NSTEMI (n=16)	61.4 ± 5.12	3 (18.75%)

TABLE-6

Comparison of Mean CRP Values in Patients of UA and AMI with and without complications

Types of ACS	CRP value in patients with complications	CRP value in patients without complications	P value
UA	33.36 ± 12.34 mg/l (n=8)	11.05 ± 4.07 mg/l (n=8)	< 0.001
AMI	52.45 ± 21.52 mg/l (n=28)	10.32 ± 4.51 mg/l (n=8)	< 0.001

DISCUSSION

Conventional risk factors do not always explain the increasing incidence of CHD in developing countries like India. Increasing evidence that inflammation is an important determinant for development of atherosclerosis has led to the evaluation of inflammatory markers as variables for risk stratification and prognosis determination in patients of acute coronary syndromes. Several studies have shown an association of ACS with inflammatory markers such as CRP, fibrinogen, IL6, TNF α[4,5,6] CRP is a cheap and readily available laboratory marker for determining prognosis in ACS.

Although several data support the role of inflammatory response in long term clinical events in AMI, data defining the association between baseline CRP elevation and subsequent development of heart failure within this clinical entity is limited. Our data showed that mean CRP level was significantly higher (P<.001) in patients who developed heart failure than in those who didn't. In an elaborate study, *Giuseppe et a/*[7] have also shown that serum CRP levels were higher in those cases of AMI who had heart failure than those who did not. These data suggest that CRP may predict the risk of heart failure or may play a direct role in augmenting microvascular inflammatory response after ischaemic insult.

In other words, the marked CRP rise in patients with ACS with heart failure at entry or, in those who developed heart failure in the subsequent days may not only be an epiphenomenon but may represent a pathogenic process that leads to myocardial damage and left ventricular dysfunction[7]•

However, the cut off values for CRP prediction of events were based on statistical tests and not on prospective data. Only longitudinal studies in larger groups will confirm the validity of these cut offs.

In a study by *Abdelmouftaleb et al* 8 comparison between patients of ACS and stable coronary artery disease (CAD) has shown higher CRP levels in the ACS group. This is supported by the hypothesis that there was no correlation between the extent of CAD and CRP levels. It therefore suggests that inflammation might be an important triggering mechanism of acute coronary events, related to plaque rupture rather than a promoter of chronic atherosclerosis although it has been suggested that CRP might play an atherogenic role through an interaction with low-density lipoprotein.

In our study, it was observed that mean CRP value was significantly higher in the AMI group than in UA (P<.001). The observed difference of overall mean CRP values between STEMI and UA and NSTEMI and UA were statistically significant at (P<.001). and (P<.02) respectively. In each category, patients who had complication had higher CRP levels than those who did not have complication (P<.001).

We also studied the time related association between inflammatory reaction and heart decompensation not only using clinical signs of heart failure but also LVEF, an objective estimate of LV dysfunction obtaining parallel results. This observation was also made by *Toshihisa et al*[9] who concluded in his study that peak CRP levels correlated inversely with EF.

Previous studies examining the relationship between CRP and cardiovascular mortality in patients after ACS have found that peak CRP level predicts both in-hospital mortality and long term outcome.[7] The present analysis confirms the prognostic significance of elevated CRP beyond that defined by traditional risk predictors after an ACS. In agreement with the result of others, CRP level proved to be a stronger predictor of sudden death in patients with an ACS. However, studies in large population including coronary angiography and thrombolytic treatment would throw more light on this promising biologic marker.

Although the precise role of CRP requires further elucidation a focus on CRP within the first 3 days after an ACS may prove useful for identification of patients who are at greater risk of mortality.

CONCLUSION

In conclusion, therefore, elevated C-reactive protein is an important predictor of short term prognosis in patients of acute coronary syndrome. The present study shows consistent elevation of CRP in all patients of ACS when compared to controls,

the degree of elevation being maximum in patients with STEMI and minimum in those with unstable angina. Elevated CRP level predicted the occurrence of short term complications especially heart failure and sudden death in cases of ACS.

Raised CRP level within the first 3 days in AMI should alert physicians for possible risk of increased morbidity and mortality in patients of ACS.

Therefore, CRP level proves to be a novel biologic marker which should be estimated as early as possible to prognosticate cases of ACS for improvement of clinical outcome. However, these results need to be validated by larger, multicentric, prospective studies to provide definite guidelines for determining CRP level in cases of ACS in order to improve short term morbidity and mortality.

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Original Article

CLINICO PATHOLOGICAL OBSERVATION ON CASES OF CHIKUNGUNYA

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ABSTRACT

After the first epidemic of Chikungunya was described in 1952 in Tanzania several epidemics has come up in different parts of the world particularly in Africa and Asia. Of late from 2005 an epidemic of this illness has broke out in many states of India. Several districts of Orissa have been affected by this disease. Not all cases have been confirmed to be cases of Chikungunya, but few have certainly been confirmed either at NICD New Delhi or at the National virology Institute, Poona. We observed 280 cases of Chikungunya at OPD of MKCG Medical College Hospital and some leading clinics of Berhampur. Few (15cases) samples were sent for study of antibodies against Chikungynya which was positive in 12cases. Hence majority of our cases were probable cases of Chikungunya in true sense of epidemiology. All the cases were thoroughly examined and necessary investigations were done to exclude other causes of acute arthritis. All data were collected and later on statistically analyzed. Majority cases came in the month of August to October. Females were affected more than males. Lower limb joints were affected more than upper limb joints. Fever and arthritis were observed in all cases. Rashes were seen in few cases. Majority had poly-articular involvement. The most common joints to be affected were ankle, knee and elbow. About 10% patients showed relapse; all ultimately recovered. There was no residual deficit after three months of follow up. There was no mortality.

INTRODUCTION

Epidemics of Chikungunya have been reported from different parts of world after it was first time observed in Tanzania in 1952[1]. In Asia mostly it has been noticed in South East Asia. [2, 3] In India it has also been reported in epidemics earlier[4, 5]. It was last reported in epidemic form in India in 1973. Since January 2005 countries in Indian ocean including India are experiencing another epidemic which has affected more than a million cases[6,7,8] This epidemic also affected many districts of Orissa. This study was conducted on cases coming from southern districts of Orissa and adjoining part of Andhra Pradesh, India. It covered an area of 4000 square kilometer. The epidemic spread over a period of about one year, though maximum cases were in the months of August, September and October. We discuss here our observation on these cases. There were quite interesting observations in relation to clinical features and treatment.

MATERIALS AND METHODS

This work has been done by observation of cases in the MKCG Medical College, Berhampur and some leading clinics of Berhampur town. Berhampur is the referral center for the area where the epidemic occurred. Cases of fever with arthritis or followed by arthritis coming from the epidemic area were provisionally diagnosed as cases of Chikungunya. History of arthritis in any form in the past were enquired and if found were excluded from the study. In all the cases history were carefully collected with regards to onset, symptoms, progress and treatment already received. All were examined in detail. The joints involved, the severity of involvement, other features like fever, rashes etc were noted. The cases were investigated to exclude any specific type of arthritis like rheumatic,

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rheumatoid, goutic, septic etc. Those who showed evidence of such arthritis were excluded from the study. After all these exclusions cases with the most possible diagnosis of Chikungunya were kept for statistical analysis. In a few cases (fifteen) blood samples were sent for antibodies against Chikungunya virus. It was not possible nor is it practically possible to send the blood samples for confirmation in all cases. Hence in epidemiological term most of our patients were probable cases of Chikungunya. The cases were treated with NSAIDs, aspirin, prednisolone or combination of aspirin and prednisolone. Those who were severely affected (crippled) were given the combination therapy. In the initial part of the epidemic cases were treated with NSAIDs, but as relapse occurred in a few and inadequate response, later part of the epidemic cases were only treated with aspirin, prednisolone or both. The cases were followed up for 3 months.

Observation and discussion

We observed 280 cases of which 123 cases were male and 157 cases were female (Table:2). This shows that the arthritis due to Chikungunya predominantly affects females. This might be due to they spend more time indoor and are more likely to be bitten by Aedes mosquitoes which are found in domestic or peri-domestic environment. More than 60% of the cases belonged to 30 to 50 years age group. There were only 4 cases below 15 years and no case above 60 years of age (Table : 2). The rarity of cases in the extreme age group is difficult to explain.

Though cases came throughout the year, but majority came in the later part of the rainy season, between August and October. This is due to the breeding season for mosquitoes. However the number of cases appeared to rise by January and February (Table:1). This surge might be due to more mosquito bite, as people do not use fan during this time (Winter season) while sleeping.

The clinical presentation varied from fever, headache, conjunctival congestion, dry cough and sore throat (Table:3). All these features were present in the initial febrile phase of the illness. None of them were present in the phase of arthritis. Skin rashes were seen only in very few cases (1.4). Rashes have been noticed by others in higher proportion of cases.[9]As we saw the cases in the late phase (in the phase of arthritis not during the febrile phase) rashes might have disappeared in some cases. The outstanding clinical feature was acute arthritis (100%). Fever was present at the outset in all cases. It was low to moderate grade and lasted only for 2 to 3 days. In some patients it was noticed that by the time arthritis developed there was no fever. The time lag between fever and arthritis varied from 6 days to 10 days in this group of cases. It was also observed that more than one member of the family were affected in 162 cases.

Majority of the cases it was a polyarticular disease. Monoarticular and oligoarticular forms were also seen. The lower limb joints were more commonly involved than upper limb joints. Spine was affected only in 5% of the cases. The big joints were more frequently and more severely affected than the small joints of the big joints shoulder was least affected (30 cases). Joint pain was very severe (4+) in 175 cases. The pain affected their life very adversely; they were confined to bed, had to defaecate near the bed (at times standing), were required to be fed by others. (Table: 4) One significant observation was subcutaneous swelling around the involved joints mimicking filarial lymphangitis. No fleeting character was seen in any case and effusion into joint space was present in 25% of cases. Arthritis was present in two distinctive forms. In one form arthritis started with the onset of illness and in the other arthritis appeared after a gap of one week of the disappearance of acute febrile illness.

Differential count and total leukocyte count were normal in all cases. However ESR was raised in most of the cases. In 23 cases it was less than 25, in 55 cases it was between 26-50, in 200 cases it was between 51-75 in two cases it was between 76-100 mm first hour. In none it was more than 100. Throat swab culture was negative in all cases where it was done (particularly in those ASO was positive).

However ASO titer was elevated in 28 cases. X-ray of the relevant joints (done in 25 cases) did not show any bony abnormality, except soft tissue swelling. Serum uric acid level was assessed in those cases having involvement of the small joints of the feet; but it was normal in all. Ig M antibody for Chikungunya was done in 15 cases (7 female, 8 Male); twelve were positive. Though it was done in few cases but its positivity in all cases suggests that it was an epidemic of Chikungunya.

Table : 1 Monthly distribution of cases

Month	No of cases	%
March 06	7	2.5
April 06	12	4.28
May 06	15	5.35
June 06	18	6.42
July 06	25	8.92
August 06	44	15.7
September 06	**56**	**20.0**
October 06	**53**	**18.9**
November 06	10	3.5
December 06	7	2.5
January 06	15	5.35
February 06	18	6.42
Total	**280**	**100**

Table: 2 Age and sex distribution of the cases

Age group in years	Male	%	Female	%	Total	%
< 10	0	0	0	0	0	0
11-20	7	2.5	6	2.1	13	4.6
21-30	20	7.1	23	8.2	43	15.3
31-40	44	15.7	49	17.5	93	33.2
41-50	42	15	64	22.8	106	37.8
51-60	10	3.5	15	5.35	25	8.9
>60	0	0	0	0	0	0
Total	**123**	**43.9**	**157**	**56.1**	**280**	**100**

Table: 3 Clinical Manifestations

Symptoms	No of Cases	%
Fever	**280**	**100**
Rashes	4	1.4
Arthritis	280	100
Respiratory symptoms (Cough, sore throat)	188	67.1
Headache	210	75
Conjunctival Congestion	218	77.8
Similar symptoms in Other members of family	162	57.8

Table: 4 Features of Arthritis

(a) Type of Arthritis

Type of arthritis	No of cases	%
Monoarticular	15	5.3
Oligoarticular	68	24.2
Polyarticular	197	70.3

(b) Joints affected

Joints affected	No of cases	%
Ankle	220	78.5
Knee	182	65
Hip	64	22.8
Elbow	148	52.8
Shoulder	30	10.7
Wrist	86	30.7
Small joints (hand)	66	23.5
Small joints (feet)	82	29.2
L S Spine	14	5

(c) Follow up (for 3months)

Outcome	No of cases	%
Relapse (Mostly treated with NSAIDs)	28	10
Deformity	0	0
Complications	0	0
Death	0	0

The cases were treated with NSAIDs like Ibuprofen, Diclofenac, Nimesulide, Naproxen, Aceclofenac and others. Response to these drugs was unsatisfactory in few cases. In fact some of these cases showed relapse.Later, we treated these cases like that of Acute Rheumatic fever; either by aspirin alone or prednisolone or combination of both in the recommended doses. This regimen was planned thinking it to be an immunological inflammation. Combination was given to those cases who were incapacitated by pain. Response was best seen with combination group (within 5 days), better with prednisolone alone (8 days) and least with aspirin alone (10 days).

On 3 months follow up of the cases no residual damage was seen in any of the patients. None developed any other complications; though complications[10] like encephalitis, myocarditis, Guillan Barre syndrome, pericarditis and ocular complications[11]have been reported. Death has been reported by others[12] but none of our cases died.

CONCLUSION

The predominant manifestation of this illness was arthritis. The lower limb joints are more frequently involved than upper limb. Peri -articular subcutaneous swelling is an outstanding feature of Chikungunya arthritis. Pain is very severe, confining the patients to bed. Females are more commonly affected than males. The predominant age groups affected are 31-50 years (>60%), some how it spares the extremes of age. The arthritis could be due to direct viral infection as well as appears to be an

immunological inflammation. Response to conventional NSAIDs was unsatisfactory in some cases, but good response to aspirin, prednisolone or combination of both. As there were few cases of relapse following treatment with NSAIDs, we feel the later regimen is more appropriate for all these cases. There was no residual deficit in any case and no complication observed.

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Original Article

INCIDENCE OF CARDIOVASCULAR MORBIDITY IN PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

Though in diabetics the cardiovascular changes start earlier in the course of the disease, in most of the cases features of nephropathy antedate that of cardiovascular involvement. Before the patient dies of diabetic nephropathy, he or she carries the risk of dying due to cardiovascular involvement at any time. So this study was conducted to observe the incidence of cardiovascular morbidity in patients with diabetic nephropathy. Fifty cases of diabetic nephropathy, either diagnosed earlier or recently diagnosed were included as per the inclusion and exclusion criteria mentioned in the text. It was observed that, 52 % showed cardiovascular changes in the form of silent ischemia (76%), stable (14%) & unstable angina (06%) and AMI (04%). Hence all the cases of diabetic nephropathy in what ever form they may present should always be treated aggressively for all sorts of cardiovascular morbidity.

Key Words : *Diabetic nephropathy, cardiovascular morbidity*

INTRODUCTION

Diabetes Mellitus is the most common metabolic disorder in all age groups after second decade. It is one of the leading causes of morbidity & mortality. Its worldwide prevalence is 2.5% and in India it is 1-2%.[1]Diabetic Nephropathy and cardiovascular diseases are two common chronic complications of both Type I & Type 2 diabetes mellitus and together they account for 50-80% of death in diabetics.[2] Diabetic Nephropathy is defined as persistent proteinuria (> 0.5 gm /24hr) in a patient with diabetes with concomitant retinopathy and elevated blood pressure, but without UTI, other renal diseases or heart failure.[3]

CE Mogensen in 1985 classified diabetic nephropathy into 5 stages:

1. Stage of Hyperfiltration
2. Renal changes without clinical signs
3. Stage of incipient nephropathy
4. Stage of overt nephropathy
5. ESRD

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The first three have been described as preclinical phase & the last two as clinical or overt nephropathy. Microalbuminuria (defined as urinary albumin excretion more than 30mg./24 hrs to 300mg./ 24hrs regardless of the method of urine collection) has emerged as recognized independent cardiovascular risk factor in addition to being a predictor of overt diabetic nephropathy.[4]It has been described to be associated with essential hypertension, hypertriglyceridaemia, hypercholesterolemia & endothelial dysfunction, which are all features of metabolic syndrome. The concurrence of microalbuminuria and hyperinsulinaemia were found to be a strong predictor of coronary artery disease. [5, 6]

In our country Coronary artery disease in diabetics, has an incidence of 6.6 to 33% as compared to 42-74% in western world. Cardiovascular involvements in diabetics are mainly manifested as pump failure (80-85%), sudden arrythmogenic death (10%) and frequently increased incidence of silent myocardial ischemia. In one study cumulative incidence of IHD was 8 times higher within 6 years of onset of proteinuria and patients

developing persistent proteinuria retrospectively also had clustering of risk factors for cardiovascular disease.[7]

Patients having proteinuria also have higher blood pressure, higher atherogenic blood lipid levels and more fibrinogen than the patients without proteinuria.[8] As per Framingham study, 25% of myocardial infarction in diabetics are silent because of involvement of autonomic nervous system.[9]This autonomic neuropathy is also responsible for sudden cardiac death in diabetics. Retrospective studies show that patients with AMI are having renal dysfunction, which is an independent predictor of death.[10,11] Diabetics with chronic kidney disease and end stage renal disease, have three key mechanical contributors of CCF, like pressure overload, volume overload and cardiomyopathy. Approximately 20% of patients approaching haemodialysis have diagnosis of CCF.[12]With this background information, this present study was designed to find out incidence of cardiovascular morbidity in patients with established or newly diagnosed cases of diabetic nephropathy.

AIM

To find out the incidence of cardiovascular morbidity in patients with established or newly diagnosed cases of diabetic nephropathy.

Materials & Methods

The present study was carried out during the period from 2005 to 2007 in the Department of Medicine, M.K.C.G. Medical College & Hospital, Berhampur.

Selection of Cases:

1. 50 Cases of Diabetic Nephropathy (either established or newly diagnosed), admitted to the Department of Medicine were included in this study.
2. Cases of all age groups above 18yrs and both sexes were taken.
3. Lactating mothers, pregnant women, seriously ill patients, patients with UTI and patients with febrile illnesses were excluded from the study.
4. Each of the 50 cases of diabetic nephropathy were subjected for cardiovascular evaluations for silent ischemia, stable angina, unstable angina, AMI, heart failure (Systolic or diastolic) by detailed history taking , clinical examination and investigations like ECG ,TMT, echocardiography, biochemical & serological tests.
5. History of breathlessness (NYHA Classification), angina, syncope, palpitation, edema (Generalized/Feet), and any past history of hospitalization for cardiovascular disease was also noted.

OBSERVATION

In our study, 64% male & 36% female had evidence of diabetic nephropathy in its different forms with male female ratio of 1.7: 1.Out of the total number patients. 90% cases were Type 2 DM and the rest were Type 1. As duration of diabetes increased, nephropathy changes also increased. In the present study, renal involvement found in different forms are as follows- microalbuminuria in 10(20%), frank proteinuria in 20(40%), renal failure in 15(30%) and ESRD in 5(10%) cases. Out of these patients with nephropathy, 26(52%) had cardiovascular changes. Amongst the patients of microalbuminuria and frank albuminuria, 40% cases in each group had cardiovascular changes. The incidence of cardiovascular changes was higher in renal failure and ESRD cases (60% and 100% respectively). Out of those cases with cardiovascular changes, around 76% had silent ischemia, 14% had stable angina, 6 % had unstable angina & 4% had AMI. The severity of cardiovascular morbidity was proportionate with the severity of nephropathy.

DISCUSSION

Out of 50 cases of studied, 32 cases were male and 18 cases were female (Ratio 1.7:1). Finn R and others showed a male preponderance in development of proteinuria with a ratio of around 1.7:1.[13]The renal involvement was ranging from simple microalbuminuria to the dreaded condition of ESRD. Cardiovascular morbidity was observed in different forms such as silent ischemia, stable & unstable angina and AMI. The cardiovascular morbidities were directly proportional to the degree of renal involvement. Silent myocardial ischemia as discovered by doing ECG was present in majority of

cases. As literature shows most of the silent ischemia might be due to the coexistence of autonomic neuropathy in these group of people.[10]Tuomilehto J, Dinneen SF and others reported a 2 to 3 fold increase in cardiovascular morbidity in patients with microalbuminuria and 10 fold increase in patients with frank proteinuria as compared to normoalbuminuric patients with Type 1 & Type 2 diabetes mellitus.[14,15] Once the creatinine level is raised, the risk of cardiovascular complications increases exponentially.[16] Rutter and others in 2000 had reported silent ischemia in 65% cases of microalbuminuria.[17] Similarly, Inoguchi T and others reported 43% cases of silent ischemia in patients with microalbuminuria . [18]

SUMMARY & CONCLUSION

Most of the patients who had diabetic nephropathy had evidences of cardiovascular changes and the changes were proportional to that of the degree of nephropathy. Though in diabetics the cardiovascular changes start earlier in the course of the disease, in most cases features of nephropathy antedate that of cardiovascular involvement. Hence all cases of diabetic nephropathy in whatever form they may present should always be treated aggressively for all cardiovascular risk factors.

ACKNOWLEDGEMENT

We are very much thankful to Prof. Gagan Ch. Mishra, Professor of Medicine, K.I.M.S., Bhubaneswar for some of his suggestions while preparing the paper.

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Original Article

SLEEP DISORDERS-A TEN YEAR EXPERIENCE AT KALINGA HOSPITAL

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ABSTRACT

In all, there were 25 patients admitted who had a diagnosis of sleep disorder. They include 17 cases of OSA, 6 cases of OHS, one case of complex sleep disorder, and one case of paediatric OSA (POSA). Sleep study was done in 12 cases of OSA, and only in one case of OHS. Only 3 cases underwent full night polysomnography. All patients admitted with respiratory failure needed non invasive ventilation. Seventeen of the above patients are alive and doing well.

INTRODUCTION

Sleep disorders are common and can affect anyone, from every social class and every ethnic background. Obstructive Sleep Apnoea (OSA) is a disease of increasing importance because of its neurocognitive and cardiovascular sequelae. Approximately 24% of men and 9% of women have OSA, with and without excessive daytime sleepiness. The occurrence of OSA has been linked to serious long-term adverse health consequences; such as hypertension, metabolic dysfunction, cardiovascular disease, neurocognitive deficits and motor vehicle accidents. The surges in hypoxaemia, hypercapnia, and catecholamine associated with this disorder have now been implicated in development of hypertension, but the association between obstructive sleep apnoea and myocardial infarction, stroke, and congestive heart failure is not proven. Continuous positive airway pressure, the treatment of choice for obstructive sleep apnoea, reduces sleepiness and improves hypertension.

Obesity hypoventilation syndrome (OHS) is a well-known cause of hypoventilation. Abnormal central ventilatory drive and obesity contribute to the development of OHS. However, no specific body mass index is associated with the development of OHS. A large percentage of patients with obesity hypoventilation syndrome have OSA. The patients with both OSA and OHS have worst gas exchange abnormalities and more severe pulmonary hypertension when compared with the patients with OSA only. However, OHS is an autonomous disease.

Sleep disorders are probably the most common medical conditions that often remain undiagnosed and untreated for a significant period of time before appropriate evaluation and treatment are instituted. This delay results partly from a relative lack of awareness by the public of the nonspecific signs and symptoms of sleep disorders and partly from inadequate training and experience in sleep-related disorders among health care professionals [1].

Materials & Methods

All patients diagnosed as obstructive sleep apnoea or obesity hypoventilation syndrome who were admitted to Kalinga Hospital during the period of Oct' 1999 to Sept'2009 were included in the study. The demographic data, history, clinical features, comorbidity, sleep study (if done), treatment, morbidity and mortality wee analysed. The diagnosis of the above cases were done from history, observation of sleep disorder and hypoxia during admission and on sleep study.

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RESULTS

In all there were 25 patients admitted who had a diagnosis of obstructive sleep apnoea or obesity hypoventilation syndrome. They included 17 cases of obstructive sleep apnoea and 6 cases of obesity hypoventilation syndrome, one case of complex sleep disorder and one case of paediatric obstructive sleep apnoea (POSA). (Table-1)

Table 1. Types of Sleep Disorders	
Obstructive Sleep Apnoea	17
Obesity Hypoventilation Syndrome	6
Complex Sleep Apnoea	1
Paediatric Sleep Apnoea	1

The age range in OSA was 45-75 years (mean 61 years) and 30-74 years in OHS cases. Obesity (BMI>30) was present in 6 out of 17 cases of OSA and all cases of OHS. Hypertension was present in 5 cases of OSA and 1 case of OHS. Clinical symptoms included history of snoring ranging from 5-25 years in all cases of OSA and only in cases out of 6 in OHS. Daytime sleepiness was present in all cases of OSA and 5 out of 6 cases of OHS. 11 out of 17 cases of OSA and all the cases of OHS presented to the hospital with respiratory failure. (Table-2) The duration of day time sleepiness ranged from 3 months-6 years with a median of around one year.

Table 2. Clinical Features of OSA (n-17)	
Snoring	17
Daytime Sleepiness	17
Respiratory Failure	11
Hypertension	6
Obesity	8
Hypothyroid	3
COPD	5

Sleep disorder was present for 3months-4 years with a median of around one year in most cases. Sleep disorder was so severe in some cases that they were unable to lie flat in bed and were sleeping in a chair for the last few months.

All the above cases were diagnosed from history and clinical observation.

Sleep study was done in 12 cases of OSA and only in one case of OHS. Only 3 cases underwent full night polysomnography. The rest underwent bedside sleep study by a portable sleep study machine (Reslink, Resmed). 11 out of 12 cases of OSA were severe (AHI>30) and one case had moderate OSA (AHI 15-30). In one case of OHS where sleep study was done AHI was 11.6 (mild OSA).

All patients admitted with respiratory failure needed noninvasive ventilation. Subsequently 12 out of 17 cases of OSA went home with home CPAP (5 with ordinary CPAP and 7 with autotitrable CPAP). Two patients refused to buy CPAP and two improved with weight reduction. Out of the 6 cases of OHS 6 went home with BiPAP ventilator, 3 of them required long term oxygen therapy for hypoxia. One could not afford BiPAP & went home without BiPAP.

Seventeen of the above patients are alive and doing well. One patient of OSA who had carcinoma lung died in the hospital. One case of OHS who could not afford BiPAP went home and died subsequently. The other patients were discharged home. Subsequently 5 patients of OSA have died. One case died one year later with respiratory failure because he had started CPAP on his own without titration & follow up. One of them did not buy CPAP and was readmitted with respiratory failure 1 year later and died in the hospital due to with holding of ventilatory support. Another case with associated COPD died due to acute exacerbation of COPD during transit to our hospital. Two other patients died of non respiratory causes after 7 years & 2 years after starting CPAP at the age of 75 & 72 respectively.

There was one case of Complex Sleep Apnoea who was 73 years of age, had Parkinsonism, hypertension, diabetes and had been admitted 1 year earlier for subdural hematoma and underwent

drainage. He presented with day time sleepiness and was observed to have obstructive sleep apnoea and hypoxia. Autotitrable CPAP was tried but he did not benefit. He was given the option of Tracheostomy but his relatives did not agree. He had a sudden cardiac death 1 month later.

There was one case of Paediatric sleep apnoea. He was a mentally retarded child with seizures. He developed obstructive sleep apnoea at the age of 8 years and underwent adenoidectomy at 9 years of age. There was recurrence of obstruction after 1 year and he had to undergo emergency tracheostomy at 11 years of age. A trial with CPAP & BiPAP were unsuccessful and he was advised to continue with tracheostomy.

DISCUSSION

Obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSA) is one of the most common dyssomnias diagnosed and treated in sleep disorder centres. It is associated with serious adverse consequences if untreated. According to the American Academy of Sleep Medicine (AASM) *International Classification of Sleep Disorders: Diagnostic and Coding Manual[5].* OSA is characterized by repetitive episodes of complete (apnoea) or partial (hypopnoea) upper airway obstruction occurring during sleep. By definition, apnoeic and hypopnoeic events last a minimum of 10 seconds or longer. Obstructive sleep apnoea occurs because of functional obstruction in the collapsible portion of the upper airway during sleep. In patients who have OSA, the airways are characteristically smaller because of facial-oral abnormalities (ie, hypognathia, retrognathia, small mid-facial structures) or excessive tissues (extra pharyngeal fat pads, enlarged adenoids or tonsils, excessive uvulopalatopharyngeal tissues, tongue) around the airway. When the patient is awake, a compensatory increase in neuromuscular tone of the upper airway or pharyngeal and hypoglossal muscles keeps the airway patent. With sleep onset, the loss of the neuromuscular tone leads to collapsibility of the airway, which is worse during rapid eye movement (REM) sleep. The resulting increase in airway resistance and a more negative intrathoracic pressure caused by increased respiratory efforts tips the balance of Starling's forces toward further airway collapse [6]. Once the airway is obstructed, oxygen levels tend to drop, and carbon dioxide levels may rise. After a certain period of time, the brain signals the patient to arouse, which restores the muscle tone of the pharyngeal dilators. A loud snore usually accompanies the initial restoration of airway patency. Sleep resumes, but this cycle of events caused by recurrent pharyngeal airway collapse can occur hundreds of times throughout sleep. The multiple sleep disruptions or fragmentations (expressed as arousal index, ie, arousals per hour) correlate strongly with excessive daytime sleepiness (EDS). These recurrent apnoeas-hypopnoeas, hypoxemia and hypercapnia, and arousals are associated with increase sympathetic activation, hypertension, and adverse cardiovascular outcomes [2-4].

Obstructive apnoea events are most often associated with recurrent sleep arousals and recurrent oxygen desaturation. Three cardinal symptoms of sleep apnoea include snoring, sleepiness, and significant sleep apnoea episodes.

Snoring is the most common symptoms of OSA. Approximately 50% of men and 40% of women are occasional snorers; 25% of men and 15% of women are habitual (almost daily) snorers. About 50% of these habitual snorers have upper airway resistance syndrome [7] or OSA and are at increased risk of developing hypertension, coronary artery disease, myocardial infarction, and cerebrovascular disease. All our cases of OSA had snoring and daytime sleepiness. Approximately 30% of patients with a BMI greater than 30 have OSA, and 50% of patients with a BMI greater than 40 have OSA. Obesity was present in 8 out of 17 cases of OSA.

EDS is the primary symptoms of OSA but may not be apparent in some patients. Sleepiness may be perceived as fatigue and tiredness.

In the primary care setting, OSA should be considered in patients who have newly diagnosed hypertension, especially in the absence of family history of high blood pressure. Resistant hypertension in spite of multiple antihypertensive medications may

be caused by OSA. Successful treatment of OSA results in control or resolution of hypertension. OSA should also be suspected in patients who have paroxysmal atrial fibrillation, idiopathic cardiomyopathy, secondary pulmonary hypertension, premature coronary disease or heart attack, and strokes. Patients who have OSA frequently suffer from concomitant heartburn or acid reflux disease, unexplained morning headaches, a diminished sense of well being, depression, chronic muscle aches, fibromyalgia, progressive weight gain or inability to lose weight, glucose intolerance, or metabolic syndrome (syndrome X).

Polysomnography (PSG) is used to diagnose OSA. Polysomnography is the gold standard for diagnosing OSA. PSG is, however, expensive, time-consuming, and not always readily accessible. Hence, alternative diagnostic methods such as home-based testing have been evaluated. Only three cases underwent full night polysomnography for diagnosis as this facility is not available in our state. Tonelli de Oliveira et al indicate that in-home respiratory monitoring can be used to diagnose obstructive sleep apnea syndrome. In nine cases bedside sleep study was done with Reslink of Resmed. All the rest were diagnosed with bedside respiratory monitoring.

Various effective therapeutic modalities include weight loss (by diet and exercise or surgery), positional therapy, oral appliances, continuous positive airway pressure (CPAP), and radiofrequency (RF) ablation therapy and surgery. Weight loss should always be advised for patients who are overweight. Recently, dramatic results have been reported with gastric bypass surgery or gastric banding [8]. Two patients improved with weight reduction. OSA can be reversed quickly with the appropriate titration of continuous positive airway pressure (CPAP) devices. CPAP is the standard treatment option for OSA [9]. In patients who cannot tolerate CPAP, a trial of BiPAP is warranted. However, BiPAP is too expensive to be used as first-line therapy, and it has no distinct advantages over CPAP therapy. Twelve patients out of 17 used CPAP. Oral appliances that move the tongue or mandible anteriorly can significantly enlarge the pharyngeal airway and have greater patient acceptability and compliance than CPAP. Oral appliances control snoring in about 73% to 100% of patients but relieve apnoea in only 51%. Oral appliances are not as reliable as CPAP therapy and have variable efficacy for moderate-to-severe OSA. Hence, oral appliances are recommended only for snoring and mild OSA and may be considered for some patients who have moderate OSA for which CPAP therapy was not effective [1].

Radiofrequency Ablation therapy for treatment of snoring and sleep apnea is also being tried. The RF energy applied to the pharyngeal tissues, nasal turbinates, or the base of the tongue denatures cellular proteins, resulting in reduced tissue volume with minimal scar formation. Radiofrequency ablation can be done as outpatient procedure with minimal side effects. Efficacy data show limited improvement, however [10].

Surgery is another alternative treatment modality for OSA in children and adults. Adenoidectomy and tonsillectomy, with or without nasal septoplasty, are quite effective in children, but these patients are at risk of recurrence of sleep apnea as they grow into adulthood. There has been recent interest in the use of postoperative orthodontic devices in these children for maxillary or mandibular expansion that might prevent future relapse of OSA. In adults, success rates with uvulopalatopharyngoplasty vary from 30% to 50%. Additional genioglossal advancement with hyoid myotomy surgery improves success rates to 60%. Maxillary-mandibular advancement surgery is an extensive surgery of the mandible and maxillary bones that effectively expands the airways. It is usually reserved for patients in whom less intrusive surgical treatments have been unsuccessful. Success rates approaching 90% to 95%, similar to those of CPAP therapy, have been reported but have not always been found reproducible by other surgeons.

Tracheostomy bypasses the upper airway and is the most effective surgical procedure for treatment of OSA; it is virtually 100% effective. Unfortunately, tracheostomy is a disfiguring procedure and decreases the patient's quality of life. Tracheostomy is now reserved for patients with severe OSA in

whom other medical and surgical treatment modalities fail. Tracheostomy is also used for airway protection during upper airway reconstructive surgery.

Currently, there are no effective medications to prevent the collapse of airways during sleep in OSA. Some animal researches are being conducted using selective serotonin reuptake inhibitors. Stimulants such as modafinil are effective in improving persistent EDS in patients who have OSA successfully treated with CPAP.

Finally, treatment of OSA is most successful when an individualized approach is based on disease severity, on the specific features of the upper airway anatomy, and on patient preferences, expectations, and desires.

Obesity hypoventilation syndrome

Patients with obesity hypoventilation syndrome have a higher incidence of restrictive ventilatory defects when compared with patients who are obese but do not hypoventilate. Studies have shown that patients with obesity hypoventilation syndrome have total lung capacities that are 20% lower and maximal voluntary ventilation that is 40% lower than patients who are obese who do not have hypoventilation.

These patients demonstrate an excessive work of breathing and an increase in carbon dioxide production. Inspiratory muscle strength and resting tidal volumes also are reported to be decreased in patients with obesity hypoventilation. Pulmonary compliance is lower in patients with obesity hypoventilation syndrome when compared with patients who are obese who do not have hypoventilation. Obesity increases the work of breathing because of reduced chest wall compliance and respiratory muscle strength. An excessive demand on the respiratory muscles leads to the perception of increased breathing effort and could unmask other associated respiratory and heart diseases.

CONCLUSION

Sleep disorders are common and going to increase due to increasing obesity in the society. It leads to increased cardiovascular mortality. It is grossly underdiagnosed. Therefore training of healthcare professionals and awareness in public has to be increased to prevent morbidity and mortality due to sleep disorders which are treatable.

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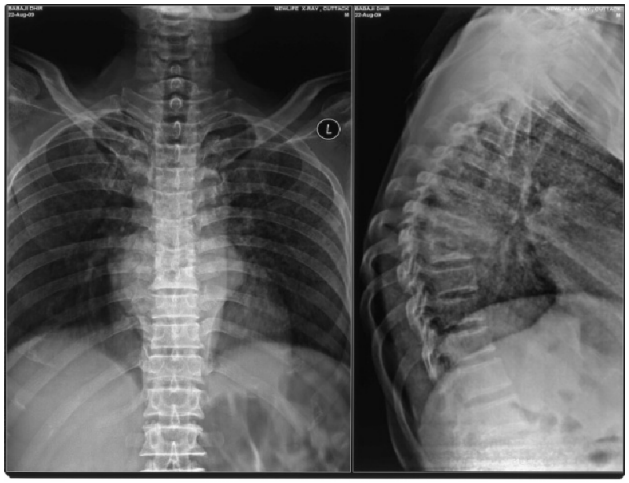
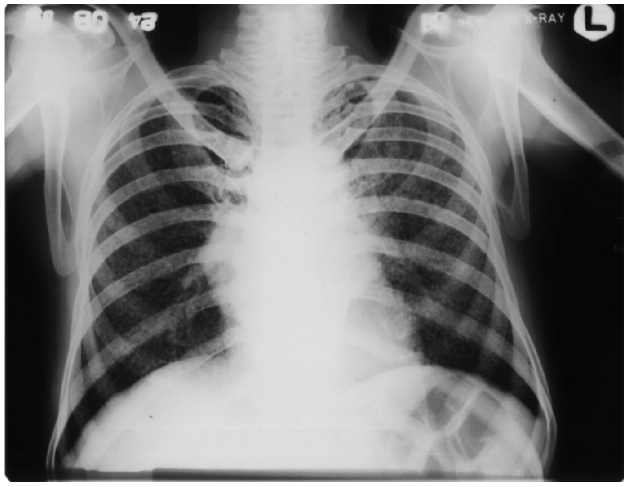
Pictorial CME

A CASE OF MILIARY TUBERCULOSIS WITH POTT'S SPINE

SK Mahapatra*, R Mohanty*, Sarita Behera, A N Sahu***,
R P Kumar****, S Kumar******





A 56yr old male presented with low grade fever for 4 months, progressive weakness of both lower limbs for 3 months. Examination of the patient revealed features of compressive thoracic myelopathy at T10 spinal level with a gibbus at T7-8 level. X-ray of thoracic vertebrae (AP & Lateral) showed narrowing of intervertebral disc space at T6-7 and T7-8 level, paravertebral abscess at the same level, and destruction of 7th thoracic vertebra confirming it to be a case of TB spine with compressive myelopathy. Further the same thoracic vertebral lateral view x-ray showed miliary shadows in lung fields.

It's interesting for its x-ray which shows typical TB spine findings along with miliary shadow in the same picture double confirming our diagnosis. Further it's rare due to miliary tuberculosis (haematogenous spread) and TB spine (usually reactivation) occurring in the same patient. Only two such cases are reported - one from Indianapolis, USA, in a prisoner[2]; another from New Delhi, India[3].

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Pictorial CME

CHRONIC TOPHACEOUS GOUT

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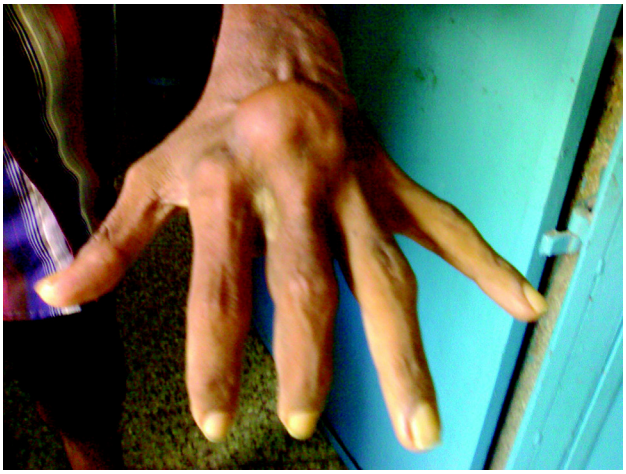

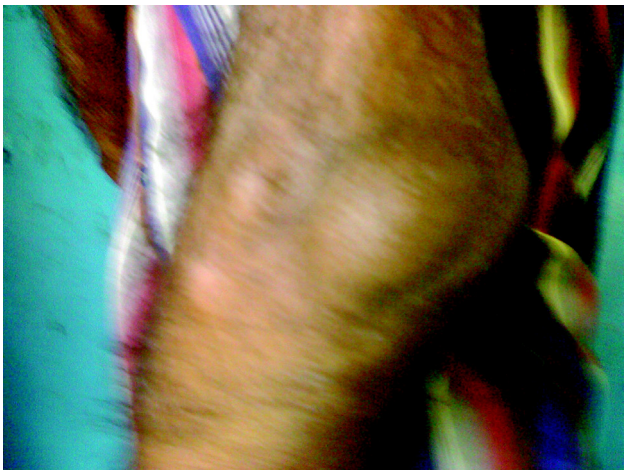

A 36 yr. old male patient presented with pain of bilateral small and large joints for last 6 years and gradually, progressive swellings over dorsum of hand and elbow joint for last 3 years. Several times over the years he was on analgesics and antirheumatoid drugs prescribed by local physicians. There was no history of early morning stiffness, diabetes mellitus, hypertension, alcohol intake. Physical examination revealed average body built, symmetrical polyarthritis, irregular, firm, non tender nodules of varying size over dorsum of hands, around elbow joint and two small nodules over dorsum of right foot. Complete hemogram was normal except ESR 84 mm (1st hour). Blood sugar, Blood urea/S.creatinine, LFT, S.lipid profile were within normal limit except mild rise in triglycerides. S.uric acid was 14.3 mg/dl, CRP-6.5 mg/L, RA factor was negative. FNAC from nodule overlying dorsum of hand revealed monosodium urate crystals surrounded by macrophages. X-ray of joints of hand revealed Erosions with sclerotic bony margins. Hence, a diagnosis of **"Chronic tophaceous Gout"** was made. Patient was treated with oral colchicine followed by oral colchicine and Allopurinol.

Tophaceous gout is the consequence of chronic inability to eliminate urate as rapidly as it is produced. As urate pool expands, deposition of urate crystals appear in cartilage, synovial membranes, tendons, soft tissues and else where. It occurs when recurrent acute gout and hyperuricemia get untreated and when there is failure to eradicate causative factors like excessive alcohol consumption, obesity, diuretic therapy. More commonly found in gout secondary to myeloproliferative disorders, in Juvenile gout complicating glycogen storage disease (GSDS), in Lesch-Nyhan syndrome and after allograft transplantation in patients treated with cyclosporine. Usual sites of nodules are extensor surfaces of fingers, hands, forearm, elbows, achilles tendon, helix of the ear, rarely in myocardium, valves, cardiac conduction tissue, various parts of ear, and larynx. Large nodules may ulcerate discharging white, chalky, pasty materials composed of urate crystals. Secondary infection of tophi in rare. They can produce limitation of joint movement by involvement of the joint structure directly or of a tendon serving the joint. No diarthrodial joint is immune to gouty arthritis, although joints of feet are notoriously involved in the acute attack, it is the hand where evidence of chronic gout is more evident. Histopathologically shows monosodium urate crystals surrounded by chronic inflammatory cells. Polarising microscope reveals classic needle shaped, negatively birefringent crystals.

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Review Article

RECENT ADVANCES IN ENTERIC FEVER

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EPIDEMIOLOGY

Enteric fever is a systemic infection caused by salmonella enterica serotype typhi(S.typhi) and serotypes paratyphi A,B and C . Humans are the only host for these pathogens which are transmitted by fecal contamination of food and water.

S. typhi affects approximately 21 million cases with 2.1 lakh deaths annually. The incidence is highest in Asia (Table-1), especially in the Indian subcontinent (>100 cases /1lakh person per year)[1]. In a recently concluded study on disease burden of typhoid fever in 5 Asian Countries, the burden was highest in India(493.5 /1lakh population) in contrast to China (29.3 /1 lakh population). From Kolkata urban slum population the annual incidence of typhoid fever has been 494 cases /1 lakh population.[2]

TABLE-1

Annual Incidence of Typhoid Fever per 1 Lakh Population:[1,2]

Africa	50
Asia	274
Latin America	53
Australia	<1
Europe	3
North America	<1

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Most of the patients of typhoid fever in USA was from Indian subcontinent[3]. Travel to Indian subcontinent is associated with highest risk of contracting enteric fever. Highest burden of disease is between 5-15 years (57%)[2].

Previously S. paratyphi was thought to have caused 10% cases of enteric fever as a milder form of disease. However 5.4 million people were affected by Paratyphoid in the year 2000. Recently the incidence paratyphoid has increased even reaching 50% of cases of enteric fever[4].

There is increased incidence of paratyphoid A among returning travelers from endemic area. An outbreak of enteric fever caused by S. paratyphi A was reported from India & Nepal. Paratyphoid has highest incidence in teenagers & young adults in contrast to typhoid which is more common in children. This is possibly due to different mode of transmission. S. typhi mainly transmitted by house hold contact, in contrast S. paratyphoid A mainly transmitted by contaminated food from a street vendor[5].

Clinical Features :

The majority of patients with typhoid fever seen in affluent countries present with the triad of persistent fever, headache and abdominal symptoms (mainly abdominal pain and diarrhoea). Diarrhoea is present in approximately 50% of patients. Constipation is equally well known. Their symptoms rarely progress beyond this stage. In developing countries patients tend to present later and are more likely to be seen with the vast array of less common symptoms and complications that are associated with typhoid fever. Prominent temperature pulse dissociation is a well known feature of typhoid but it is not invariably present. [6]

Table -2

Published studies on the prevalence of multidrug-resistance and nalidixic acid resistance among salmonella enteric serovar Typhi in India[20].

Authors	Place of Study	Study Period	No of isolates Tested	MDR-ST n (%)	NARST n(%)
Renuka et al	New Delhi, AIIMS	2000-03	442	160(38)	340(81)
Walia et al	New Delhi, SJH	2001-03	377	60(16)	282(75)
Manchanda et al	New Delhi CNCH	2004-05	56	1(2)	48(86)
Reveendran et al	New Delhi SGRH	2005-06	431	64(15)	396(92)
Raya et al	Chandigarh	2002-03	70	13(19)	48(69)
Sen et al	Kolkata	2003-05	195	28(14)	120(62)
Jog et al	Mumbai	2003-05	73	≤5 (≤7)	52(71)
Vedyalakshmi et al	Mangalore	2005-06	71	1(1)	33(46)
Joshi et al	Bangaluru	2004	25	0	17(68)
Lakshmi et al	Hyderabad	2001-04	60	≤25 (≤42)	58(97)
Madhulika et al	Puducherry	2002-03	157	61(39)	131(83)
Rupali et al	Vellore	2000	109	54(50)	38/50(76

In one Indian study from JIPMER Pondicherry; atypical manifestations (46.9%) observed were burning micturation with normal urine examination (15.6%), Encephalopathy in 1st week (3.1%), Isolated Hepatomegaly (6.2%), Pneumonitis (3.1%), Bone marrow suppression (6.2%). Patients with MDR strains have atypical manifestations . Atypical manifestations do not necessarily mean a worse prognosis. [7]

Mild and inapparent infections are frequent. Diarrhoea may occur even during 1st week & children may present with high fever & febrile convulsion. Chronic or recurrent fever with bacteremia occurs in association with concurrent schistosomiasis. [8]

Fever is persistent with relatively little diurnal variation is being common. Rigors are not typical of typhoid but may be observed in 2nd & 3rd week of Infection. In two studies from India, fever was remittent in 30-60% of cases, sustained in 22-25% & intermittent in 15-46%.[6] Conjuctivitis was reported in upto 44% patient, but is less common. [9] Bacteremia is uncommon & occurs mostly in immunocompromised host or those with underlying conditions. Multidrug resistant (MDR) typhoid and paratyphoid infections are more severe with high rate of toxicity, complication and mortality than infections with sensitive strains, which may be related to virulence of MDR S. typhi as well as higher number of bacteria.[11]

Diagnosis (Table-3)

According to the World health organization (WHO), a confirmed case of typhoid fever is defined, as a patient with fever(>38^0 C) that has lasted for at least 3 days, with a laboratory confirmed positive culture of S. typhi. Probable case of typhoid fever is a patient with fever (>38^{0}C) that has lasted for >3 days, with a positive serodiagnosis or antigen detection test but without S. typhi isolation. [10]

Diagnosis of typhoid fever is based on three principles:

A. Isolation of organism.

B. Detection of microbial antigen

C. Titration of antibody against causative organism.

Table -3 .Laboratory Diagnosis of Typhoid [11]

Diagnostic Test	Sensitivity range(%)	Specificity range (%)
Microbiological tests		
Blood Culture	40-80	NA
Bone marrow culture	55-67	NA
Urine Culture	0-58	NA
Stool Culture	30	NA
Molecular Diagnostics		
PCR	100	100
Nested PCR	100	100
Serological Diagnosis		
Widal Test (Tube dilution and Slide agglutination)	47-77	50-92
Typhidot	66-88	75-91
Typhidot-M	73-95	68-95
Tubex	65-88	63-89
Others		
Urine antigen detection	65-95	NA

NA-not available

Isolation of organism

Blood culture is the standard diagnostic method and is usually positive in about 80% during 1st week and decline later. In practice only 40-60% cases, blood culture becomes positive. Another alternative is clot culture[12]. Here 5ml of blood is collected, allowed to stand for clot formation, serum is pipetted off and used for widal test. The clot is lysed by streptokinase, then cultured. Clot culture yields higher rate of isolation than blood and bactericidal action of serum is obviated. Stool culture and urine culture is positive after 1st week but is having lower sensitivity. Bone marrow culture is more sensitive but invasive.[11]

Detection of microbial antigen

Typhoid bacilli antigen is consistently present in blood in early phase of disease and also in urine. Antigen can be demonstrated by sensitized staphylococcal co-agglutination test. Staph. aureus (cowan I strain) which contains protein A is stabilized with formaldehyde and coated with S.typhi antibody. When 1% suspension of such sensitized Staph. aureus cells is mixed on a slide with serum from patient in 1st week, typhoid antigen present in serum combines with antibody attached to Staph. aureus cells, produces visible agglutination in 2min. This is rapid, sensitive and specific but not positive after 1st week.[12]

Sero Diagnosis

(1). Widal test:[13] Widal test reaction involve the use of bacterial suspensions of S. typhi and S. paratyphi A, B, heated to retain only the O and H antigen. These antigens are employed to detect corresponding antibodies in the serum of patients suffering from typhoid fever.

The IgM somatic O antibody appears first. IgG flagellar H antibody usually develops more slowly but persists for longer. False positive results are seen in Malaria, Dengue, Milliary tuberculosis, endocarditis, chronic liver disease, Brucellosis and other non enteric salmonellosis. Cross reaction with antigens of other bacteria, lack of standardization and maintenance of antigen results in lack of sensitivity and specificity in diagnosing typhoid fever.

Though it is replaced in western countries where typhoid fever is low, it is still used with variable success in developing countries for its availability and low cost.

It is generally accepted that towards the end of the 1st week of illness titers of either O or H antibody may rise to as high as 1:160. Though many stress that single agglutination test has no diagnostic value, there are several reports suggesting its utility in countries where exposure to typhoid is less. A 1:50 or 1:100 titer on an initial single test usually correlates fairly well with exposure to typhoid fever[13]. In endemic area a four fold rise or greater rise in O or H agglutinin titer in serum specimen obtained 2-3 weeks apart are helpful in diagnosis of typhoid fever but it is too late. In a recent study in endemic area 53% case of typhoid fever had O or H antibody <1:40 and 26% had titer 1:320 suggesting low sensitivity[14]. Taking positive titer e"1:80 as diagnostic of typhoid fever Taiwo SS et al observed H positive in 95%cases and O positive in 92.5% cases. In healthy people 13.8% were positive for O and 18.5% for H antibody.[15] Taking the cut off value of e"1: 200 titer as positive for typhoid fever, widal test has 52% sensitivity and 88% specificity, positive predictive value 76%, negative predictive value 71%.[16] Therefore widal test will continue as a helpful test with all its limitation and there is need to improve the test in future.

Recent advance include the **(2). Tubex test**[17], which can detect IgM O9 antibodies . The O9 antigen used in the test is extremely specific because its immunodominant epitope is a rare dideoxyhexose sugar in nature . This antigen has been found in serogroup D salmonellae but not in other microorganisms. A positive result invariably suggests a Salmonella infection. Tubex detects IgM antibodies so aids in the diagnosis of current infections.

Another rapid serological test, **(3). Typhidot test** makes use of the 50 kD antigen to detect specific IgM and IgG antibodies to S. typhi and takes 3hours to perform. This dot enzyme immune assay (EIA) test offers simplicity, speed, specificity (75%) , economy, early diagnosis, sensitivity(95%) and high negative and positive predictive values. The detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection.[18]

A newer version of the test**, Typhidot-M test** was recently developed to detect specific IgM antibodies only. **(4). DOT EIA** (enzyme immuno assay) **IgM test** has shown 91.4% sensitivity and 90% specificity in comparision to widal test which is sensitive in 42.88% and specific in 85% cases. It is positive in 43.5% in 4-6 days of illness which rises to 92.9% in 6-9 days and 100% after 9 days.[19]

Urinary Vi Ag ELISA & PCR based assay are under development.[8]

Drug Resistance & Treatment: (Table-4)

Over the last decade, several studies from different parts of India have consistently reported a very high prevalence of nalidixic acid resistance among S.typhi isolates[20]. Nalidixic acid resistance has been used as an indirect evidence of increased MIC. The prevalence of nalidixic acid resistance S. typhi (NARST) was 57%. Comparable levels of nalidixic acid resistance were reported from Vietnam ((44%) and Pakistan (59%) . However, the prevalence of multidrug-resistance(MDR)(MDR means resistance to chloramphenicol, ampicillin, and cotrimoxazole) in India was lower (7%) as compared to Vietnam (22%) and Pakistan (65%) and U.S.A 13%. However 85% of MDRST and 94% of NARST cases in U.S.A traveled to the Indian subcontinent while 44% of those with susceptible infections did.[3].

Three large randomized controlled trials (RCTs) on the treatment of NARST infection have been completed recently. From these trials it emerges that: (I) high-dose ofloxacin (20mg/kg/day for 7 days) is inferior to oral azithromycin (10mg/kg/day for 7 days), (ii) oral cefixime even when used at a dosage of 20mg/kg/day for 7 days is far inferior to gatifloxacin (10mg/kg/day for 7 days), and (iii) azithromycin (20mg/kg/day for 7 days) and

Table -4 Recommended antibiotic treatment for typhoid fever.[11]

Susceptibility	Drug	Daily dose mg/kg	Course (Days)
Uncomplicated typhoid fever			
Fully sensitive	Fluoroquinolone(such as ofloxacin or ciprofloxacin	15	5-7
Multidrug Resistant	Fluoroquinolone	15	5-7
Quinolone 7	Azithromycin or	8-10	
Resistant	Ceftriaxone	75	10-14
Severe typhoid fever requiring parenteral treatment			
Fully sensitive	Fluoroquinolone	15	10-14
Multidrug resistant	Fluoroquinolone	15	10-14
Quinolone	Ceftriaxone or	60	10-14
resistant	Cefotaxime	80	10-14

gatifloxacin (10mg/kg/day for 7 days) are similar in efficacy, achieving fever clearance in about 80% of patients by day 7 of treatment. Moreover, the clinical and microbiological responses to gatifloxacin and azithromycin are comparable to that with ceftriaxone. Interestingly, a combination of ofloxacin and azithromycin was found to be less efficacious than azithromycin alone for the treatment of NARST strains.[20]

In one open study on efficacy and safety of levofloxacin in treatment of uncomplicated typhoid fever, showed that levofloxacin 500mg/day for 1 week obtained 100% clinical efficacy with minimal adverse reaction. No carrier state was detected and non of the cases relapsed. Average defervescence occurred within 2.5 days.[21]

The peak serum level achieved following an oral dose of 500mg of azithromycin is 0.4 μg/ml, which is well below the MIC of azithromycin (4-32 μg/ml) for S.typhi. However, clinically, azithromycin is effective for the treatment of typhoid fever. This apparent paradox is due to the fact that azithromycin gets concentrated intracellularly to 50-100 times the serum levels. Not withstanding, about one third of S.typhi is extracellular in location, although typhoid fever is a prototypical intracellular infection. Azithromycin may not be effective against the free-living sub-population of S.typhi, and exposure to sub-therapeutic concentrations of azithromycin in the plasma may promote the emergence of resistance to azithromycin.[20]

Ceftriaxone should be given for a period of at least 10-14days (75mg / kg / day). Current indication for the used third-generation cephalosporins are (I) treatment of hospitalized patients with complicated/severe typhoid fever; and II) as a second –line drug for the retreatment of patients that fail fluoroquinolones or azithromycin. Recently, an increasing trend in the MICs of third –generation cephalosporins has been reported from Northern India.[20]

A recent study has shown a shifting of susceptibility to conventional drugs like chloramphenicol, ampicilin and cotrimoxazole. 50 isolates of salmonella obtained from blood culture were subjected to antibiotic sensitivity testing for 10 drugs. In the study, 70% and 30% of the isolates were S. typhi and S. paratyphi-A respectively. They were highly sensitive to chloramphenicol (86%) ampicillin (84%) and cotrimoxazole (88%). Highest sensitivity was seen for cephalosporins, followed by quinolones. 12% were MDR and showed the presence of plasmids.[22]

In another study 96% of the isolates were found to be nalidixic acid resistant while all isolates were found to be ciprofloxacin sensitive. The difference between MIC of ciprofloxacin for NAR & nalidixic acid sensitive isolates was found to be statistically significant. This increase in MIC of ciprofloxacin in S. typhi may result in delayed response and serious complications.[23]

In a recent 2008 Cochrane review fluoroquinolones were found to be better in reducing clinical relapse rate compared to chloramphenicol; and azithromycin is better than fluoroquinolones in populations that include cases of drug resistant strains. Azithromycin performed better than ceftriaxone. It appears that gatifloxacin and azithromycin are now the treatment of choice for typhoid fever cases with MDR and NARST. [24,25]

PREVENTION

Vaccinations:-Two most readily available vaccines are the parenteral capsular polysaccharide Vi vaccine and the oral live attenuated Ty 21a vaccine.

Parenteral Vi vaccine- it is single dose regimen and revaccination is done every 3 years. It does not protect against S.paratyphi A or B, since these strains do not express the Vi polysaccharide. Oral Ty21a vaccine- it is 3 dose regimen given every alternate day . It confers substantial cross-protection (vaccine effectiveness, 49%) against S.paratyphi B but not against S.paratyphi A.

Klugman et al. reported a vaccine effectiveness of 55% during 3 years of follow –up for Vi vaccine and that of 62% during 7 years of follow-up for Ty 21a vaccine.[26]

Vi conjugate vaccine - Vi vaccine conjugated to a non toxic recombinant Pseudomonas aeruginosa exotoxin A, recently evaluated in Vietnam and shown to have 91.5% protective efficacy.[8]

CONCLUSION

Typhoid fever is a serious public health infectious disease of great magnitude . India is having highest incidence of typhoid fever with rising MDR and NARST. Resistance to quinolones are increasing but still effective Azithromycin, Ceftriaxone, newer quinolones are promising drugs for treating MDR typhoid. Vaccination against typhoid fever should be promoted to reduce disease burden.

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Review Article

CONTROL OF TUBERCULOSIS – THE DOTS STRATEGY

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Tuberculosis is a major cause of morbidity and mortality world over particularly in developing countries with significant public health implications. Nearly 1/3rd of the World Population is infected with *Mycobacterium tuberculosis* and is at risk of developing the disease in future. More than 90% of Global TB cases and death occur in the low and middle income countries where about ¾ of these cases affect the most economically productive age group (15-59 years) with significant socio economic impacts (2).India is the highest TB burden country accounting for 21% of the global incidence and it is estimated that 1.9 million new cases (incidence) were from India in 2007. India is 17th among 22 High Burden Countries (HBC) in terms of TB incidence rates (1). Of this number, 0.8 million are infectious new smear positive Pulmonary TB cases. Nearly 40% of the Indian population is infected with the TB bacillus. The estimate of TB incidence in India is based on findings of the nationwide annual risk of TB infection (ARTI) study conducted in 2000-03. The national ARTI was estimated at 1.5% i.e. 75 new smear positive pulmonary TB cases are expected per 100,000 population annually. The prevalence of TB has been estimated at 3.8 million bacillary cases for the year 2000, by the expert group of Govt. of India(3,4).

The main reasons for the increasing burden of TB globally are poverty and the widening gap between rich and poor in various populations particularly in the developing countries; neglect of the disease because of inadequate case detection, diagnosis and cure; inadequate National Control Programmes and collapse of the health infrastructure due to economic crises or civil unrest and the impact of the HIV pandemic. Governments in many high burden countries have neglected TB Control in the past. The existing Tuberculosis programmes have failed to achieve high detection and cure rates for infectious, smear-positive patients. The WHO declared TB a global emergency in 1993 realizing its growing importance as public health problem. It developed the DOTS strategy (Directly Observed Treatment, Short Course) in 1994 as the new frame work for effective TB control (6,7).DOT represents the basic minimum necessity for control of tuberculosis. The strategy have been adopted in many countries with flexibility and adaptation to the existing needs of the community (9,10).

The global targets and indicators for TB control were developed within the frame works of the Millennium Developments Goals (MDG) in 2006. The targets are to halt and to begin to reverse the incidence of TB by 2015 and reduction by 50% in the prevalence and mortality rates by 2015 relative to 1990 levels (Goal 6, Target 6c). The Stop TB Partnership targets the achievement of the case detection rates of 70% and a cure rate of at least 85% for such cases as established by the World Health Assembly in 1991. The ultimate goal of eliminating TB, defined as the occurrence of less than 1 case per million populations per year by 2050 (14,15).

RNTCP in India

The Revised National TB Control Programme (RNTCP) of India, based on the internationally recommended Directly Observed Treatment Short-

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course (DOTS) strategy, was launched in 1997 and was expanded across the country in a phased manner with support from the World Bank and other development partners. The objectives of the programme are to

a. To achieve and maintain cure rate of at least 85% among New Sputum Positive (NSP) patients

b. To achieve and maintain case detection of at least 70% of the estimated NSP cases in the community

Full nation wide coverage was achieved in March 2006 covering over a billion populations (1114 million) in 632 districts / reporting units. In terms of treatment of patients, RNTCP is the largest and the fastest expanding programme in the world. In 2005 alone, 1.29 million TB patients, in 2006, 1.39 million and in 2007, 1.48 million patients have been enrolled for treatment. In 2008 1.51 million patients have already been placed on treatment (17).

Treatment success rates have tripled from 25% to 86% & TB death rates have been cut 7-fold from 29% to 4% in comparison to the pre-RNTCP era. Since its inception, the Programme has initiated nearly 10 million patients on treatment, thus saving nearly 1.8 million additional lives. The programme has consistently maintained the treatment success rate >85% and NSP case detection rate (CDR) close to the global target of 70%. In 2007, RNTCP has achieved the NSP CDR of 70% and treatment success rate of 86% which is in line with the global targets for TB control. In the year 2008, the NSP CDR is 72% and NSP treatment success rate is 86%.

Monitoring, supervision and evaluation: All states are currently implementing the 'Supervision and Monitoring strategy' – detailing guidelines, tools and indicators for monitoring the performance from the PHI level to the national level. The programme is focusing on the reduction in the default rates amongst all new and re-treatment cases and is undertaking steps for the same.

TB HIV coordination : The collaborative activities which were being undertaken in 14 states earlier have been scaled up to involve all the states in 2008. National AIDS Control Programme (NACP) & RNTCP have developed "National framework of joint TB/HIV Collaborative activities" in 2007, and then revised in 2008, which redefines the scopes of TB/ HIV collaborative activities being implemented in the country in Fiscal 2008. Year 2008 saw continued increase in the quantum of referrals between the programme. In the year 2008 more than 0.16 million ICTC clients were referred to RNTCP for TB diagnostic evaluation. 0.13 million TB patients were tested for HIV and more than 20,000 patients were detected to also be HIV-infected.

Impact of the programme:

a. TB mortality in the country has reduced from over 42/100,000 population in 1990 to 28/100,000 population in 2006 as per the WHO Global TB Report 2008.

b. The prevalence of TB in the country has reduced from 568/100,000 population in 1990 to 299/100,000 population by the year 2006 as per the WHO Global TB Report, 2008

c. Repeat population surveys conducted by TRC indicate an annual decline in prevalence of disease by 12%.

Drug Resistance and TB Control Programme

Multi-Drug Resistant Tuberculosis (MDR-TB) has come as a major challenge to the global effort in the TB control in the world (18). The most recent estimates based on data from different countries of the world on drug resistance surveys or routine surveillance (DRS) suggest that 5,10,545 cases of the MDR-TB occurred in 2007 (1). MDR-TB has been reported in almost all parts of the world, primarily as a consequence of poor treatment services, which have not only increased the costs

towards treatment, but also increased the risk of transmission of these resistant strains of the bacilli. In 2006, following the identification and reporting of the extensively drug-resistant TB (XDR-TB)- (*a form of MDR-TB with additional resistance to at least one of the second line injectables like amikacin, kanamycin or capreomycin and one of the flouroquinolones*), WHO has classified it as a serious emerging threat to global public health, especially in countries with high HIV prevalence.[6] It is also to be realized that management of MDR and XDR-TB is more complex and difficult. Besides establishing accredited, quality assured laboratories, the duration of treatment, and cost of 2nd line drugs complicate the issue further. The current strategy to manage MDR-TB is the DOTS-Plus, which is a method of managing MDR-TB patients within the existing DOTS programme. Many countries are scaling up their DOTS Plus Strategy to manage such cases. It is further to be remembered that treatment outcome of these cases are not very encouraging (20,21).

MDR and XDR-TB in India

The emergence of resistance to drugs used to treat TB, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective TB control. Several small surveys conducted across the country have shown the prevalence rates of MDR-TB in the country at around 3% among new cases, and 12% among retreatment cases (22,23). A large scale population based survey in the states of Gujarat and Maharashtra has also indicated similar resistance levels (new-3% and retreatment-12-17%). Available information suggests that the proportion of MDR-TB is relatively low in India. However, this translates into a large absolute number of cases, with an estimated annual incidence of 110,000 cases of MDR-TB. XDR-TB has been reported in India by isolated studies with non-representative and highly selected clinical samples. The magnitude of the problem remains to be determined due to the absence of laboratories capable of conducting quality assured second line Drug Susceptibility Testing (DST). However, what is frightening is the potential threat of XDR-TB in India, with unregulated availability and injudicious use of the second line drugs along with non-existence of systems to ensure standardized regimens and treatment adherence for MDR-TB outside the national programme. The problem of MDR and XDR-TB in India and across the world raises the possibility that the current TB epidemic of mostly drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. If this happens it would jeopardize the progress made in recent years to control TB globally as well as in India and would also put at risk the plans to progress towards a world where TB ceases to be a public health problem.

RNTCP activities of India 2008 (17)

The Revised National Tuberculosis Control Programme, since its inception in 1997 has trained over half a million staff in the health system, evaluated more than 30 million people with suspected TB, examined more than 100 million sputum slides and treated more than 8.2 million patients, thereby saving 1.4 million additional lives. This rapid expansion has not compromised on the quality of services. The results meet the internationally set benchmark of a treatment success rate of >85% among new sputum positive pulmonary TB cases. Case detection rate as per global target of 70% has been achieved.RNTCP is committed to implementing the 2006 Global Strategy to Stop TB and reaching the TB related targets of the Millennium Development Goals by 2015. The RNTCP II aims to provide a road map for TB control to achieve the long term goal, by 2015, of reducing the prevalence of TB by 50%.DOTS is the most useful and successful strategy in the world today to control the menace of tuberculosis. The RNTCP of India is again a full proof and successful programme to combat the disease although maintaining and sustaining the

programme in future will be the real challenge.

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Current Concept

FUTURE THERAPIES IN HEART FAILURE

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The worldwide prevalence and incidence of Heart Failure (HF) are approaching epidemic proportions, as evidenced by the relentless increase in the number of HF hospitalizations, the number of HF related deaths and the astronomical costs involved in its treatment. It is estimated that close to 23 million people are affected worldwide with HF. Table 1 enumerates the risk factors for HF in the Framingham offspring cohort study, while table 2 enumerates the causes of HF. Although several reports have suggested that the mortality for HF patients is improving, the overall mortality rate remains higher than for many cancers. In the Framingham study only 25% of men and 38% of woman with HF survived 5 years.[1] It is therefore, a matter of intense clinical research to find newer treatment modalities in order to minimise the morbidity and mortality of heart failure.

Table-1 : Risk Factors for Cardiac Failure: Framingham Offspring and Cohort Study*

Risk Factor	Age and Risk Factor-Adjusted Hazard Ratio		Prevalence (%)		Population Attributable Risk (%)	
	Men	Women	Men	Women	Men	Women
High blood pressure (≥140/90 mm Hg)	2.1	3.4	60	62	39	59
Myocardial infarction	6.3	6.0	10	3	34	13
Angina	1.4	1.7	11	9	5	5
Diabetes	1.8	3.7	8	5	6	12
Left ventricular hypertrophy	2.2	2.9	4	3	4	5
Valvular heart disease	2.5	2.1	5	8	7	8

*Subjects aged 40-89 year; 18-years follow-up.
From Levy D, Larson MG, Vasan RS, et al: The progression from hypertension to congestive heart failure. JAMA 275:1557, 1996

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Table-2 :
CAUSE OF CHRONIC HEART FAILURE (HF)

Myocardial disease
Coronary artery disease Myocardial infarction* Myocardial ischemia*
Chronic pressure overload Hypertension* Obstructive valvular disease*
Chronic volume overload Regurgitant valvular disease Intracardiac (left-to-right) shunting Extracardiac shunting
Nonischemic dilated cardiomyopathy Familial/genetic disorders Infiltrative disorders* Toxic or drug-induced damage Metabolic disorder* Viral or other infectious agents
Disorders of rate and rhythm Chronic bradyarrhythmias Chronic tachyarrhythmias
Pulmonary heart disease
Cor pulmonable
Pulmonary vascular disorders
High-output states Metabolic disorders Thyrotoxicosis Nutritional disorders (beriberi)
Excessive blood flow requirements Systemic arteriovenous shunting Chronic anemia

* Indicates conditions that can also lead to HF with a preserved ejection fraction.

1. B-Type Natriuretic Peptides (BNP)

BNP is a potent vasodilator; studies :have shown a consistent fall in right atrial, pulmonary artery and pulmonary artery wedge pressure[2•3] with BNP use. In addition, mean arterial pressure and systemic vascular resistance fall while the cardiac index increases. At low doses < 0.01 ug/kg/min the heart rate declines and there is renal artery vasodilation. Based on animal studies BNP is thought to act as a neurotransmitter causing changes in salt appetite, vasopressin secretion from the hypothalamus and angio-tensin II induced water intake.[4] Clinical trials using nesiritide have proved equivocal and meta analysis have not shown conclusive evidence of improved mortality over the short term.[5•6] Present recommendation for nesiritide use by an expert panel chaired by Eugene Braunwald has made the following recommendations:

1. Continuing enrollment in ongoing nesiritide trials.
2. The conduct of large, placebo controlled outcome trials of several thousand patients, adequately powered to detect a 15% difference in mortality compared to standard therapy.
3. Nesiritide infusions should be limited to those patients who are hospitalised and where the benefit outweighs the potential risk of the drug.
4. Nesiritide infusion should not replace diuretics.

Therapeutic Strategies

1. Nesiritide is a useful adjunct to standard therapy for acute decompensated HF especially in patients who are not hypotensive.
2. A bolus of 2μg/kg/min followed by a 0.01μg/kg/min infusion is the recommended starting dose.
3. High dose diuretic use may cause renal dysfunction.
4. High cost, lack of clear clinical benefit beyond other less expensive and more readily titratable agents and potential safety concerns have limited its use.

2. Calcium Sensitizers

Levosimendan is a novel agent that increases myocardial contractility and produces peripheral vasodilatation through myofilament calcium sensitization by calcium dependent troponin C binding and activation of vascular smooth muscle potassium channels. It is available in more than 40 countries.

Dose: Initiate a continuous infusion at a rate of 0.05 - 0.10 μg/kg/min which can be uptitrated to 0.20 μg/kg/min.

In clinical trials[7] levosimendan has been shown to significantly increase cardiac output, reduce pulmonary capillary wedge pressure (PCWP) and after-load and improve dyspnoea. There are contradictory reports of greater incidence of atrial fibrillation and failure of sustenance of early reduction of mortality beyond 180 days. These studies and ongoing trials need to be more completely analysed before changes in current recommendation can be made.

3. Cardiac Myosin Activators

The cardiac myosin ATPase is a structurally distinct component of the molecular motor responsible for myocardial contraction. A number of cardiac myosin activators such as CK-1827452, have been developed which appear to accelerate the strong binding of the activated myosin to actin increasing productive mechanical work as well as inhibiting nonproductive cleavage of ATP by myosin, decreasing ATP consumption. These agents increase cardiac contractility without increasing intracellular calcium transients. In the first human study CK-1827452 administered in an ascending dose protocol with randomised placebo to 34 healthy men, significantly increased left ventricular (LV) ejection fraction and fractional shortening. Current evaluation is being done in Phase II studies.

4. Istaroxime

Derangements in myocardial calcium cycling are associated with systolic and diastolic dysfunction. Istaroxime is a novel compound structurally unrelated to digoxin with a dual mechanism of action: (a) Inhibition of Na+/K+ ATPASE which increases intracellular calcium and inotropy and (b) stimulation of the sarcolemmal calcium pump (SERCA 2a) resulting in more rapid calcium uptake into the sarcoplasmic reticulum which improves myocardial relaxation or Insitropy. In the first in human study of patients with stable chronic heart failure and EF - 40%, randomised with placebo, Istaroxime increased cardiac contratility. Further studies are based on this encouraging result.

5. Natriuretic Peptides

Search continues for agents that will promote natriuresis as well as improve renal function in the clinical setting.

Carperitide : is a recombinant human natriuretic peptide, which has been marketed in Japan since 1995.

Ularitide : Is human recombinant urodilatin, an isoform of ANP, discovered in human urine. Urodilatin is synthesized in the kidney and secreted into the renal tubule where it promotes sodium excretion via natriuretic peptide A receptors. Two large studies[11,12] of altitude demonstrated dose dependent decreases in PCWP, systemic vascular resistance, increases in cardiac output and decreases in patients dyspnoea. These studies have formed the basis of future clinical trials.

6. Adenosine Antagonists

Adenosine acting via the renal aldosterone A1 receptors induces afferent arteriolar vasoconstriction and mediates tubulo-glomerular feedback, all of which decrease GFR. A small cross over study of adenosine antagonist, BG 9719 in chronic HF patients demonstrated that A 1 antagonism could

increase both urine output and GFR and could act synergistically with furosemide producing even greater diuresis without change in GFR[13]. Phase II studies have evaluated another A 1 antagonist (KW-3902) with similar encouraging results Phase III trials will hopefully confirm these promising findings.

7. Vasopressin Antagonists

Two types of vasopressin receptors have been identified.

V_1a : Mediates vasopressin induced vasoconstriction.

V_2: Mediates water resorption from the kidney.

Conivaptan is a combined V_1a and V_2 receptor antagonist that has been shown to significantly decrease PCWP and right atrial pressure as well as increasing urine output.

Tolvaptan and Lixivaptan are selective V_2 receptor antagonists. The ACTIVE-CHF study[15] demonstrated that Tolvaptan treatment of patients with CHF (EF ~ 40%) and fluid overload, significantly reduced body weight and improved serum sodium concentration.

8. Endothelin Antagonists

Endothelin (ETI) is one of the most potent vasoconstrictors and its increase in HF is associated with malignant ventricular arrhythmia and increased mortality. Tezosentan, an ET1 receptor antagonist has been shown to reduce LV filling pressure, decrease after load, increase cardiac output and improve symptoms of dyspnoea.[7] However, large trials have not proved encouraging till date.

Device Therapy

Cardiac resynchronization : Approximately one-third of patients with a depressed EF and symptomatic HF manifest a QRS duration longer than 120 ms. This electrocardiographic manifestation of abnormal inter or intraventricular conduction has been used to identify patients with dyssynchronous ventricular contraction. The' mechanical consequences include suboptimal ventricular filling, a reduction in LV contractility, greater severity of mitral regurgitation and paradoxical septal wall motion. Biventricular pacing or cardiac resynchronization therapy (CRT) stimulates both ventricles nearly simultaneously, thereby improving the coordination of ventricular contraction and reducing the severity of mitral regurgitation. Based on the aggregate of clinical experience, CRT is recommended for patients in sinus rhythm who have an EF less than 35 percent and QRS width more than 120 milliseconds and who remain symptomatic (NYHA Class III or IV) despite optimal medical therapy.

Nonpharmacological Strategies

Our current therapeutic approach to treatment of heart failure relies on symptom relief with medicines and probably device therapy to some extent. There is still scope for further improvement in the field of heart failure treatment and current research is focused on new and exciting fields like the concept of myocardial repair and regeneration and pharmacogenomics.

Myocardial repair and regeneration:

Heart failure may develop as a consequence of myocyte loss or dysfunction, eventually leading to left ventricular remodelling and cardiac decompensation. Replacement of dead or dysfunctional cardiac myocytes through cell based therapies represents a logical and novel option for the treatment of HF.

Stem/Progenitor Cells

Two types of stem cells are used in the treatment schedules of clinical trials of heart failure.

1. Embryonic Stem (ES) Cells
2. Adult stem cells.

Embryonic stem cells have the capacity to give rise to all cell types of the body and are able to form tissues and organs whereas most adult stem cell are more specific and the use of adult stem cells for organogenesis has not yet been explored.

Embryonic stem cells can be propagated in cell culture and by changing the cultivation conditions embryonic stem cells form embryoid bodies. Within an embryoid body approximately 5 to 10 percent of embryonic stem cells differentiate into cardiomyocytes. It would therefore seem that ES cells are ideal candidates for in vivo cardiac repair. However, animal studies have shown a dose-dependent incidence of tumor formation after transplantation of ES cells into mice. Therefore the

safety of ES cells transplantation remains an unsolved question.[16]

Adult stem cells comprise at least three different groups: bone marrow derived stem cells, the circulating pool of stem or progenitor cells and tissue resident stem cells.

Out of these, bone marrow derived stem cells are the best studied and used in most clinical trials. Bone marrow contains a complex assortment of haematopoetic stem cells, mesenchymal stem cells and multipotential adult progenitor cells.

Tissue Engineering

Tissue engineering in its pure sense aims at providing tissue grafts. So far, it has been challenging to generate tissue in vitro with contractile force and at a size sufficient to support the failing heart. Among culture conditions used for generating/creating myocardial tissue in vitro are: (1) implantation of engineered rat heart tissue from neonatal rat cardiomyocytes in rats with myocardial infarction (2) Engineered tissue containing skeletal muscle derived cells[18] and (3) embryonic stem cells for generation of heart tissue in vitro. **In** addition novel biomaterials have been developed to be used as ventricular restraints and to provide scaffolds for in vitro tissue engineering.[19],[20]

Clinical Application of Stem Cells

1. The first clinically relevant cells proposed for cardiac myocytes were skeletal muscle myoblasts, injected directly into the ventricular wal1.[20]
2. Bone marrow is at present the most frequent source of stem cells used clinically for cardiac repair. Bone marrow aspirate contains mixture of cells with varying percentage of haematopoietic stem cells.

Routes of Application

Progenitor cells for cardiac repair can be delivered in different ways:

1. Intracoronary infusion using standard balloon catheters has been used in all clinical trials due to its ease of administration.
2. Injection of cells into the ventricular wall via a percutaneous endocardial or surgical epicardial approach.

Clinical Trial Results

Overall the clinical data available indicate that cell therapy with bone marrow derived cells is feasible and safe at least for the follow-up presently available (up to 5 years in the pioneering studies). None of the studies so far reported an increased incidence of arrhythmia in patients of AMI. However, such has not been the scenario in patients with chronic ischaemia and poor left ventricular function. Life threatening arrhythmias developed in clinical trials.[21] These arrhythmias could be related to lack of electrical coupling of skeletal muscle to neighbouring cardiac myocytes. Therefore, currently the implantation of skeletal myoblasts requires the implantation of an implantable cardioverter-defibrillator (ICD).

Bone marrow derived progenitor cells have been employed in several small non randomised trials for chronic ischaemic HF. Cells have been injected to areas of hibernating myocardium.[22],23 Three such studies have shown a significant increase in global left ventricular ejection fraction associated with decreased end systolic volumes as well as improvement in exercise capacity.

GENE THERAPY

Gene therapy represents another emerging therapeutic approach for the treatment of **HF.** Three elements are necessary for the successful clinical application of any gene therapeutic approach.

1. A vector or packaging system to deliver the genetic material e.g. recombinant adenovirus, adeno virus associated virus.
2. Vector needs to be adequately delivered to the affected tissue(s) e.g. intracoronary and direct injection, pericardial injection.
3. Identify the appropriate gene targets to modulate; The major promising targets for gene transfer have been those genes that regulate the beta adrenergic receptor (AR) signalling pathway and genes that regulate calcium handling in the heart.[24] Considerable work remains to be done with respect to improvements in vector technology, methods for cardiac gene delivery and perhaps most importantly what gene targets are safe to target in clinical trials in **HF** patients.

PHARMACOGENETICS

Given the tremendous heterogenicity that exists in HF patients it is likely that genetic variations play a significant role in determining drug metabolism, disposition and functional activity in HF patients. A beneficial effect in a positive clinical trial implies

that all patients will receive the same degree of benefit from the drug that is given. However, a more likely outcome is that a given therapy will have a markedly positive impact in some patients, a more modest effect in others and probably ineffective or may be harmful in others. Recent advances in the field of pharmacogenetics suggest that a careful analysis of underlying gene polymorphisms within a given patient may enable clinicians to develop personalised therapeutic regimens for HF patients. For example insertion or deletion within the gene the ACE gene or beta or alpha adrenergic receptor genes may influence the pharmacological response in HF patients. It is worth emphasizing that personalizing therapeutic approaches in HF based on genetic background is far from fully developed and will need to be carefully evaluated in suitable patient populations before this type of information can be used to guide clinical practice.

METABOLIC MODULATION

Optimization of myocardial energy utilization represents another unique approach for the treatment of HF. In the normal heart, free fatty acid oxidation is the preferred fuel for production of energy, producing approximately 4 times the ATP per mole of substrate utilized, when compared to glucose. However, FFA oxidation consumes 10-12 percent more oxygen and is therefore likely to prove deleterious under conditions wherein oxygen is a limiting substrate, such as occurs in the failing heart, where glycolysis will be the more efficient pathway. Therefore shifting energy utilization from FFA to glucose would optimise metabolic efficiency, reverse abnormalities in the cellular milieu and improve cardiac function.

The prototype partial inhibitors of fatty acid oxidation (PFOX), etomoxir, oxfenicine, and perhexiline act by inhibiting carnitine palmitoyl transferase1 (CPT1), the gatekeeper of fatty acid entry into the mitochondria. However, in the absence of a negative feedback loop these agents can lead to accumulation of unmetabolized lipids in cardiac myocytes, which may lead to lipotoxicity induced cardiac myocyte cell death. Two other pFOX inhibitors, Trimetazidine and Ranolazine have shown encouraging results in HF patients.[25,26] Although the use of pFOX inhibitors appears promising, it bears emphasis that all of the clinical studies todate are small and have design flaws with lack of long-term outcome data. Accordingly additional studies will be required before this therapy can be used in HF patients.

IMMUNO MODULATION

Over the past decade a variety of different anti-inflammatory strategies have been tried in small clinical trials in patients with chronic HF. Two different anti-inflammatory approaches have not favourably impacted morbidity and mortality in clinical trials.

(a) Targeted anti-cytokine approach with a tumor necrosis factor (TNF) antagonist in the RENEWAL Trial [Randomised Etanercept Worldwide Evaluation].27

(b) Intramuscular injections of autologous blood in the ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy) Trial.[28] There have been encouraging results in the use of HMGCoA reductase inhibitors (statins) as adjunct to conventional treatment of CHF. In addition small non-randomised trials have shown some benefit for therapy with immunoadsorption.[29] Large clinical trials are required before recommending any of these therapies for HF. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) and GISSI - HF Trials will provide more definitive answers to the role of statins in HF.

CONCLUSION

Clearly HF is a dynamic disease process with new trials underway and new discoveries ongoing. HF poses tremendous challenge and there are substantial opportunities to improve care. It has been clearly documented that not enough has been done to ensure the use of evidence-based, guideline - recommended therapies and optimize care in patients with HF. Future therapies involving newer drugs and device therapies provide considerable hope for the outcome of chronic HF patients. Non pharmacological strategies like myocardial repair and regeneration, tissue engineering and gene therapy are novel approaches that hold considerable promise for the emerging therapeutic trends of HF.

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Current Concept

USE OF PCR AS A DIAGNOSTIC TOOL IN SICKLE CELL CLINIC

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INTRODUCTION

The polymerase chain reaction (PCR) is a technique widely used in molecular biology, microbiology, genetics, diagnostics, clinical laboratories, forensic science, environmental science, hereditary studies, paternity testing, and many other applications. It was invented by Kary Mulis in the year 1983 [1]. The PCR reaction takes place in a machine called PCR machine, also called Thermal Cycler since the basic principle of the technique lies in changing the temperature of the PCR mixture in a controlled cyclic manner. The purpose of a PCR is to make a huge number of copies of a ribonucleic acid both DNA and RNA.

PCR working principle

PCR is used to amplify specific regions of a DNA/ RNA strand. This can be a single gene, a part of a gene, or a non-coding sequence (intron). Most PCR methods typically amplify DNA fragments of up to 3 kilo base pairs (kb), although some techniques allow for amplification of fragments up to 40 kb in size [2,3].

PCR is commonly carried out in a reaction mixture of 10-200 ìl in small reaction tubes (0.2-0.5 ml volumes) in a thermal cycler. The thermal cycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction. Many modern thermal cyclers make use of the Peltier effect which permits both heating and cooling of the block holding the PCR tubes simply by reversing the electric current. Thin-walled reaction tubes permit favorable thermal conductivity to allow for rapid thermal equilibration. Most thermal cyclers have heated lids to prevent condensation at the top of the reaction tube. Older thermocyclers lacking a heated lid require a layer of oil on top of the reaction mixture or a ball of wax inside.

Traditionally, PCR is performed in a tube and when the reaction is complete the products of the reaction (the amplified DNA fragments) are analysed and visualised by gel electrophoresis. However, Real-Time PCR permits the analysis of the products while the reaction is actually in progress. This is achieved by using various fluorescent dyes which react with the amplified product and can be measured by an instrument the tube.

PCR Thermal cycling steps:

There are three major steps in a PCR, which are repeated for 30 or 40 cycles. This is done on an automated cycler, which can heat and cool the tubes with the reaction mixture in a very short time.

- *Initialization step*: This step consists of heating the reaction to a temperature of 94-96°C (or 98°C if extremely thermostable polymerases are used), which is held for 1-9 minutes.
- *Denaturation step*: This step is the first regular cycling event and consists of heating the reaction to 94-98°C for 20-30 seconds. It causes melting of DNA template and primers by disrupting the hydrogen bonds between complementary bases of the DNA strands, yielding single strands of DNA.
- *Annealing step*: The reaction temperature is lowered to 50-65°C (depending on the primer used) for 20-40 seconds allowing annealing of the primers to the single-

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stranded DNA template. Typically the annealing temperature is about 3-5 °C below the Tm (melting temperature) of the primers used [4]. The polymerase binds to the primer-template hybrid and begins DNA synthesis.

- *Extension/ elongation step*: The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme [5]. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5' to 3' direction, condensing the 5'-phosphate group of the dNTPs with the 3'-hydroxyl group at the end of the nascent (extending) DNA strand.

  The extension time depends both on the DNA polymerase used and on the length of the DNA fragment to be amplified.

  The amount of DNA target is doubled, leading to exponential (geometric) amplification of the specific DNA fragment.

- *Final elongation*: This single step is occasionally performed at a temperature of 70-74°C for 5-15 minutes after the last PCR cycle to ensure that any remaining single-stranded DNA is fully extended.

- *Final hold*: This step at 4-15°C for an indefinite time may be employed for short-term storage of the reaction.

The PCR amplified product is visualized under UV light against a standard DNA ladder/ marker and the results can be documented by a Gel Documentation System.

PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications. These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes; the diagnosis of hereditary diseases; the identification of genetic fingerprints (used in forensic sciences and paternity testing); and the detection and diagnosis of infectious diseases.

Sickle cell hemoglobinopathy is a common problem and is prevalent in 13 out of 30 districts in Western Orissa. The gene frequency is 15.1% in certain caste populations(Kar). Around 1200 patients of Sickle Cell Disease attend to the outdoor of V.S.S. Medical College, Burla which is the tertiary care health centre of Western Orissa. Patients of Sickle Cell Disease attend to the various specialities of this institution and the annual admission rate is 300 patients per year. Besides Sickle Cell Disease malaria is a common public health problem in Western Orissa. Majority of these malaria cases are caused by Plasmodium falciparum infection with significant morbidity and mortality. Malaria is an important cause of Vaso-occlusive crisis in patients of Sickle Cell Disease. It also adds to mortality of these patients.

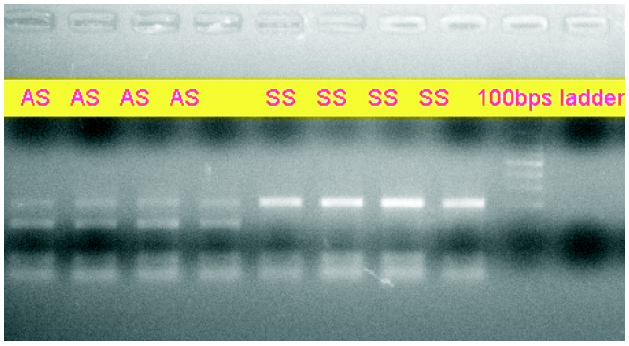
Keeping the above problem in view the Department of Biotechnology, Government of India, New Delhi has funded a research project on sickle cell disease entitled “Study Of Morbidity Pattern In Sickle Cell Disease In Western Orissa And Its Correlation With Genetic Factors, Fetal Hemoglobin Concentration And Different Epistatic Factors Like Malaria” in the V.S.S. Medical College, Burla. Under this project we havee setup a Molecular Biology laboratory at the sickle cell clinic of this institution. We are carrying out molecular diagnosis of sickle cell disease and other hemoglobinopathies and malaria by PCR.

PCR based study of Hemoglobinopathies and Infectious disease (Malaria) in Molecular Biology laboratory at Sickle Cell Clinic, V.S.S.Medical College, Burla :

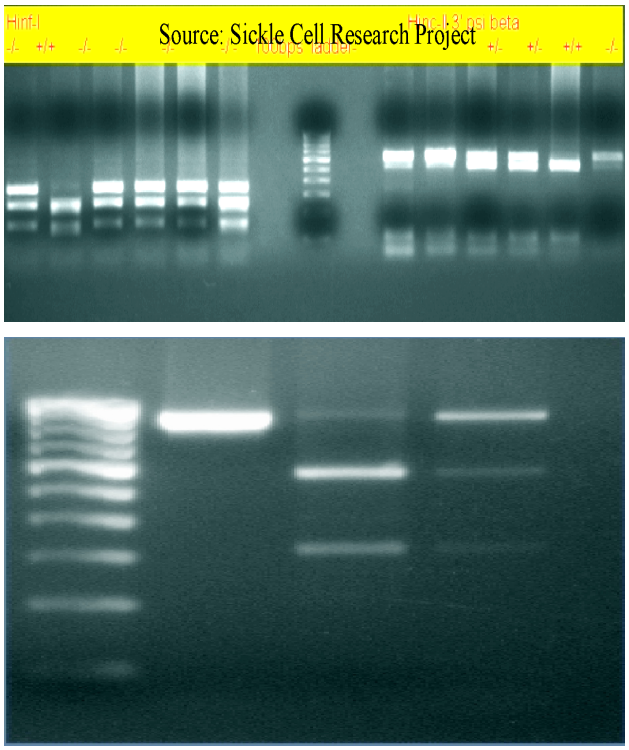
RFLP-PCR:

- Detection of structural hemoglobin variants like HbS (sickle cell mutation), HbD using DdeI and EcoRI restriction enzymes respectively.
- RFLP based genetic diversity study of Beta globin gene cluster (haplotype analysis) is done for HincII å, XmnI 5’γG, HindIII ãG, HindIII ãA , HincII øâ, HincII 3’øâ, RsaI 5’â, AvaII â & HinfI 3’â restriction sites (Mukherjee et al, 1997) .

DdeI restriction digestion for detection of Sickle cell disease.



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



100bp control (—) (+-)

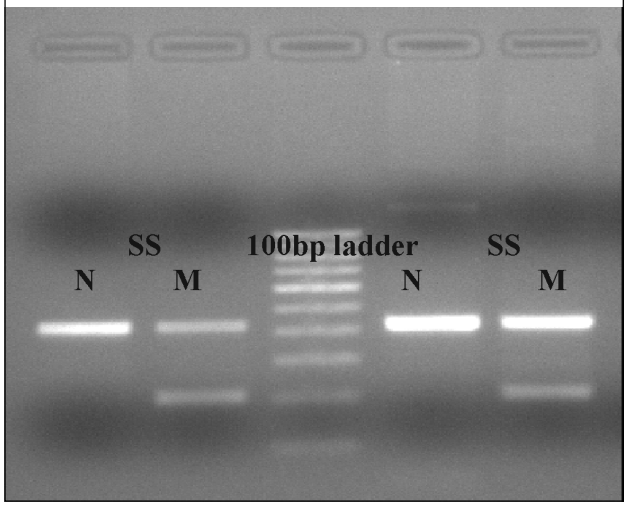
Detection of HbD by restriction digestion with enzyme EcoR1. (—) indicates absence of HbD mutation; (+-) indicates presence of HbD mutation in one strand

ARMS-PCR:

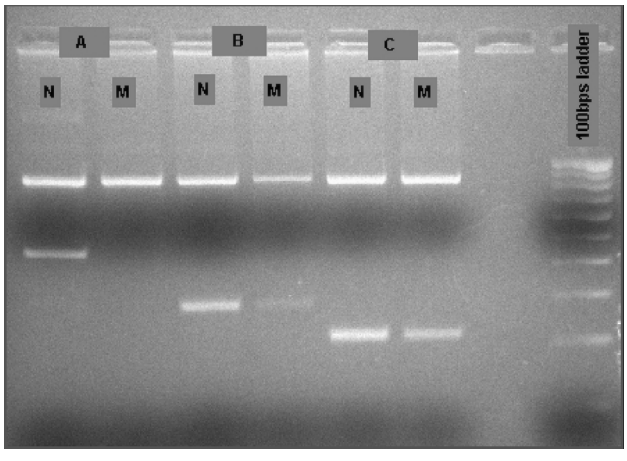
- Detection of HbS (sickle cell mutation), HbC, and beta thalassemia mutations (IVS1-1nt G-T, IVS 1-5nt G-T, cd 8/9 +G, cd 41/42 (-TCTT), HbE (cd 26G-A) & 619bps deletion)

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

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



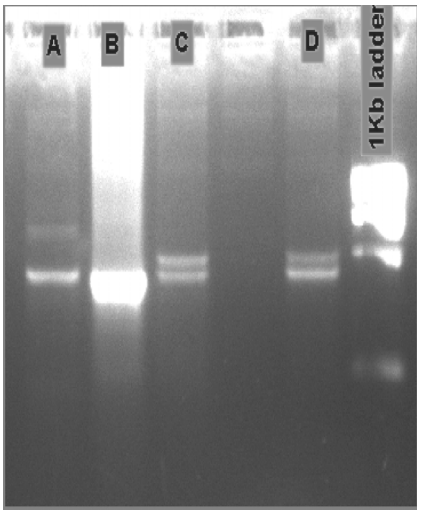
Thalassemia detection by ARMS PCR: Sample A: Homozygous (normal) IVS 1-1nt G-T , sample B: Heterozygous IVS1-5nt G-C, Sample C: Heterozygous cd 8/9 +G



Source: Sickle Cell Research Project

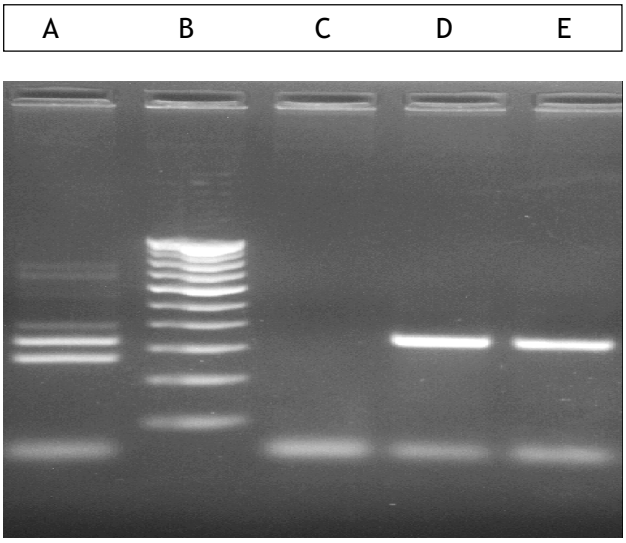
Multiplex PCR:

- Detection of alpha globin gene mutations (alpha gene 3.7 and 4.2 deletion)[10]
- Species detection of Plasmodium parasite i.e., falciparum & vivax [11].



Alpha Thalassemia detection by Multiplex PCR: LaneA - normal alpha2 gene, LaneB- alpha4.2-alpha 4.2 double gene deletion, LaneC & D-alpha 3.7 deletion (*Source: Sickle Cell Research Project*)

Source: Sickle Cell Research Project

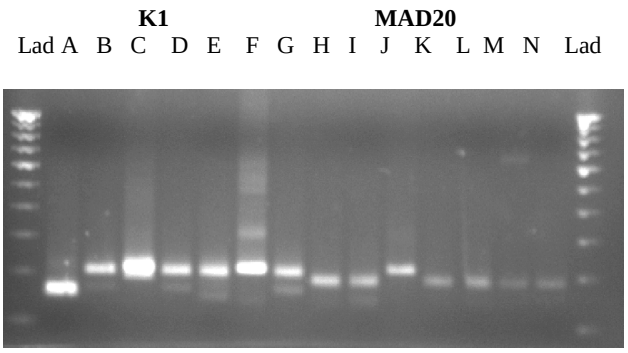


Detection of Plasmodium sp. Infection: Lane A: Mixed (P.falciparum & P. vivax) infection (346 & 266 bp); Lane B: 100 bp ladder LaneC: Negative control Lane D * E:P.falciparum (346 bp)

Source: Sickle Cell Research Project

Nested PCR:

- Detection of multiplicity of P.falciparum infection and multiclonal infection on the basis of genetic diversity of msp1 an msp2 genes of P. falciparum.



P. Falciparum genetic diversity: Lane A-G: diversity in K1 allele of MSP1 allele; Lane H-N: diversity in MAD20 allele of MSP1 allele (*Source: Sickle Cell Research Project*)

P. Falciparum genetic diversity: Lane A-G: diversity in K1 allele of MSP1 allele; Lane H-N: diversity in MAD20 allele of MSP1 allele (*Source: Sickle Cell Research Project*)

In the Sickle Cell Clinic & Molecular Biology Laboratory, V.S.S. Medical College, Burla PCR based methodology has been employed for detection of the following cases:

	Genetic Analysis	No cases detected
1.	Sickle cell disease	1235
2.	Beta globin gene cluster analysis	292
3.	Sickle –β Thalassemia	98
4.	Alpha Thalassemia	200
5.	HbC hemoglobinopathy	3
6.	HbD hemoglobinopathy	15
7.	HbE hemoglobinopathy	8
8.	Differential detection of P.falciparum & P.vivax	80
9.	Genetic diversity of msp1 ansd msp2 gene of P.falciparum	60

In conclusion PCR is the most versatile molecular diagnostic tool which can be used for confirmation of various genetic and infectious diseases like HbS , Alpha & beta thalassemia, other structural hemoglobinopathies. Proper diagnosis of these diseases can help for better management and treatment of the complications of the otherwise life threatening diseases. Besides PCR has got a very important role to play in confirmatory diagnosis of malaria, study of drug resistance and in molecular study which will help in development of candidate vaccine.

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Case Report

AN UNUSAL CASE OF SPINAL NEUROCYSTICERCOSIS -A CASE REPORT

B. K. Barik*, H.N. Praharaj**

ABSTRACT

A young male presenting with features of high cervical cord compression, subsequently found to have intramedullary neurocysticercosis, a rare entity.

Key words : *Neurocysticercosis (NCC), Spinal neurocysticercosis (SNCC), intra medullary, Tinea Solium, MRI.*

INTRODUCTION

Neurocysticercosis is most common parasitic infestation of CNS[1]. The incidence of spinal involvement is 1.5-3%[4]. Spinal neurocysticercosis usually appears due to mass effect. Most cases occur in subarachnoid space but intra medullary location is extremely rare[1]. Here we report a case of intramedullary neurocysticercosis (reported about 50 cases sofar)[4] and discuss the disease.

CASE REPORT

A 26 year named BC , from Salepur presented to this hospital in June 2008 with c/o of head ache & neck pain(1 month), numbness of right side of face(15 days),inability to hold objects properly in right hand (15days).He was alright 1 month back. Started with continuous headache relieved with analgesics, without associated vomiting, nasal stuffiness or blurring of vision. After 15 days he developed numbness of right side of face & noticed weakness of right hand which gradually progressed so that he could not hold any object properly. There was no history of fever, root pain, or convulsion. There was no bladder or bowel involvement. There was no h/o Diabetes, trauma, hypertension or tuberculosis. Family history was not suggestive. He was not habituated to alcohol or smoking. There was no contact history& he was unmarried.

On examination he was of average built having BP- 130/80 mm of Hg; pulse 68/ min, regular; without pallor, jaundice or lymphadenopathy.

CNS examination of the patient revealed conscious with normal higher functions including speech. All the cranial nerves were intact except diminished pain sensation on right side of face. Motor system showed normal bulk with increased tone of muscles in legs & arms. Power was grade V in both lower limbs but grade IV in both upper limbs. Hand grip was weak on both sides, right >left. Bicep & triceps reflexes were exaggerated on both sides with normal supinators. Knee & ankle jerks on both sides were exaggerated. Plantar was extensor on right but flexor on left. Sensory system was normal. Skull & spine was normal without any meningeal or cerebellar signs. Fundus was normal.

Other systems like CVS, GIT, respiratory did not reveal any abnormalities.

Routine investigations like Hb%, DC, TLC, FBS, urea, creatinine serum K+, Na+ were normal. ESR was 25/1st hour & Mx was negative. Chest X-ray & cervical spine X'ray were normal. CSF study was normal. MRI of brain & spinal cord showed ring enhancing tiny lesions at cervico medullary junction inside the medullary central canal with consequent syrinx formation. (Figure-1, Figure-2) Anticystocercal antibody was positive.

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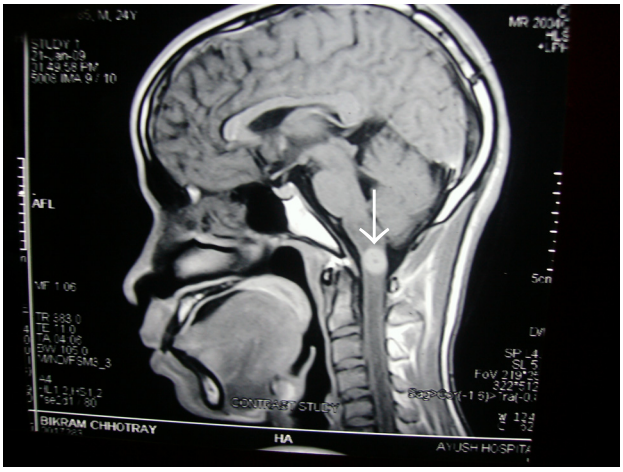

Figure-1 (Intra medullary ring enhancing lesion at Cervico medullary junctin)

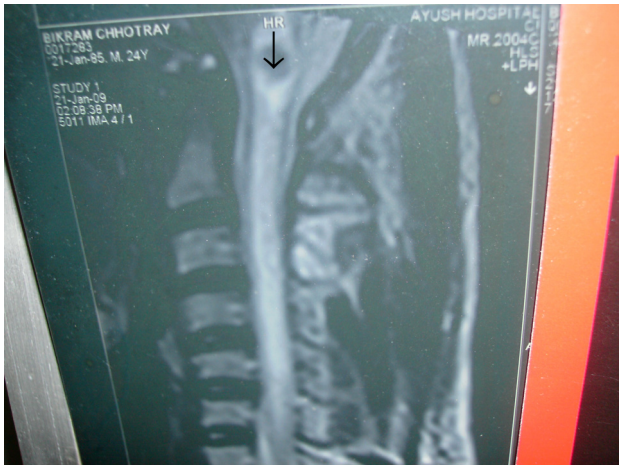

Figure-2 (Syrinx formation)

A young male presenting with gradual onset of assymetrical weakness of upper & lower limbs, with headache & diminished pain sensation of right side of face without significant involvement of lower limbs with features of UMN involvement in the form of hypertonia & hyper reflexia of all limbs below C4 without sensory level a provisional diagnosis of high cervical cord compression (intramedullary) was thought of, probably involving trigeminothalamic tract(right) & corticospinal tract below pyramid (right). With the investigations the patient was diagnosed as a case of SNCC with obstructive syringomyelia.

The patient was treated with Albendazole 400 mg twice daily for 28 days with oral prednisolone in tapering dose.In the next followup after one month he complained of progressive weakness of upper limbs with no response to Albendazole.Hence he was advised for neurosurgical consultation for excision of the cyst.

DISCUSSION

Neurocysticerosis is the most common parasitic infestation of CNS caused by ingestion of eggs of *Taenia Solium*[3].*T.Solium* has its definite host in human being where adult worm stays in intestine laying eggs which are taken by pigs who are intermediate hosts. The embryo cross the intestine and reside in CNS, muscles, eyes and skin as cysticerci.Human beings have the disease when they ingest the eggs instead of Pigs. The eggs hatch in the intestine and develop into cysticerci in the above mentioned organs.

Usual organs involved in Neurocysticerosis are brain, eye, subcutaneous tissues.Common presentation of cysticerosis of brain are headache, seizure and focal neurological deficit.

Spinal neurocysticerosis is a rare presentation; the incidence ranging from 0.7-5.85%[1,3].Spinal forms have been identified in vertebral, extradural, intradural, intramedullary regions.Intramedullary cysticerosis is very uncommon[1]. Migration of the cysticercus through the ventriculo-ependymal pathway and haematogeneous dissemination has been identified as pathogenic mechanism[1,4].

In absence of previous history or subcutaneous nodule it may be difficult to suspect clinically intramedullary cysticerosis.High eosinophil count with soft tissue calcification though suggestive is rare.Result of surgery has not been encouraging due to parenchymal gliosis as a result of toxic waste from larva, pachymeningitis and vascular insufficiency.

But in the era of microsurgery good outcome has been reported. Medical treatment of intramedullary lesions can be considered in patients of stable neurological status but impossible in acute or progressive cases.Post operative anticerceal drugs should be given as it is a generalized disease with focal manifestation[1].

SNCC is rare compared to intracranial as cysticerci do not pass through subarachnoid space at cervical level due to its size(sieve effect).Besides CSF reflux at craniovertebral junction propels floating cysts back into intracranial space than spinal canal.

Several possible mechanisms of spinal invasion are:-

(a)Ventricular cysticerci pass through Magendie or Luschka foramen, migrate by gravity through subarachnoid space to inoculate spinal cord commonly cervical region.

(b)Haematogeneous spread explain intramedullary lesion,commonly thoracic area due to increased blood flow.

(c) Intraventricular hypertension enables migration through a dilated ependymal canal into spinal cord explaining intramedullary invasion.Other favorable conditions favoring spinal invasion may be due to NCC-related hydrocephalus and/or meningitis, use of antiepileptic drugs like Carbamazepine or Phenytoin which can after immune function leading to parasitic infestation[3].

The location of mass lesion, its size, the inflammatory response generated by cyst breakdown are important factors for management.Brain blood flow is 100fold greater than spinal explaining more intraventricular lesion.In spinal form thoracic region having more blood flow explains high incidence.The location of cysticerci is cervical - 34%,thoracic - 44.5%, lumbar -15.5% and sacral- 6%.MRI is the investigation of choice.

Concurrent intracranial lesion are seen in spinal involvement. As long as cysticercus is viable there is relative host immune tolerance. Massive antigen response occurs with death of parasite with intensification of immune/inflammatory response. Surgery is required for diagnosis and treatment though outcome is mixed. Albendazole or Praziquantel with or without steroid are used. Albendazole is preferred as blood level are increased with steroid.Spinal intramedullary cysticercosis represents a challenge for diagnosis & surgery. Patient recovery is variable. Despite promising reports the safety and efficacy of medical treatment remains unproved[4].

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   Focal spinal intramedullary cysticercosis.

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Case Report

SPINAL EPIDURAL ABSCESS PRESENTING AS SEVERE SEPSIS –A CASE REPORT

P.K. Thatoi*,N.Dhal*, R. Mohanty, B.K. Das***, S. Mishra******

ABSTRACT

A young male presented with severe back pain, continued fever and difficulty in walking. Clinical examination revealed Features of sepsis and paraplegia. Laboratory investigation showed neutrophillic leukocytosis with raised ESR. MRI of spine showed Epidural abscess.

Key words : *Spinal cord, Epidural abscess, sepsis.*

Spinal epidural abscess is a rare condition that can be fatal if left untreated. The medical literature contains only 24 reported series of at least 20 cases each (1,). Risk factors for epidural abscess include immunocompromised states such as uncontrolled diabetes mellitus, chronic alcoholism, malignancy, HIV infection, as well as spinal procedures including epidural anaesthesia and spinal surgery or trauma. The signs and symptoms of epidural abscess are non-specific and can range from low back pain to paraplegia. The treatment of choice in most patients is surgical decompression followed by four to six weeks of antibiotic therapy. The most common organism in spinal epidural abscess is Staphylococcus aureus.

Illustrative Case

An 18 year old male presented with severe back pain for 12 days, continued fever for 10 days and difficulty in walking for last 2 days. Patient had no history of trauma or spinal procedures. He is not a diabetic or hypertensive with no history of tuberculosis or any chronic disease.

The patient was alert and oriented, and the positive physical findings included pulse -104/min, respiration rate -28/min, blood pressure-90/70 mmHg, grade-one power around all joints of both lower extremities with absence of deep tendon reflexes, plantar B/L flexor. Tenderness on palpation of lower thoracic spine and upper lumbar region with no external evidence of injury. He had retention of urine.

His chest and abdominal radiographs were unremarkable. Lab investigations showed leukocytosis e.g. TWBC 22,000 with 90% neutrophils and an elevated ESR - 100mm in 1st hr, other routine blood investigations were normal. Patient was hospitalized and treated as a case of severe sepsis with IV fluids and broad spectrum antibiotics, but the source of sepsis was not identified.

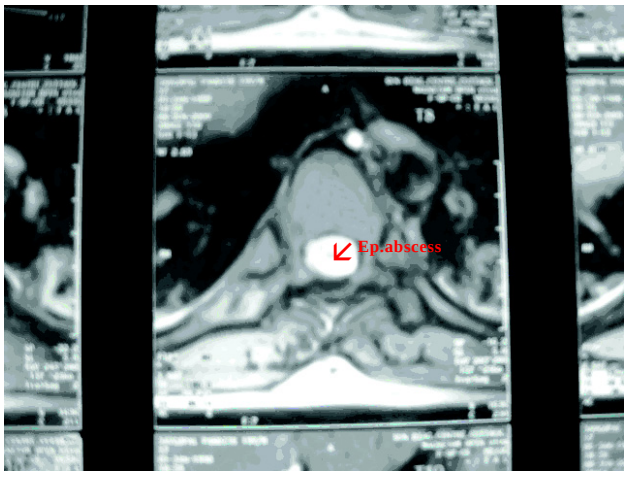

Fig.1 (Epidural abscess)

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****Prof of Neurosurgery, SCB Medical College,Cuttack.

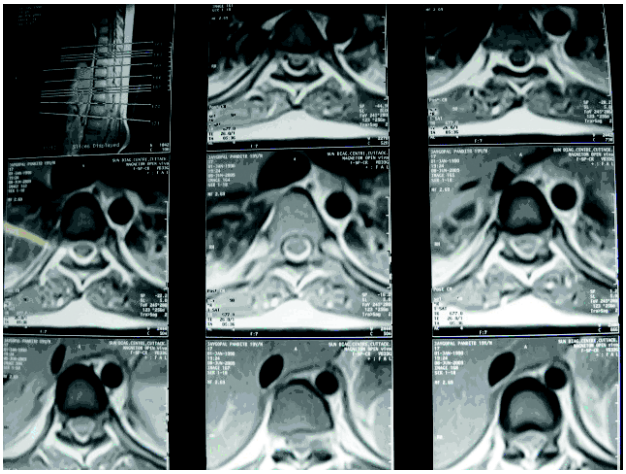

Fig.2

On the third day of hospitalization MRI of spine (Fig.1 & 2) showed spinal epidural abscess; posteriorly placed, extending from T6 to L3 vertebral level. Subsequently the patient was transferred to neurosurgery department where surgical decompression was done. The pus culture and sensitivity report showed Staph.aureus , and sensitive to Imipenem & gatifloxacin . The patient improved gradually, his lower limb power became grade-three on 10th postoperative day. He was discharged with two months of oral antibiotics.

DISCUSSION

In this patient there was no obvious risk factor for spinal epidural abscess. The diagnosis must be made promptly because delay in treatment can result in irreversible neurologic damage. The presentation of spinal epidural abscess can be nonspecific. Fever, malaise and back pain are most consistent early symptoms. Local tenderness, with or without neurologic deficit, is the usual physical finding, and leukocytosis may be the only abnormal laboratory finding. Both surgery and medical treatment produce good outcomes when patients are treated early.

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Case Report

ATYPICAL PRESENTATION OF MULTIPLE MYELOMA

Gandharba Ray*, Bijaya Laxmi Parija, Purna Chandra Dash***, N. R. Murmu*****

ABSTRACT

A 30 year female admitted with generalized bone pain, loss of weight and severe anemia was diagnosed as a case of multiple myeloma on the basis of bone marrow examination.

Key words : *Multiple myeloma, Young age, Negative M band, Non Secretory Multiple Myeloma*

INTRODUCTION

Multiple myeloma (MM) represents a malignant proliferation of plasma cells derived from a single clone that accounts for about 1% of malignant disorder. It results in a number of organ dysfunction and symptoms of bone pain, pathological fracture, renal failure, susceptibility to infection, anemia, hypercalcemia and occasionally clotting abnormalities, neurologic symptoms and manifestations of hyperviscosity. MM has strong correlation with age and risk increases with age peaking at about 60-70 years. MM is rare in patients of < 40 years. Here we report a case of MM at the age of 30 with negative 'M' band in serum electrophoresis.

CASE REPORT

A female of 30 years presented with generalised bodyache and low backache with loss of appetite and loss of weight for 4 months. There was no history of fever, bleeding diathesis.

On examination, she was found to have severe pallor, blood pressure (110/70 mmHg), Temperature (98^0 F), generalised bony tenderness, No lymphadenopathy, no purpura, no hepatosplenomegaly and all other system examination revealed no abnormality.

Laboratory Investigations :

Hb% = 6 gm%, ESR = 170 mm in first hour

TLC = 9800/cmm, DC = N - 60%, L – 35%, E – 2%, M – 3%

Peripheral Smear Comment = RBC - Mild hypochromia, anisocytosis, marked degree of rouleaux formation

Platelet = Adequate, WB Series = Normal, No premature cells, FBS = 100 mg%

Serum Urea = 260 mg%, Serum Creatitine = 5.4 mg%, Serum Calcium = 10 mg%

LFT = Serum Bilirubin (Total) = 0.6 mg%,

AST = 44 IU/ml, ALT = 45 IU/ml, ALP = 200 IU/ml

Ultra Sound of Abdomen and Pelvis = Normal

Urine Bence Jone's Protein = Negative

Serum electro phoresis for M Band = Negative

X-ray of Skull = Shows punched out lesion in skull (Fig.-1)

X-ray of Pelvis Joint = Rarefaction and multiple osteolytic lesion(Fig.-2).

Bone marrow Examination = Hyper cellular marrow with pleomorphic myeloma cells upto 80%.

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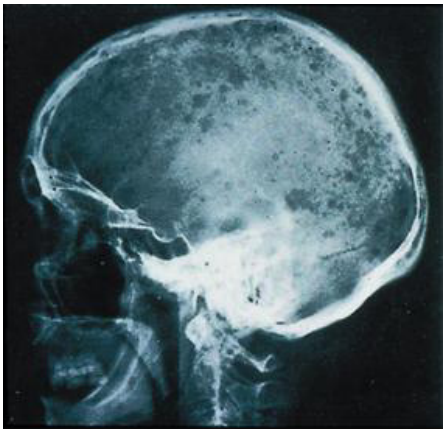
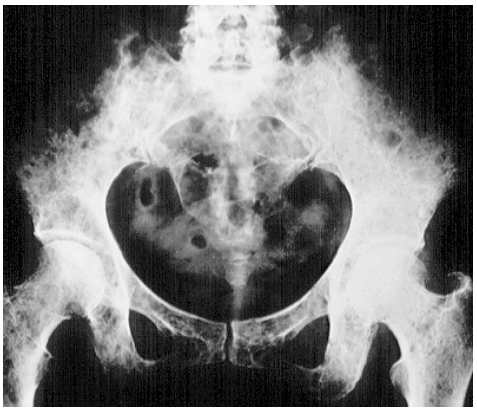
(Fig.-1)
X-ray of Skull showing punched out lesion



(Fig.-1)
X-ray of B/L Pelvic Joint Showing osteolytic lesion



Patients was diagnosed as case of multiple myeloma because of bone pain, anemia, high ESR, raised Sr. Calcium, Multiple osteolytic lesion in skull and pelvic joint and plasma cell > 80% in BM Examination. Patient was put on thalidomide (200 mg) daily and Dexamethasone (40 mg) daily for 4 days in every 15 days interval and was discharged. On follow up after 2 months, there was improvement in bone pain, ESR was decreased, and Sr. urea and Sr. Creatinine decreased.

DISCUSSION

Multiple myeloma is a disease of elderly. But literature shows the percentage of multiple myeloma in younger age group < 40 years is only 3.3 %.

The Clinical course in young individual is generally indolent and survival rate is longer. Our patient although presented in a severe form but the response to treatment was very good.

Patient was diagnosed as a case of multiple myeloma but serum electrophorosis showed negative M band. It is described in the literature that Non-secretory multiple myeloma is a variant of classical form of multiple myeloma and they have a similar clinical presentation except for the absence of Monoclonal Gammopathy. It accounts for only 1-5% of all cases of MM.

Two types of Non-secretory multiple myeloma have been described in the literature. In the first type, the plasma cells produce Immunoglobulin but are not able to secrete it out of the cell. This is known as Producer type or True non-secretory myeloma. In the Non-producer type plasma cells are unable to produce immunoglobulin.

Several hypothesis have been proposed regarding the pathogenesis of Non-secretory multiple myeloma. The Non-producer type may result from problems with the assembly process of protein, thereby lead to difficulty with immunoglobulin heavy and light chain synthesis. In the Producer type the protein synthesis mechanism may be functioning but rapid degradation of the immunoglobulin may follow.

Clinically, when a patient is suspected as case of multiple myeloma only negative serum electrophoresis for M band does not exclude the diagnosis of multiple myeloma. So Bone marrow examination always to be done to exclude the diagnosis of multiple myeloma.

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Case Report

ACUTE PANCREATITIS – A RARE COMPLICATION OF SICKLE CELL DISEASE

***Ayaskanta Kar, **Manoj Kumar Mohapatra, ***Manas Kumar Panigrahi**

ABSTRACT

Acute pancreatitis is a rare complication of sickle cell disease (SCD). A 21 year old male of SCD complicated with acute pancreatitis as a manifestation of vasoocclusive crisis has been reported here in view of its rarity.

***Key Words** : Sickle cell disease, Acute Pancreatitis, Vasoocclusion.*

INTRODUCTION

Sickle cell disease is one of the most common hemoglobinopathies, characterized by chronic hemolytic anaemia and vasoocclusive painful crisis.[1] The pathogenesis is due to point mutation in the β globin gene that changes the sixth aminoacid from glutamic acid to valine in the β chain of globin producing abnormal sickle hemoglobin (Hbs).[2] The tendency of deoxygenated sickle hemoglobin to undergo polymerization underlies the innumerable expression of the disease.[3] Virtually every organ system of the body is subjected to vasoocclusion which accounts for the majority of clinical manifestation of the disease and characteristic acute and chronic multisystemic failure. Acute pancreatitis has been described as a rare manifestation of vasoocclusive painful crisis.[4,5]

CASE REPORT

A 21 years old male patient presented to emergency dept. of V.S.S. Medical College, Burla in July 2008 with complaints of pain abdomen, vomiting for two days. The pain was over the epigastrium and around the umbilicus, moderate intensity, dull aching and was radiating to back. He was a known case of sickle cell disease for last 10 years and was on folic acid. He had undergone surgery for avascular necrosis of head of femur of right side one year back in this medical college. No past history of similar attack. He is not an alcoholic.

On examination, the patient was of average body built, there was icterus, pallor, pulse rate – 90/mt, BP – 110/70 mm of Hg, temp. – 100°F, respiratory rate – 20/mt. Abdominal examination showed epigastric tenderness, without any local rigidity and guarding and rebound tenderness. There was no obliteration of liver dullness. Bowel sounds were sluggish. Examination of other systems revealed no clinical abnormality. Laboratory investigations were Hb – 11.2gm%, TWBC – 7,400/cmm, with differential count of N 72%, L 25%, E 3%; FBS – 66mg%, Serum (Sr.) biliruin – 0.9 mg/dl, SGOT 151 U/L, SGPT – 107 U/L, Alk. Phosphatase 189 U/L. Sr. urea 31 mg%, Sr. Creatinin 0.7mg%, Sr. Na+ 143 mmol/L, Sr. K+ 5.0 mmol/L, Sr. calcium – 1.17 mmol/L, Sr. Amylase – 4497.0 IU/L& Sr. Lipase – 1780.0 U/L. Sr. Triglyceride – 125.7mg%; Hb electrophoresis showed 'SS' band; HPLC showed Hb A_0 – 4.9%, HbA2 – 2.2%; HbF – 26.0%, Hb'S' window – 66.1%, USG of abdomen revealed enlarged and hypoechoic pancreas (Fig.1) with collection in the pelvic cavity, moderate splenomegaly, normal biliary tree, no gallstones. Contrast enhance CT scan of abdomen revealed diffuse swelling of whole pancreas with homogenous contrast enhancement (Fig. 2), without any focal hemorrhage or calcification noted. Straight X-ray of abdomen showed "Colon cutoff" sign (Fig. 3). In view of the clinical picture and investigations a diagnosis of SCD complicated with

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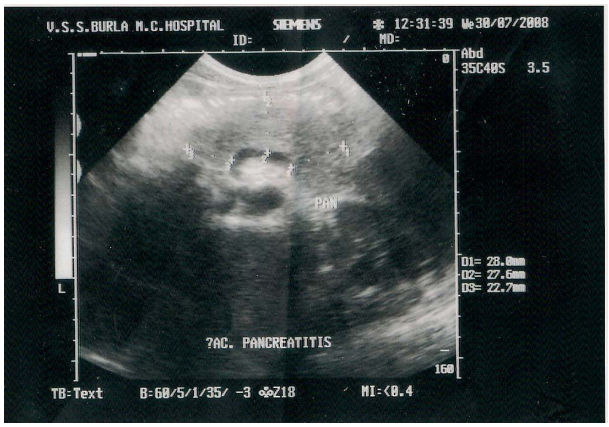

Fig.1

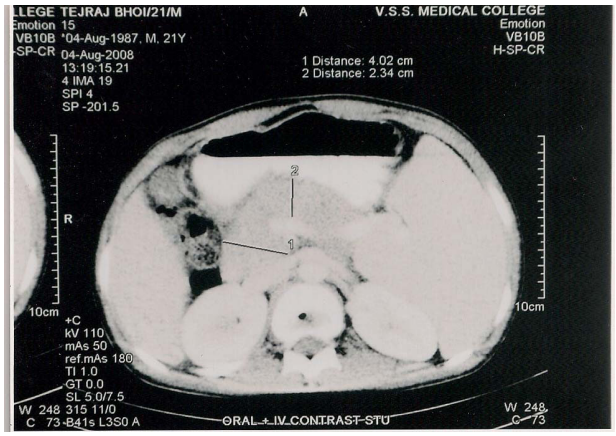

Fig. 2

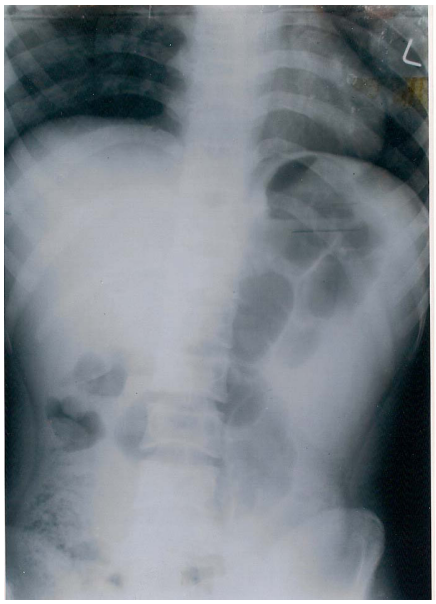

Fig. 3

acute pancreatitis was made and treated accordingly. He received inj. Piperacillin and Tazobactam, Inj. Pantoprazole, IV fluids, and parenteral nutrition. Over the next several days his pain resolved and oral feeding was resumed and patient was discharged.

DISCUSSION

Acute pancreatitis is an acute inflammatory process of the pancreas with varying involvement of other regional tissues or remote organs.[6] Mild form consists of minimal or no organ dysfunction and severe form manifests as organ failure and / or local complications such as necrosis, abscess and pseudocyst formation. Amongst common etiologies of acute pancreatitis; gallstones and alcohol intake comprises 70% of the cases.[6] Other etiologies being hypertriglyceridemia, blunt abdominal trauma, post ERCP, post abdominal surgery, drugs (azathioprine, Sulfonamide, Valproic Acid, tetracycline) and sphincter of Oddi dysfunction.[7] There are only few reports of SCD causing acute pancreatitis.

In sickle cell disease the abnormal hemoglobin (Hbs) when deoxygenated form a gelatinous network of fibrous polymers that stiffen the erythrocyte membrane and they lose pliability to traverse the small capillaries.[2] Sickle red cells demonstrate abnormal adherence to vascular endothelium,[3] hence clog the small capillaries and cause vasooclusion and tissue ischemia, which is the dominant component of the clinical course. Pathogenesis of acute pancreatitis in SCD are microvessel occlusion with resultant ischemia and activation of pancreatic enzyme and injury to the pancreatic tissue,[1] endothelial damage leading to microthrombi and ischaemia and subsequent triggering of pancreatic auto digestion[8]; biliary obstruction due to pigmentary gall stone.

Abdominal pain is a common component of sickle cell painful crisis and is attributed to occlusive small infarct of mesentery and abdominal viscera.[1] Other gastrointestinal complications are Budd-Chiari syndrome, pigmentary gall stone etc. The clinical feature of abdominal pain due to sickle cell vasoocclusive crisis may be indistinguishable from those of acute intra abdominal disease process, such as acute cholecystitis, appendicitis, splenic sequestration. Acute pancreatitis is rarely included

as a cause of pain abdomen in patients with SCD.[1] Diagnosis of acute pancreatitis is based on the presence of abdominal pain, nausea, vomiting, fever, tachycardia and laboratory studies frequently reveal leucocytosis, hypocalcemia, hyperglycemia.[7] The diagnosis is confirmed by the biochemical markers of pancreatic injury as evidenced by three fold or greater elevation of serum amylase and/or lipase.[7] Serum lipase has higher sensitivity and specificity. CT scan is a reliable and non invasive imaging technique to evaluate pancreas. CT scan can confirm the clinical impression of acute pancreatitis even in the face of normal serum amylase level.[7] Contrast enhanced CT is the diagnostic technique of choice because of its ability to demonstrate presence and extent of necrosis. Plain radiograph of abdomen is a non specific modality of investigation and shows no abnormality in mild case to localized Ileus (sentinel loop) or "Colon cut off" sign in more severe disease.[6] Ultrasonography is done to evaluate the gall bladder. Pancreas is usually diffusely enlarged and hypoechoic in USG study.[6]

In this case report, we described a patient with SCD who developed acute pancreatitis as evidence by more than three fold increase in serum amylase to lipase levels, USG abdomen and contrast enhanced CT scan of abdomen showing features of acute pancreatitis and straight X-ray abdomen showing "Colon cut off" sign and clinical evidence showing marked epigastric tenderness. Of note, in this case there was no evidence to implicate drug or toxin induced injury, obstructive or metabolic etiology. thereby suggesting that pancreatitis was secondary to ischaemic injury from sickling in this patient.

Therapies including hydration, correction of electrolyte imbalance, bowel rest and prophylactic antibiotic in some cases should apply to patients with SCD and pancreatitis, as they would for patients with pancreatitis of other etiology.[1]

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Case Report

ACINETOBACTER BAUMANII INFECTION - A CASE REPORT

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ABSTRACT

Acinetobacter are gram negative coccobacilli and ubiquitous in nature. Quiet frequently they are recovered from inpatients who are hospitalized for prolonged illness and often multiple times. Although originally considered to be a low grade opportunistic pathogen Acinetobacter species has emerged to be one of the common nosocomial pathogen. These isolates are often MDR. It still remains a physician's dilemma whether to treat such isolates or not to treat considering them as commmensals.

Key words : *Acinetobacter, MDR (multi drug resistant), nosocomial.*

INTRODUCTION

Though Acinetobacter are highly prevalent in the environment, they are only occasionally been cultured from the moist skin of healthy human-beings. They have been commonly documented from the hospitalized inpatients especially in ICU settings who are immunocompromised and /or having co morbid conditions. The respiratory tract and & IV devices are the most common sources of bacteremia .Infections of the urinary tract, postoperative sites, biliary stents, Para nasal sinuses, eye & peritoneum are less common.

Among many Acinetobacter species *A.baumanii* is the most common isolate followed by *A.lwoffi* Until recently *A.baumanii* was best known as an agent of nosocomial pathogen. However it has been described to cause severe acquired pneumonia & meningitis. Acinetobacter species are often extensively resistant to commonly available antimicrobial agents like that of antipseudomonal penicillins, 3rd.generation Cephalosporins, Fluoroquinolones, Aminoglycosides and Aztreonam. Polymyxin-B or Colistin has been used with some success & carbapenams (imipenem, meropenem) are often active against these species. Empirical combination therapy has been advocated when A.baumanii is isolated pending susceptibility test.

CASE REPORT

A 72 yr. old known diabetic & hypertensive presented to the emergency department for incoherent talk since last two days. The patient was on Metformin 1gm, Glimepride 2 mg,Losartan – Hydrochlorothiazide (50mg +12.5mg). 12 days prior to this event the patient was hospitalized in this institution for severe falciparum malaria(cerebral + hepatopathy). He was treated with Artesunate, Ceftriaxone & was put on an indwelling catheter to prevent bed wetting.

The patient was afebrile, pulse 90/min, BP-140/90 mm Hg, respiratory rate was 16/min.Chest, heart and abdominal examination were not noteworthy. There was no focal neurological deficit. The patient was admitted with a provisional diagnosis of metabolic encephalopathy. Investigations revealed TLC, DLC, RPG, Urine (RE, ME), BUN, Serum creatinine all were within the normal range. Serum Sodium was 115 meq/lt & Potassium was 4.3 meq/lt. ECG, X-ray chest & CT Scan of the brain were unremarkable. Blood and urine culture reports were awaited.

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The patient was given oral supplementation of common salt & the patient recovered his sensorium gradually over 48-60 hrs. On 3rd day of hospitalization the blood culture showed no growth & urine culture showed *A.baumanii* which was sensitive only to Imipenam-Cilastatin and Tigecyclin. Since the patient's general condition and vital signs improved dramatically without any antibiotic, so we observed the patient in the inpatient department for 7 days and then discharged for follow-up in the outpatient department with repeat urine culture after 1 month. The repeated urine culture showed the same organism and same susceptibility test. The patient was asymptomatic all throughout.

DISCUSSION

Acinetobacter has emerged as one of the common nosocomial pathogens. A variety of human infections caused by *Acinetobacte*r has been described by Lyon et al. Such as pneumonia (endotrachial tube or tracheostomy induced), skin and wound infections, urinary tract infection (after instrumentation), meningitis (in neurosurgery patients), peritonitis (peritoneal dialysis induced). Sporadic cases of endocarditis, conjunctivitis, osteomylitis and synovitis have also been described. Being ubiquitous in the environment strains of *Acinetobacter* are widely distributed in hospital environment. They easily colonize the oral cavity, airways, urinary and GI tract. They are also found on moist skin areas of both patients and health care workers. *Acinetobacter* can be a pathogen or comenssal in a hospital environment. When isolated from blood they are invariably considered to be pathogens but when isolated from other samples like that of wound surfaces and urine they can be either comenssal or pathogen.

In this case report we document a case of asymptomatic MDR *A.baumanii* infection which probably colonized the urinary tract during indwelling catheterization in hospital and persisted even after 50 days of discharge from the hospital. Though many cases of Acinetobacter colonization of urinary tract are documented during in-hospital stay of the patients, we could not find any other article regarding the persistence of *Acinetobacter* in urinary tract even after discharge from the hospital. SP Yavankar et al have described asymptomatic MDR *Acinetobacter* on the moist skin of tribal population of Maharastra but do not mention anything about the urinary tract. In this case we did not treat the infection as we were lucky enough that the patient was asymptomatic all throughout. Had he been febrile or lab report suggested pictures of sepsis because of some other reasons, we might have attempted to treat A.baumanii with Imipenam or Tigecyclin adding a tremendous burden on economy of the patient without any cause. So till clear-cut guidelines come to treat such infections the physicians will be in a dilemma.

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