ORISSA PHYSICIANS JOURNAL

ESTABLISHED IN 2005 Vol. 4 2008 www.apiorissa.org

ISSN 0973-2853

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ISSN 0973-2853

ORISSA PHYSICIANS JOURNAL

Official Journal of API, Orissa Chapter

Advisory Board 2008

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. Bidyut Kumar Das
for the Association of Physicians of India,
Orissa State Branch,
Department of Medicine, S.C.B. Medical College, Cuttack-753007, Orissa, India.

Printed at

Graphic Art Offset Press, Nuapatna, Cuttack-1.
Email: bidyutdas@hotmail.com
website : www.apiorissa.org

OPJ Vol.4 * 2008

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Editorial

The editing of a journal is an onerous task, especially when chasing deadlines for completion of work, while at the same time waiting for articles to arrive till the last minute, and expecting perfection in the end. The bottomline is the quality of the journal that should kindle the curiosity of the reader to have a look and stimulate the intellectual thirst of the prospective readers to go through the article. Most go through the first ritual but I am not sure if the second objective has many takers.

Our effort has been to raise the bar with regard to quality of production of the journal, and publish decent articles of topical interest to make physicians read and carry a message from each piece of creative effort. I am still not sure about the impact our effort has made on the physicians, but not many critical inputs have been received either, which perhaps goes to show a silent appreciation. Despite best efforts it has not been possible to get original articles, which should first be considered for publication in an impact journal, for obvious reasons. But I am sure many have good articles which can be published in state journals have not seen the light of day due to paucity of time. Writing and publishing an original article is a grind that most people who have published in peer review journals will appreciate. The quality of the journal will depend on good articles and we need to introspect on that.There has been a change this time and hopefully it will get better in days to come.

Every year a change ushers which is natural and welcome. Ideas change and bloom with right nurturing. The nascent journal , still a toddler, is taking careful steps to maturity. Guidance is vital in the long trek through hard times.Flowering of OPG will depend heavily on the gardener who nourishes it. It is our earnest request to physicians to lend a helping hand in years to come for the growth of their brainchild which will see tumultuous days ahead.

Dr Bidyut Kumar Das

Dr Jayanta Kumar Panda

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Original Article

CORONARY ARTERY DISEASE AND RISK FACTOR ASSOCIATION : A STUDY OF URBAN RURAL DIFFERENCES

U. K. Patnaik, Rina Mohanty****

The growth of urbanization and changing food habits have seen an increase in the incidence of Coronary Heart Disease (CHD).1 Similar changes are now occurring in the developed world including India. Most studies in risk factor contribution towards CHD has occurred in urban areas 2,3,4 -while addressing the difference in urban-rural divide has been limited to only a few studies.[4],5 The present study examines the prevalence of risk factors in patients admitted with CHD to the Medicine Department of S.C.B. Medical College, Cuttack and compares their differences amongst urban and rural inhabitants.

Methods :

Five hundred and twenty consecutive case of CHD admitted to the Medicine Wards were included in the study. They comprised cases of acute, myocardial infartion, stable angina and unstable angina. The study population was divided into two groups depending on whether they resided in Urban or Rural areas. The following data were collected from all patients: 1. Age, 2. Sex, 3. Family history of CHD, 4. Smoking status, 5. Blood pressure, 6. Diabetic status, 7. Fasting lipid profile.

The study used the following definition of CHD- either a history of chest pain as per WHO'S questionnaire on angina[6] or a doctors diagnosis of heart attack (Table 1). Hypertension was considered

TABLE-1 : Revised Definition of Myocardial Infarction (MI)

Criteria for Acute, Evolving, or Recent MI

Either of the following criteria satisfies the diagnosis for acute, evolving or recent MI

1. Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following :
   a) Ischemic symptoms
   b) Development of pathological Q waves in the ECG
   c) ECG changes indicative of ischemia (ST segment elevation or depression)
   d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
2. Pathological findings of an acute myocardial infarction

Criteria for Healing or Healed Myocardial Infarction

Anyone of the following criteria satisfies the diagnosis for healing or healed myocardial infarction :

1. Development of new pathological Q waves in serial ECGs. The patient mayor may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized depending on the length of time that has passed since the infarction developed.
2. Pathological findings of a healed or healing infarction

CK = reatine kinase; ECG = electrocardiogram.

From Alpert JS, et al: Definition of myocardial infarction - a global consensus document of The Joint ESC/ACC/AHA/ WHF/WHO Task Force for the Redefinition of Myocardial Infarction, 2007 (in press).

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on the basis of the Joint National Committee (JNC) VII[7] criteria i.e. systolic blood pressure of 140 mm Hg or more and/or diastolic pressure of 90 mm Hg or more or being on autihypertensive drugs. Diagnosis of diabetes was based on classification scheme of the American Diabetes Assriation (2006) [ADA] (Table 2).

TABLE-2

Diagnostic Criteria for Diabetes Mellitus, Impaired Glucose Tolerance, and Impaired Fasting Glucose According to the American Diabetes Association

Diabetes Mellitus

Symptoms of diabetes (e.g polyuria$_r$ polydipsia$_r$ unexplained weight loss) and a casual plasma glucose concentration > 200 mg/dL (11.1 mmoljL)

OR

Fasting plasma glucose > 126 mg/dL (7.0 mmoljL)

OR

2-hr plasma glucose > 200 mg/dL (11.1 mmol/L) during an oral glucose, tolerance test (OGTT)

2-hr plasma glucose > 140 mg/dL (7.8 mmoljL) but <200 mg/dL (11.1 mmol/L) during OGTT

Impaired fasting glucose (IFG)

2001 definition: Fasting plasma glucose ≥ 110 mg/dL (6.1 mmoljL)

but < 126 mg/dL (7 mmol/L)

2004 definition : Fasting plasma glucose > 100 mg/dL (5.6 mmol/L)

but < 126 mg/dL (7 mmol/L)

From Diagnosis and classificatioin of diabetes mellitus. Diabetes Care 2006; 29 (Suppl.1) : S43-S448. Copyright American Diabetes Association.

RESULTS:

The risk factors for CHD are presented in Table 3. The prevalence of smoking was significantly higher in the rural patients as compared to those from urban areas. Hypertension and diabetes were higher in patients admitted from urban as compared to those coming from rural areas. When examining the prevalence of hyperlipidaemia (Table 4) it was seen that all measured parameters (total cholesterol, TC triglycerides, TG, High density lipoprotein HDL, Low density lipoprotein LDL, and very low density lipoprotein VLDL) were almost similar in urban and rural areas.

TABLE-3

	520 cases	
	Urban	**Rural**
Total No. of cases	212 (40.76%)	308 (59.23%)
Family history of CHD	4 (1.88%)	6 (1.95%)
Smokers	66 (31.13%)	156 (50.65%)
Hypertension	96 (45.28%)	94 (30.52%)
Diabetes	108 (50.94%)	128 (41.56%)

DISCUSSION :

Most of the conventional risk factors i.e. hypertension and diabetes were higher in urban compared to rural population. This could be attributed to the more stressful life style, food habits and lack

TABLE-4

Biochemical Parameters	Urban (Mean values (mg/dl)	Rural
Total cholesterol	173 mg/dl	183.43
Triglycerides	140.66	130.96
HDL	42.33	45.47
LDL	99.16	111.3
VLDL	22.5	24.87

of adequate exercise in urban areas. According to Marmot and Syme 8 acculturation plays an important role in IHD causation. Smoking however was significantly higher among rural patients. Lack of awareness of the harmful effects of tobacco due to poor education could be a major contributing factor for the high incidence of smoking in rural areas.

A recent review of Indian studies has concluded that the rates of CHD, hypertension, diabetes and obesity are low among the rural population of India. 9 The lifestyle in villages is still very traditional and a vegetarian diet is often consumed. A cause of concern however is the high' incidence of smoking in rural areas which could will offset the gains of lower incidence of hypertension and diabetes. Not surprisingly the incidence of CHD is quite significant also, in rural areas. Lipids did not show much difference in rural and urban areas thus signifying the effect of an 'Urban way of life' as a major contributing risk factor for CHD. It therefore seems advisable to retain the traditional way of life in order to prevent an evidence of CHD in the country.

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PREDICTION OF LENGTHS OF HOSPITAL STAY OF MALARIA PATIENTS

Saroj K Mishra*, Neeru Singh, Rajalaxmi Mishra*****

ABSTRACT

Background: Duration of the hospital stay is an important question in the minds of both health care providers as well as the recipients. Malaria continues to be a major cause of hospitalized patients in different parts of the country including Orissa. However, there is no objective tool to predict the length of hospital stay (LOS).

Material & Methods: An analysis of the hospital records of the malaria patients admitted to Ispat General Hospital, Rourkela, was conducted. The factors influencing the length of stay were identified and a multiple regression analysis was performed to develop a linear equation.

Results It was observed that certain parameters viz., presence of severe anemia, jaundice, acute renal failure, or cerebral malaria, were major influencing factors, so also the type of therapy required (oral or parenteral antimalarial therapy; even ICU care). However, age, sex, place of residence (and thus the distance from the hospital) were not found to be of important determinants. The simplified LOS prediction was = 2.5+ 2.5 Severe anemia + 0.5 Jaundice +1 acute renal failure+1.5 cerebral malaria + 0.5 Level of therapy [where, the severe anemia, jaundice, acute renal failure, cerebral malaria are considered as present=1, or absent=0; and for level of treatment : oral antimalarials=1, parenteral antimalarials =2, and need for ICU intervention (ventilator, dialysis etc)=3]

Conclusion: The LOS of a malaria patient can be estimated easily and rapidly by a simple formula, which does not require sophisticated investigations. The prediction rule can be used (i) at the time of admission as well as (ii) during the hospital stay. As the present study is from a single centre, it needs to be validated in different geographical settings, and further simplified and improved by a multi-centre collaborative study.

INTRODUCTION :

When a patient is admitted to a hospital, one of the important questions which arise in the mind of the health care providers, patients or their relatives, as well as the administrators is the duration of hospital stay of the patient. When the patient is kept in the critical care unit or high dependency unit, the survival is the most important concern. In malaria prone areas, many of the hospital beds in the referral centres are occupied by patients with malaria. The cost of treatment is dependant on several factors, one of these being the period of stay.

Malaria being a disease mostly in the developing countries, the treatment is availed at different levels: (a) at home, (b) at the nearby health facilities and (c) referral centre for severe malaria cases; where the patient is shifted to a hospital far away from own place of residence. Relatives of patients are concerned regarding the length of stay in a tertiary care hospital and the cost associated with it.

A large number of the beds are occupied by these patients, during the peak transmission period,

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making it a major administrative problem. The LOS of admitted patients is one of the indicators of bed occupancy, planning and rotation of staff deployment, etc and the resource utilization.1-3

Similarly, from the point of view of the health care providers and administrators, no tool is available to predict the length of stay for the malaria cases. When confronted by a questioning/ inquisitive relative, the treating doctor only extends a rough estimate depending on his own experience, which is purely subjective. In practical situation, the statements are variable for different doctors and thus totally confusing to the relatives.

In the present study, it is attempted to identify various determinants on LOS, and to develop a mathematical model which can be used objectively for each patient admitted to a hospital. We tried to make it simple and easy to remember. It is attempted that it must be calculated rapidly and must not require too many lab data.

Material & Methods :

a. Hospital: Ispat General Hospital is situated in Sundargarh district of Orissa. It is a 685 bed hospital under of a Public sector steel plant.

b. It has eleven bed Critical care units. There are facility for haemodialysis, peritoneal dialysis, blood banking, 24 hour emergency, haematology and biochemical laboratory etc.

c. Catchment area : Patients come from the urban areas of Rourkela, villages, forested areas, as well as mines areas. The district lies between 210 35 / N and 220 35 / N latitude, and between 830 32 / E and 850 22 /E longitudes at an altitude of 300 - 6 00 m above sea level. The annual rain fall ranges between 160 to 200 cm.

d. Subjects: All patients admitted to the Internal Medicine Dept of Ispat General Hospital, Rourkela with confirmed malaria.

The study has two parts: (a) analysis of the malaria and (b) Multiple regression analysis.

In the first phase, database was collected prospectively in a format which includes age, sex, demographic data, treatment received before admission, biochemical and hematological reports, presence of seizures, treatment details, and the outcome. All those who expired were excluded from the study. 700 patients with complete data were analysed.

Statistics: Student's t test was used to differentiate between male vs female; adult vs children; Rural vs urban; patients with acute renal failure (sr Creatinine >3 mg/dl) , jaundice (sr Bilirubin > 3 mg/dl) , severe anemia (Hb < 5 gm/dl) or cerebral malaria (unarousable coma or GCS <10).

The difference is considered to be significant if $p < 0.05$.

In the second phase Multiple Regressions was performed to find out the relationship of the above parameters and to get a linear equation.

It will be in the form of

$$LOS = a1x1 + a2x2 + a3x3 + a4x4 + \ldots + C$$

OBSERVATIONS :

In the study we collected the data of those adult patients who survived and were discharged from the hospital. 700 surviving patients were analysed for the prediction of length of hospital stay. Out of these, 188 were females and rest were males. 62% were entitled patients (either employees or their dependants, or retired employees of the steel plant : all of these get free medical treatment) and 38% were from different walks of life, including people from villages, township and traders. These patients were treated in the hospital on payment basis. Their income and socio economic conditions varied widely. 60% were from urban areas, and others were from suburbs or villages.

The comparisons of length of stay in different groups are depicted in the Table-1. As it appears, the length of stay was significantly longer in patients with severe anemia, acute renal failure, cerebral malaria and jaundice. Thus LOS was 2.87(±1.68) days when the patient was having uncomplicated

Table 1
Characteristics of malaria patients and LOS

Determinants	Characteristics	No of patients	LOS (± SD)	P value
Entitled	Entitled NE	433 267	3.99(±2.00) 4.95(±2.95)	0.000*
Sex	Male Females	512 188	4.29 (±2.39) 4.52(±2.61)	0.299
Residence area	Rural Urban	257 443	4.62(±2.75) 3.91 (±1.73)	0.000
Acute renal failure	Sr Creatinine >3mg/dl Sr Creatinine < 3mg/dl	29 671	8.66 (±4.45) 4.17(±2.14)	0.000
Cerebral malaria	GCS <10 GCS >10	61 639	7.41(±2.11) 4.06(±2.08)	0.000
Severe anemia	Hb<5.1 G HB>5 g/dl	18 620	5.89(±2.65) 4.37(±2.46)	0.027
Jaundice	Bil >3mg/dl Bil < 3 mg/dl	139 561	5.81(±3.33) 3.99(±2.03)	0.000
Complications	Uncomplicated Single Multiple	390 181 129	2.87(±1.68) 4.33(±1.68) 6.78(±3.53)	0.000
Level of treatment	Oral drugs Parenteral (QBH/AS)	115 585	2.97(±21.18) 4.62(±2.54)	0.000

malaria, which went on increasing in presence of complications. Thus LOS was 8.66 (±4.45) days in presence of acute renal failure, 7.41(±2.11) days in patients with cerebral malaria, and 4.33(±1.68) in patients with jaundice. LOS was longer in patients, who have come from rural areas, but there was no difference in males vs females nor there was any difference whether a patient got the treatment free or on payment basis.

After the determinants were identified, a linear equation was developed by using multiple regressions.

LOS = 2.441+ 2.565 Severe anemia + 0.447 Jaundice +0.993 acute renal failure + 1.405 cerebral malaria +0.657 Level of therapy

The equation was modified to make it simple and ready to use at bedside.

Thus,

LOS = 2.5+ 2.5 Severe anemia + 0.5 Jaundice +1 acute renal failure

1.5 cerebral malaria + 0.5 Level of therapy

Where, the severe anemia, jaundice, acute renal failure, cerebral malaria are considered as present=1, or absent=0; and level of treatment is oral treatment with antimalarials =1, parenteral antimalarials (artemisinine or quinine) =2, and need for any ICU intervention (ventilator, dialysis etc)=3.

DISCUSSION :

We searched the literature to find out the studies related to LOS in malaria patients. But there were only two studies cited in the MEDLINE .1,2 However, several studies are available to predict the LOS in other clinical conditions viz, very low weight neonates in nursery, sepsis in ICU settings, patients after coronary surgery etc. 4-8

In a Critical care set up 11 the important prognostic variables for the LOS were a higher patient-age, presence of comorbidity, type of surgical approach, intra-operative respiratory minute volume, and complications occurring within 72 hours in the ICU.

In a retrospective study in Spain, 1920 episodes of community-acquired pneumonia (CAP) in 27 community hospitals were analyzed for inter-hospital variability in length of hospital stay (LOS), mortality and readmission rates.9 The overall adjusted LOS (mean+/-S.D.) was 10.0+/-9.8 days. LOS increased according to the Pneumonia Severity Index (PSI) risk class: 7.3 days for class I to 11.3 days for class V (P<0.001). In a multiple regression model, LOS increased (P<0.001) according to the hospital (inter-hospital variability), PSI risk class, complications during hospitalization, admission to ICU, need of oxygen and transfer to a nursing home.

A study from a hospital in Goa describes the determinants of LOS in malaria patients.2 The study indicated the importance of altered sensorium, presence of liver involvement, duration of therapy before admission as influencing factors. But most of the patients were uncomplicated ones. PUBMED search did not show studies on determination of LOS in severe malaria cases. Similarly publications are not available from any tertiary care hospital which manages both uncomplicated and complicated cases.

Some of the parameters in our study were similar to the Goa study. It described that the LOS was determined by presence of liver involvement (hepatitis), acute renal failure, delay after fever and level of treatment.

Table-2.

Multiple regression showing influence of factors on LOS

Factors	Beta	P value
Entitled or not	0.186	0.323
Residence	0.106	0.428
Severe anemia	2.565	0.000
Cerebral malaria	1.405	0.000
Jaundice	0.447	0.028
Acute renal failure	0.993	0.006
Level of therapy	0.657	0.000

LOS= 2.441+ 2.565 Severe anemia + 0.447 Jaundice +0.993 acute renal failure 1.405 cerebral malaria +0.657 Level of therapy

simplifying the equation for ready bedside use

LOS = 2.5+ 2.5 Severe anemia + 0.5 Jaundice +1 acute renal failure 1.5 cerebral malaria + 0.5 Level of therapy

Or

LOS = ½ [5+ 5x Severe anemia + 1x Jaundice +2 x acute renal failure 3 x Cerebral malaria + 1x Level of therapy]

Where, presence =1 , and absence = 0 for severe anemia, jaundice, acute renal failure and cerebral malaria.

For level of therapy oral antimalarials =1, Parenteral antimalaria therapy (artemisinine or quinine) =2, and need for any ICU intervention (ventilator, dialysis etc)=3

However, we have not been able to find any difference among the males and females, urban vs rural, entitled vs non-entitled groups on LOS. But, as expected the LOS is higher in patients with any or more complications. It was noted that all complications are not similar, and they influence the survival in a different weighted capacity. Similarly they also influence the LOS.

In a previous study, we had proposed prediction rule for the Survival of the patients with severe malaria.10 In the present one, we derived a very simple prediction rule for the LOS. It does not involve sophisticated data collection, estimation or analysis. Still it extends valuable information, which will be helpful to the clinicians. In addition, the formula can be used to modify the result/ prediction in the course of time if any new complication arises.

However, we have analyzed the data of only one year, and that too only among the adults. It is proposed that such studies may be undertaken among children too. It should also be validated in cohorts from different geographical regions.

Acknowledgement: We are thankful to the management authorities for the all round support and encouragement for research and training of malaria. SKM extends his sincere thanks to the staff of IGH.

Funding: None

Conflict of interest: None

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CLINICAL PROFILE AND OUT COME OF ACUTE PANCREATITIS

P.K. Mohanty*, D. K. Patel, L. K. Dash*****

ABSTRACT

Twenty two cases of acute pancreatitis were studied with an aim to analyze their clinical behaviour and outcome. Mean age of presentation was 38 years with M:F of 3.4:1. Abdominal pain, tenderness, distention and vomiting were the common symptoms. Minimal ascites was found in about 1/3rd of cases. Mean serum amylase and lipase levels on admission were 737.6 unit / L and 2122.2 U/L. Serum lipase was a superior diagnostic marker. Hypocalcemia, hyperglycemia, hypertryglyceredemia and renal failure were rarely observed. Contrast enhanced CT scan was better than ultrasonogram in detecting pancreatic pathology. CT scan severity index showed most as having mild to moderate pancreatitis. Complications noted were necrotizing pancreatitis in 11%, pseudocyst in 13.5%, pancreatic ascites in 9%, pleural effusion in 27% and recurrent pancreatitis in 22.7%. Alcohol was the predominant etiological factor (73%) compared to gall stone disease (18%). Most patients improved with conservative treatment as most of them suffered from mild pancreatitis. Delay in hospitalization resulted in delayed resolution of pain, increase length of stay in hospital and complication.

KEY WORDS : Acute pancreatitis, CT severity Index.

INTRODUCTION

Acute abdominal pain is a common clinical problem that may result from various causes including acute pancreatitis. Generally after exclusion of perforation and intestinal obstruction cases are admitted to medical wards with illdefined diagnosis like gastritis or colitis. We evaluated such cases for acute pancreatitis and studied the clinical profile and out come of cases that satisfied a diagnosis of acute pancreatitis.

Acute pancreatitis is a potentially lethal disease that is increasing in incidence[1,2,3]. In most series gall stone disease followed by alcohol abuse contribute for most of the cases of acute pancreatitis[4]. Various other causes include hypertriglyceridemia, trauma, hyperparathyroidism, viral infections, drugs, parasites, anatomical anomalies and endoscopic retrograde cholangio pancreatography(ERCP)[5]. Depending on severity it is classified into mild and severe acute pancreatitis (Atlanta classification 1992)[6]. While mild cases are self limiting the severe cases contributing to 15 - 20% of all cases may be fatal in up to 20% of them[7]. Classically acute pancreatitis presents with severe epigastric pain radiating to back and associated with nausea and vomiting[1,5]. Most of the cases (85 -90%) of acute pancreatitis resolve spontaneously after treatment is instituted[8]. The various locoregional complications include infection of necrosis, pseudocyst, pancreatic abscess, pleural effusion, pseudo-aneurysm of splenic artery, haemorrhage from erosions into splenic artery and vein, thrombosis of splenic, superior mesenteric or portal veins, duodenal obstruction, common bile duct obstruction and progression to chronic pancreatitis[9]. The systemic complications include hypovolemic shock, ARDS, multiple organ dysfunction, renal failure, hypocalcemia, exocrine and endocrine deficiency[8,9].Death may result from one or more of the complications.

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The cornerstone of management are intravenous fluid administration nil per oral and early enteric feeding[4]. The role of antibiotics remain controversial. In cases not responding limited surgery like necresectomy and lavage are performed. Severe cases need care in high dependency units or intensive therapy units[4].

PATIENTS AND METHODS

Twenty two cases who satisfied the diagnostic criteria of acute pancreatitis were included in this study. A detail clinical history was obtained in each case including specially the history of chronic alcohol ingestion, previous history of gall stone disease. A detailed clinical examination , relevant laboratory investigation and imaging studies were carried out. The laboratory investigations included estimation of various parameters like serum amylase and lipase, plasma glucose, triglyceride, serum creatinine and serum calcium level in addition to other routine tests like hemogram, electrolytes etc. The patients were subjected to ultrasonography and contrast enhanced high resolution spiral CT scan in most cases. A diagnosis of acute pancreatitis was done when serum amylase and/or lipase levels are raised more than three times the normal with clinical features suggestive of acute pancreatitis[1,5,8]. Contrast enhanced spiral CT scan of abdomen was done in case of uncertain diagnosis, and to assess the severity and extent of pancreatic damage. CT grading of severity was done based on that proposed by Balthazar et al. (Table- 1)[4,10].According to this patientsare stratified as having mild(score 0-3),moderate(score 4-6) and severe (score 7-10) pancreatitis. The cases were managed conservatively with adequate intravenous fluid, analgesia, antibiotics, nil per oral, nasogastric aspiration. The cases that did not show improvement after 7 days of therapy or with complications were referred to gastroenterologist or for surgical management. The observation made are recorded and analyzed.

RESULTS

Twenty two cases studied are analysed for various aspects. The mean age at presentation was 38 years, the youngest patient a 14 years old girl and the eldest a sixty year old male. There was a male preponderance with M:F ratio of 3.4:1 (Table-2).

The most common presenting symptom was abdominal pain and the sign was abdominal tenderness followed by vomiting and fever. Ascites was subclinical in 7 cases and clinically apparent in 2 cases (Table-3). Serum amylase was raised more than three times normal in 12 out of 20 cases and serum lipase in 21 out of 21 cases. Mean serum amylase and lipase values on admission were 737.6 U/l and 2122.2 U/L respectively. Renal failure was present only in one case and plasma glucose level varied between 64mg/dl to 124 mg/dl with a mean of 92.7mg/dl. Mild hypocalcemia was found in 5 cases with a mean serum calcium of 8.8 mg/dl. Leucocytosis was found in 8 cases.

USG of abdomen done in 20 cases revealed findings enlisted in (Table-4). In only nine cases ultrasonogram was suggestive of acute pancreatitis. Non-visualization of pancreas was noted in 5 cases, stone in gall bladder was found in 2 cases, sludge in one case and stone in common bile duct in one case.

The various features noted in contrast enhanced spiral CT scan was done in 18 cases included enlargement of pancreas, peripancreatic inflammation, and fluid collection, necrosis of pancreatic tissue and pseudocyst formation as mentioned in (Table 5). In each case a CT scan severity index (CTSI) was calculated and correlated with complications and death rate (Table – 6).

Complications found in studied cases included pseudocyst formation (3 cases), pancreatic ascites (2 cases), pleural effusion (mostly left side and in four cases bilateral) in 6 cases , and atelectasis in one case. Recurrent pancreatitis was noted in 5 cases. Shock was not present in any of the cases.

On evaluation of aetiological factors, 16 cases had history of chronic alcoholism with duration ranging from 3 to 35 years. Most of them drank alcohol of different forms daily with amount varying from 500 ml to 1500ml. The gall stone disease accounted for 4 cases out of twenty two. One of the cases was

due to blunt trauma to abdomen. In one case no etiology could be found.

All patients were initially put on conservative treatment of whom nineteen recovered. Median duration for pain to resolve was 5.5 days. The range varied from 3 to 15 days. Pain persisted longer when patients were hospitalized later. The rest three cases were referred to surgeons or gastroenterologists for treatment. No death was recorded in any of the cases. Although advised for follow up, 18 cases did not turn up again. Of 4 cases who came back for follow up 2 had recurrence, one had cholecystectomy followed by no recurrence and the last had no recurrence after initial attack.

DISCUSSION

In the present study acute pancreatitis occurred over a wide range of 14 to 60 years with a mean age of 38 years. The male to female ratio was 3.4:1. In a recent study at Chandigarh Raghu MG et al found a mean age of 42.8± 15.9 years and male to female ratio of 2.7:1 [11]. In a English study the mean age at presentation was higher (56.2 years) and almost similar proportion of men (52.3%) and women (47.7%) were affected[3]. This difference may be due to the fact that gall stone disease occurs more commonly in middle aged women.

Abdominal pain was the presenting symptom in all cases but in 72 percent of the cases a history of radiation to back was not obtained. suggesting that acute pancreatitis can occur in its absence very often. Minimal ascites on imaging studies was present in about one third of the cases (31 percent). Most of these cases improved without complication whereas those with gross ascites were associated with acute necrotizing pancreatitis and protracted course. The gross ascites may be due to disruption of main pancreatic duct or a leaking pseudocyst[8]. The minimal ascites has not been well addressed[1,5,8]. Serum amylase level was raised more than three times normal in 60 percent of cases whereas serum lipase was elevated more than 3 times normal in all of our cases suggesting it to be superior marker compared to amylase. Where lipase is available it is preferred for the diagnosis of acute pancreatitis (recommendation grade A)[4]. Hyperglycemia and hypertriglyceridemia was unusual amongst our cases. Mild hypocalcemia was found in less than one third of cases. Leucocytosis was observed in 36 percent of cases. Ultrasonogram was less sensitive and detected only 45 percent of cases which is comparable to that described in a review (30 – 50%)[5]. Pancreas was not visualized in 25 percent of cases. It was useful to evaluate gall stones, pseudocyst, pleural effusion and ascites.

Contrast enhanced spiral CT scan revealed pancreatic enlargement in all cases, peripancreatic inflammation in 72 percent cases, peripancreatic fluid collection in half of the cases, necrosis in 11 percent cases, pseudopancreatic cyst in 11 percent and ascites in one third of cases. CT severity index(CTSI) in 18 cases revealed mild pancreatitis (0 – 3) in 50 percent of the cases with no complication, moderate pancreatitis (4 -6) in 44 percent cases with a complication rate of 75% and severe pancreatitis (7 – 10) in one case with complication. No mortality was noted in any of the cases. In a tertiary centre of north India CTSI was between 1 to 3 in 19.6 percent, between 4 to 6 in 26.8percent and more than 6 in 53.6percent of cases. The higher incidence of high CTSI > 6 may be because of referral bias, more severe cases being admitted to the hospital. Recently a modified CT severity index has been proposed by by Mortele KJ et al[12]. They incorporated features reflecting organ failure and extra pancreatic complications in the scoring system which resulted in better correlation with outcome. Various complications found in the present study were pseudocyst formation (13.5%), pancreatic ascites (9%), pleural effusion (27%) and atelectasis (<1%). Pseudocyst has been described to complicate 15percent of cases in the literature[8]. In a study by Raghu MG et al. pleural effusion was found in 50percent of cases which is high compared to our finding[11]. Pleural effusion was bilateral in half of them and in half with only left side effusion. Recurrent

pancreatitis was noted in 22.7% of cases comparable to others.

Various causes of acute pancreatitis found in the study are chronic alcohol ingestion (73%), gall stone disease (18%), and trauma in one case; one case was of idiopathic origin. The aetiology was found to be gall stones in 48.3% and alcohol in 36.7% in an Indian study[11]. In western world gall stone continue to be the most common cause of acute pancreatitis, followed by alcohol together accounting for 80% of cases[5]. The increase incidence of alcoholism might be responsible for their greater contribution in our study.

The severity of acute pancreatitis was mild in 81percent and severe in 19percent of cases, which is comparable to that described by Andersson R et al[7]. Eighty five percent of patients improved with conservative treatment only, which is comparable to that described in literature. Rest of the cases were referred to surgery or gastroenterology department elsewhere. The median duration of for resolution of pain was 5.5 days with a range from 3-15 days. No death was noted among the studied cases which may be due to inclusion of less number of cases. Most of the cases were lost to follow up (85%). One case with sludge in gall bladder came for follow up after cholecystectomy and two had recurrences.

Due to nonavailability the ERCP could not be done in one case with stone in common bile duct where it was indicated; bile sampling and study for presence of microlithiasis was also not possible for the same reason.

To conclude, acute pancreatitis is not an uncommon cause of acute abdominal pain. A high index of suspicion is essential for its detection. To streamline the treatment, protocols according to guidelines should be followed after stratification into mild and severe types. Facilities of high dependency or intensive therapy units and a pancreatitis team ,. are a must for treatment of severe cases.

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CO-RELATION OF ELECTROCARDIOGRAPHIC ABNORMALITIES WITH SEVERITY OF MITRAL STENOSIS.

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ABSTRACT

Rheumatic hart disease (RHD) is still widely prevalent in our country , both in teenagers and in adults. More so mitral stenosis (MS) is frequently seen in clinical practice . In pre echo cardiographic era electrocardiographic (ECG) changes were considered as one of the main parameters to assess the severity of MS . The purpose of this study is to ascertain any correlation between ECG changes and with that of severity of MS .

70 cases of isolated MS were studied for this purpose These cases were divided in two groups Group – A and Group- B. Observation were represented in different tabular forms and statistically evaluated. Relevant observation data were discussed.

The conclusion derived from this study is that , there is no statistically significant correlation between the severity of MS and ECG changes like RVH and QRS axis deviation. LAH is frequently seen in ECG with sinus rhythm in patients having severe MS in both groups. AF is more common in group B but not statistically significant and has no relation with severity of MS.

INTRODUCTION

Rheumatic heart disease(RHD) ,because of its high prevalence, is still a major problem in our country. Moreover it occurs very often in teenagers and young adults with full pledged clinical manifestations. Rightly it is said by Indian authors that RHD runs a malignant course in our country. Although the incidence and prevalence of rheumatic heart disease is said to be declined , yet isolated mitral stenosis (MS) is frequently seen in clinical practice.(1, 2 ,3)

The purpose of this study is to ascertain the exact relationship of electrocardiographic (ECG) changes like right ventricular hypertrophy (RVH),QRS axis deviation and left atrial hypertrophy (LAH) with the severity of MS. Severity of mitral stenosis is judged from echocardiographic criteria. In pre-echo era the severity of MS was determined mainly from ECG ,that is RVH and QRS axis deviation, besides radiological and clinical signs. Cardiac catheterisation was not a routine procedure to measure gradient across the mitral valve. Moreover ECG abnormalities reflect the severity of valvular lesions are mentioned in literatures (4,5).This leads to study the correlation between ECG and severity of MS.

MATERIAL AND METHODS.

Cases of isolated MS below the age of 40 years are included in this study .These cases were subjected to detail clinical examination, blood examination particularly for Hb, ESR,C-reactive protein , ASO titre X-ray Chest (P-A) view ,12 lead ECG and Echocardiography (M-mode& 2Dwith doppler) to exclude other associated valvular lesions.

The study period extends from December 84 to June 87, about two and half years. Cases were mainly selected from cardiology OPD ,cardiology, cardio thoracic and medical wards of SCB medical college Cuttack.

Total number of cases studied were 70,out of which 36 were females. They were divided into two age groups , Group A (below 20 years) and Group B (above 20 to 40 years). The severity of MS was judged from only mitral valve orifice area

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(MVA) of 2-D Echocardiogram, The elctrocardiographic findings taken into consideration are :-

1. QRS axis deviation
2. Left atrial hypertrophy (LAH) , P- Mitrale by Macrus Index
3. Presence of atrial fibrillation (AF)
4. Presence of Right Ventricular hypertrophy (RVH) by Sokolow & Lyon criteria.
   1. R wave in V_1 & S in V_{5-6}. minimum 10.5 mm or more
   1. V_1 R exceeds 7 mm with qR pattern.
   2. V_1 S is less then 2 mm

(a) Severity of MS was classified as per MVA (Gorlin & Gorlin formula) into three categories;

1. Mild 2.5 to 1.6 cm^2
2. Moderate. between 1.5 to 1.1 cm^2.
3. Severe. less then (<) 1.0 cm^2.

Observation

AGE AND SEX DISTRIBUTION OF PATIENTS

AGE / SEX	MALE NO (%)	FEMALE NO. (%)	TOTAL NO . (%)
< 20 YEARS (Gr. A)	14 (20 %)	12 (17 %)	26 (37 %)
20-40 YEARS (Gr. B)	20 (28.5 %)	24 (34%)	44 (62.5 %)
TOTAL	34	36	70

Total number of cases of isolated mitral stenosis are 70 out of which 34 males and 36 females . In group A, 14 males and 12 females and in group B, 20 males and 24 were females.

DISTRIBUTION OF SEVERITY OF MS

SEVERITY OF MS	Group –A (n=26)			Group- B (n= 44)		
	MALE(n=14)	FEMALE(n=12)	TOTAL	MALE(n=20)	FEMALE(n=24)	TOTAL
(Mild)	3	1	4	1	1	2
(Moderate)	8	6	14	2	5	7
(Severe)	3	5	8(30.7%)*	17	18	35(79.5%)*

*P< 0.01.

Incidence of severe MS is significantly higher in Gr. B(79.5 %) than Gr. A(30.%) (p<0.01)

Out of 34 males and 36 females , 20 males and 23 females have severe MS.Group A 3 out of 14 males and 5 out of 12 females have severe MS . Similarly in GrB17 out of 20 males and 18 out of 24 females have severe MS.

INCIDENCE OF RVH(ECG) IN RELATION TO TWO AGE GROUPS

Severity / RVH	Group - A (n=26)			Group-B (n= 44)		
	MALE(n=14)	FEMALE(n=12)	TOTAL	MALE(n=20)	FEMALE(n=24)	TOTAL
Mild (n=6)	Nil	Nil	-	Nil	Nil	-
Moderate (n=21)	2	Nil	2	2	2	4
Severe (n=43)	3	2	5*	8	4	12*
TOTAL	5	2	7(26.9%)**	10	6	16(36.3%)**

* P= NS **P=NS

RVH was present in 5 males and 2 females in group A (26.9 %) and 10 males and 6 females in group B (36.3 %) respectively(p=NS). In severe MS patients 6 out of 8 (62.5%) in Gr. A& 12 out of 35 (34.4%) in Gr.B have RVH.(p= NS)

INCIDENCE OF RVH IN RELATION TO SEX :

Severe / RVH	MALE (n= 34)	FEMALE (n=36)	P
Mild (n=6)	Nil	Nil	
Moderate (n=21)	4	2	ns
Severe (n=43)	11	6	ns
TOTAL	15 (44 %)	8 (22 %)	< 0.05

The above table shows there is greater incidence of RVH in male than in female 44% vs 22% ($p<0.05$)

RELATION OF QRS AXIS WITH SEVERITY OF MS

SEVERITY	Group A (n=26)			Group B (n= 44)		
	No of Cases	Mean QRS axis	QRS axis $> 90^0$ (No)	No of Cases	Mean QRS axis	QRS axis $> 90^0$ (No)
Mild (n=6)	4	60± 12.2	nil	2	60± 21.2	nil
Moderate(n=21)	14	69.6± 16.2	4	7	79.2± 14.2	4
Severe(n=43)	8	93.7± 15.5	6*	35	87± 19.1	21*
TOTAL	26	75.5±19.6**	10(38.4%)***	44	84.5±19.1**	25(56.8%)***

*P = NS , ** P = NS ,*** P = NS

The above table indicates 6 out of 8 patients (75 %) in Gr. A and 21 out of 35 patients (60%) in Gr. B having severe MS , have RVH(p = NS). There is an increasing trend in mean QRS axis with the severity of MS in both the groups but no statistical significance is observed .

CORELATION BETWEEN MVA & QRS AXIS IN TWO AGE GROUPS

MVA.(Cm^2)	Group - A		Group- B	
	Mean QRS axis (Degree)	Correlation coefficient (r)	Mean QRS axis (Degree)	Correlation coefficient (r)
2.5 – 1.6	60 ± 12.2	r = -0.42	60 ± 21.2	r = --
1.5 – 1.1	69.6 ± 16.2	r = -0.85	79.2 ± 14.2	r = -0.41
? 1	93.7 ± 15.5	r = -0.09	87 ± 19.1	r = -0.39
TOTAL	75.5 ± 19.6	r = -0.75	84.5 ± 19.1	r = -0.45

The above table shows QRS axis and severity of MS have no correlation except an negative correlation in Gr.A (r = -0.75).

INCIDENCE OF LAH AND AF

SEVERITY OF MS	Group A (n=26)			Group B (n= 44)		
	No of Cases	LAH	AF	No of Cases	LAH	AF
Mild	4	0	1	2	0	1
Moderate	14	4	1	7	2	1
Severe	8	7*	1	35	27*	8
Total	26	11	3(11.5%)**	44	29	10(22.7%)**

*P = NS, **P = NS

The above table shows out of 8 cases of severe MS , 7 having LAH in Gr. A and 27 out of 35 having LAH in Gr. B which is statistically not significant. Incidence of AF is 11.5 % in Gr. A & 22.7 % in Gr. B (p = NS).

DISCUSSION :

There is still a high prevalence of RHD in India as reported from hospital based study . The incidence & prevalence of RHD in Orissa was first reported in 1983 , though there is a decline in incidence of RF and RHD , yet isolated MS is very often seen in clinical practice. (6,7)

In severe MS the increase in pulmonary artery pressure due to increase in left atrial pressure leads to increase in RV pressure and subsequently RV hypertrophy which is reflected in ECG as RVH.

The distribution of MS in this study is found to be not significantly different in either sex or age matched groups. Out of 70 cases 34 are male and 36 are female of which 26 belong to Gr.A & 44 to Gr.B (p=NS) .So also 58.8 % male and 63.8 % female have severe MS (p=NS) . But a significantly higher number of severe MS found in Gr. B (p=<0.01)

RVH is found in 26.9 % patients in Gr. A and 36.3 % patients in Gr. B (p=NS). The overall incidence of RVH in severe MS patients is only about 39.5 % (17 out of 43) . RVH is frequent in severe juvenile MS (8) . In this study it is found, 62.5 % in Gr. A in comparison to 34.2 % in Gr. B (p=NS). This finding is contrary to the common belief that severe MS is usually have RVH . The exact reason of this finding is not clear . However , it is initial clinical or sub clinical myocarditis which led to RV dilatation , therefore , hypertrophy is not seen in these cases , may be a possible cause . These cases need initial RV pressure , RV dimension and PA pressure study for better understanding.6

Another interesting observation regarding RVH is that it shows a male predominance , 44 % in male vs 22% in female (p<0.05).

Like RVH , a rightward axis is not a frequent association with severity of MS is found in this study . It is only seen in 38.4 % in Gr. A & 56.8% in Gr. B respectively (p=NS) . Attempt is being made to correlate the valve area with QRS axis but no correlation could be established , However a negative correlation is found (r =-0.75) in younger patients (Gr. A). This finding can not be emphasized because of small sample size and possibility of selection bias.

There is a high incidence of LAH (79%) , (34 out of 43) in patients with severe MS in sinus rhythm and there is no significant difference between the two age groups. The occurrence of AF is neither correlated with age nor severity of MS . The overall incidence is 13 out of 70 (18.5 %).

CONCLUSION

It is observed that isolated mitral stenosis is commonly seen in clinical practice with equal sex distribution but severe MS are more common in older

age group. Contrary to the common believe that, RVH is a criteria of severity of MS does not hold good in our study, because RVH is only seen in about 1/3rd of cases. Similarly mean QRS axis and rightward axis fail to correlate with severity. There is high incidence of LAH and low incidence of AF but, found to have poor correlation with severity.

Therefore the simple ECG test to determine the severity of mital stenosis is hindered by its low sensitivity and poor correlation.

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DIABETES IN PREGNANCY

Sujata Misra*, **Sidhartha Das****

Abnormalities of carbohydrate metabolism occur frequently during pregnancy and approximately 2 to 5% of all pregnancies are complicated by diabetes. 90% of these are detected during pregnancy (gestational diabetes mellitus / GDM) while the rest are pregestational and are referred to as pregnancy with pregestational diabetes mellitus (PGDM). (1) A recent survey conducted by the National Diabetes Data group (NDDG) has reported that the incidence of GDM is about 25-50/1000 pregnancies while that of PGDM is 4-15/1000 pregnancies. (2)

CARBOHYDRATE METABOLISM DURING PREGNANCY:

Maternal Physiology:

Major hormonal changes occurring in pregnancy readjust the carbohydrate metabolism in order to provide a continuous supply of nutrients to the developing fetus. This results in reduced blood levels of fasting blood sugar and amino acids, and raised post prandial blood sugar, free fatty acids, ketones, triglyceride with increased insulin secretion in response to glucose in normal non diabetic pregnant women.(3) This diabetogenic state of pregnancy is due to the production of placental sommatomammotrophins; increased production of cortisol, estriol and progesterone, and increased destruction of insulin by the insulinase produced by the placenta and kidney. (4) The other causes are: increased lipolysis and altered neoglucogenesis.

In early pregnancy (till 20 weeks), the rising estrogen level stimulates pancreatic insulin secretion and improves peripheral utilization of glucose. This leads to a decrease in fasting glucose levels, improved glucose tolerance and an increase in tissue glycogen storage.

Increased production of insulin antagonists like human placental lactogen, prolactin, cortisol, human growth hormone and progesterone in the latter half of pregnancy leads to increased blood glucose levels. This results in increased levels of basal levels of insulin in the second half of pregnancy. Further, the increased binding of insulin to adipocytes and hepatocytes results in insulin resistance due to post receptor mechanism. Women unable to cope with this pregnancy induced insulin resistance in the latter part of gestation develop raised post prandial blood glucose concentration resulting in gestational diabetes. Severe insulin deficiency can also cause fasting hyperglycemia. In women with PGDM, the insulin requirement increases in the second half of pregnancy. Moreover, a given dose of insulin has a greater hypoglycemic effect at this stage due to brisk clearance of insulin. Therefore, spontaneous hypoglycemia in an otherwise well controlled lady in the reproductive age group should raise the suspicion of conception.

As a result of the physiologic changes in pregnancy, the normal fasting blood glucose is 65$\pm$ 9 mg/dl while the mean non-fasting levels are 80$\pm$ 10 mg/dl. Postprandial elevation normally never exceeds 140 mg/dl (5).

Fetal Physiology:

Fetal pancreatic insulin secretion commences between 9-11 weeks of gestation in response to glucose and amino acid stimulation. Glucose is

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transported across the placenta by facilitated diffusion while amino acids undergo active transport. The fetus preferentially uses alanine, and this deprives the mother of a major neoglucogenic substrate. Ketones readily diffuse across the placenta but free fatty acids undergo gradient dependant diffusion. Fetal brain and liver oxidize ketones for fetal use.

The free insulin and glucagons circulating in the maternal blood do not cross the placental barrier, but, since glucose crosses in a gradient dependant manner, higher the maternal blood glucose level, greater is the transplacental transport to the fetus (6)

CLASSIFICATION AND DIAGNOSTIC CRITERIA :

In the present times, Diabetes is classified into five groups: (table 1) and Diabetes in Pregnancy is divided into two major sub-classes (table 2)

Table-1
CLASSIFICATION OF DIABETES MELLITUS

1) Insulin Dependant – Type 1
2) Non insulin Dependant – Type 2
   (a) Non obese
   (b) obese
3)Secondary Diabetes
4) Impaired Glucose Tolerance
   a) non obese
   b) obese
   c) secondary
5)Gestational Diabetes

Table-2
CLASSIFICATION OF MATETNAL DIABETES IN PREGNANCY

Pregestational diabetes
   Type 1 diabetes
   Type 2 diabetes
   Secondary Dabetes

Gestational Diabetes
Impaired glucose tolerance of pregnancy
Undiagnosed pre-existing diabetes
Undiagnosed pre-existing impaired glucose tolerance

The Diagnostic criterion for carbohydrate intolerance in pregnancy has undergone a gradual change over the last decade. Earlier, the White's Classification was regarded as the gold standard for the management of Pregnancy with Diabetes Mellitus (table3). Subsequently, a recommendation for the evaluation and classification of pregnant women with diabetes was proposed at the Fourth International Conference on Gestational Diabetes in 1988. This was later endorsed by the American Diabetes Association in 2000 and is mainly used for detection of Gestational Diabetes.(table 4)

TABLE-3
White's Classification of Diabetes Mellitus during pregnancy

Group	**Characteristics**
A	Asymptomatic Diabetes Mellitus
B	Onset of Diabetes Mellitus after 25 yrs. of age, duration 0-9 yrs and no vascular complications
C	Onset of Diabetes Mellitus before 10 – 19 yrs.of age duration 10-19yrs.,vascular complications present
D	Onset of Diabetes Mellitus before 10 yrs. of age, duration> 20 yrs. ,
E	Diabetes with nephropathy
F	Diabetes with retinopathy

TABLE-4

Detection of Gestational Diabetes

Screning Test	Plasmsa glucose level (mg/dl)
50 gm 1 hour screen	130-140

Diagnostic Criteria (mg/dl)

Diagnostic 100gm oral GTT	NDDG Adaptation	O'Sullivan	Carpenter conversion
Fasting	105	90	95
1 hr.	190	165	180
2 hr.	165	145	155
3hr.	145	125	140

If any two values are met or exceeded, the diagnosis of gestational diabetes is made.

TABLE 5

High risk patients

1. Family H/O diabetes mellitus: especially in first degree relatives
2. Previous Bad Obsteteric History : unexplained IUD; congenitally malformed fetus
3. Severe Obesity
4. Presence of glucose in the second voided urine sample
5. Maternal age>30 yrs; Weight>85 kg any time during pregnancy
6. Chronic Hypertension
7. Recurent monilial vulvovaginitis.

EFFECT OF DIABETIC STATE ON PREGNANCY

The effect of uncontrolled diabetic state on pregnancy is multifold.(Table 6). These patients have a tendency towards metabolic instability and hence need frequent monitoring, strict therapy and a well-regulated life style. The importance of maintaining a euglycemic state of pregnancy is mandatory to prevent fetal hyperinsulinemia and its attendant complications(Table7).

First trimester:

Hyperglycemia in the mother leads to fetal hyperglycemia, which if present at the time of organogenesis (2-8weeks) is associated with increased prevalence of congenital malformations. Major defects include anencephaly, spina bifida and caudal regression. (7) Malformation rate is related to the severity of maternal hyperglycemia, early onset of disease, vasculopathy, genetic susceptibility, Ketoacidosis, hypoxia, generation of free oxygen radical and genotoxicity in the teratogenic 1 period.(Table 8)(3) and and tight glycemic control can reduce this significantly.(7).

Second and Third Trimester:

Poor control of diabetes results in increased transportation of glucose and other nutrients across the placenta. Hyperglycemia in the fetus leads to increased β cell insulin secretion resulting in fetal hyperinsulinemia(8,9). Hyperglycemia along with other nutrients are responsible for accelerated fetal growth particularly in insulin sensitive tissues like liver, muscle and adipose tissue causing Macrosomia(10,11). Macrosomia is defined as birth weight that exceeds 90th percentile for gestational

age or more than 4000 gm. It predisposes to birth trauma, shoulder dystocia, prolonged labour, asphyxia and meconium aspiration.

Hyperinsulinemia is responsible for neonatal hypoglycemia as well as poor lung maturation causing respiratory distress in the newborn.The other fetal and neonatal effects are intrauterine growth retardation (20%), intrauterine death (last four weeks), hyperbilirubinemia and polycythemia(33% of neonates). Uncontrolled diabetes also causes hypomagnesemia and hypocalcemia in the neonate (12).

Effect on mother

Poorly controlled diabetes is associated with increased risk of early pregnancy loss and ketoacidosis. Fetal hyperglycemia, increased fetal urination, decreased fetal swallowing and irritation of the amniotic membrane result in increased secretion of amniotic fluid resulting in hydramnios (20%). . Pre-existing complications such as retinopathy (13) and nephropathy get worsened(7). Other maternal complications include hypertension, eclampsia, cervical dystocia, Urinary tract infection, candidiasis

In the first half of pregnancy (till 20 weeks), there is a decrease in insulin requirement. The second half of pregnancy is a period of insulin resistance and the requirement of insulin increases. The incidence of hyperglycemia is 6-41% in pregnancies complicatedby diabetes. Hypoglycemia at night (Somogyi phenomenon) and hyperglycemia at night (Dawn phenomenon) with fasting hypoglycemia are also more commonly seen.

Table 6

EFFECT OF MATERNAL DIABETES.

Fetus	Mother
Still birth	Miscarriage
Macrosomia	Polyhydramnios (20%)
Congenital abnormalities	Infection
Hypoglycemia	pyelonephritis, UTI, Monilial vaginitis
Hyperviscosity syndrome	Pre- eclampsia
Hyaline membrane disease	Preterm Labor
Hypercalcemia	Intraoperative interference
Increased Perinatal mortality	Puerperal sepsis
Morbidity	Failing Lactation
	Medical complications
	hypoglycemia, nephropathy,
	retinopathy, neuropathy

TABLE 7
Complicatons of Fetal Hyperinsulinemia

Maternal hyperglycemia
Fetal hyperglycemia
Fetal β cell hyperplasia

Decrease Surfactant — Fetal Hyperinsulinemia — increased erythropoietin production

Decrease pulmonary Maturity

Hyaliene Membrane Disease | **Delay in switch from HbF to HbA** | **Neonatal Hypoglycemia** | **Polycythemia**

Increased Growth of insulin sensitive tissue
Increased deposition of adipose tissue
Increased hepatic glycogen content

Macrosomia

TABLE 8
Factors influencing congenital malformations

Glucose control	Incidence of congenital malformations
Normoglycemia at conception	2-3%
Hypercalcemia at conception	6-12%
HbA1c<8.5%	2.4
HbA1c>8.5%	22.4%
ClassesA,B,C diabetes mellitus	3.1-4.5%
Class D,F,R,H	10.7-11.8%
Overt diabetics without vascular disease	1.6%
Overt diabetes with vascular disease	6.8%

EFFECT OF PREGNANCY ON DIABETES:

The effect of pregnancy on diabetes is largely dependant upon the optimal control of blood glucose levels. In the event of uncontrolled blood glucose levels, there is an increased risk of progression of complications like diabetic cardiomyopathy; nephropathy and retinopathy. The association of proteinuria, raised serum creatinine (>1.5mg/dl), hypertension and ketoacidosis prior to 20 weeks of gestation has an adverse effect on perinatal outcome(14, 15

Pre-Pregnancy Counselling / Assessment

Good metabolic control is the key to prevent adverse outcome and in pregestational diabetes mellitus this has to be achieved prior to planning pregnancy. The value of a pre-pregnancy clinic is well established and is widely practiced in western countries.(9) All diabetic women of reproductive age should receive pre conceptual counseling The components of pre-pregnancy clinic assessment/ counselling are :

- Risk to baby
- Maternal morbidity and mortality
- Need for meticulous control and effort required to achieve this:
  (Multiple insulin injections, self-monitoring of blood glucose, frequent antenatal visits, careful attention to diet, stop alcohol and smoking)
- Genetic counseling, contraceptive advice till a good metabolic control is achieved
- Assess and optimize glycaemic control
  (check pre and post meal glucose, glycated Hb, insulin adjustment)
- Assess complications
  (Retinopathy, nephropathy, neuropathy, Hypertension. Ischemic Heart Disease)
- Obstetric assessment

In women with good glycemic control, the frequency of congenital malformation is approximately 3%, but it rises to 22% in women with poor glycemic control. Initiation of hypoglycemic therapy after the period of organogenesis does not prevent congenital malformations. The incidence of congenital malformations can be reduced to the level of non-diabetic population by careful biochemical control, right from pre-conception period.(4,5) . Most studies have failed to identify a threshold level of glycaemic control at which incidence of congenital malformation rises. The target should therefore be a glycated Hb value within normal range at the time of conception as well as normal pre and postprandial glucose. Maternal postprandial blood glucose values have been shown to correlate significantly with fetal macrosomia.(16,17)

Folic acid and antioxidant therapy should be initiated 3-6mths prior to planning for pregnancy and should be continued during the first trimester

MANAGEMENT OF THE PREGNANT DIABETIC:

In view of the several fetal and maternal complications associated with a diabetic pregnancy, every effort should be made to achieve normoglycaemia throughout pregnancy to prevent adverse pregnancy outcome.(6,7,8,9) This would involve a multidisciplinary approach with a health

care team as shown in Table-9. The team members should ideally be present in a combined clinic or at least a ready access to all these services at frequent interval should be provided.

TABLE 9
Health Care Team For Diabetic Pregnancy

- Diabetologist
- Obstetrician
- Diabetes Specialist Nurse
- Dietitian
- Neonatal Paediatrician
- Motivated Patient

Proper management also requires increased awareness and close cooperation of the patient and her relations. There is a need of continuing education of the general practitioners and obstetricians working in the district levels.

The main principles of management are:

1. Good glycemic control
2. Prevention of obstetric complications
3. Early detection and prompt treatment of medical problems
4. Optimal time and mode of delivery
5. Arrangement for the care of the newborn

Ante natal surveillance

In addition to routine history taking and antenatal care, obstetric monitoring and monitoring of other metabolic factors is done throughout the duration of pregnancy **(Table-10)**.[7,8]

Gestational age	Screening	Therapy
-6	GHb	Normalization of GHb
-2	GHb	Recheck GHb Teach basal body temp
+2	GHb, SMBG, TFT, KFT Eye exam routine prenatal care	reinforce diet plan, insulin regimen/dose
+8-40	GHb every 4 weeks SMBG: 6/day USG at 8, 20, 24 wks repeat KFT, fundus	modify diet modify insulin admit if BP is high
+32-40	obstetric surveillance for fetal well being	increase insulin; plan delivery

GHb =glycated haemoglobin, SMBG=self monitoring of blood glucose, TFT=thyroid function test, KFT=kidney function test

Glycaemic Control During Pregnancy[6,7,8]

A carefully selected insulin regimen and home blood glucose monitoring has revolutionized the achievement and maintenance of normoglycemia. Capillary blood glucose should be measured by a glucometer before and 90-120 minutes after each meal and occasionally at 3 AM to detect asymptomatic hypoglycemia. The 7-point monitoring may not be done on the same day and may be spread over by doing 1-4 measurement everyday. Monitoring may be done more often while achieving control and at the expected time of change in requirement i.e. 2nd half of pregnancy. Targets of pre-meal capillary glucose should be between 60-90mg/dl and about 120mg/dl after meal. A mean blood glucose of 100mg/dl is also considered good control.(11)

Glycaemic control during pregnancy is achieved by modifications in the diet, insulin dose and regimen and appropriate advice on exercise as follows:

DIET

A regulated diet is a prerequisite to allow predictable and smooth glycaemic control. Caloric requirements are as shown in Table-5. The caloric restrictions should be applied to obese patients as far as possible. The diet should consist of less than 40% of complex carbohydrates and less than 30% of fats with saturated fats restricted to 10%.

Diet Calculation in Pregnant Women

WEIGHT	CALORIE REQUIREMENT
< 80% IBW	40kcal/kg/d (actual pregnant weight)
80-120% IBW	30 kcal/kg/d
120-150% IBW	24 kcal/kg/d
>150% IBW	12-20 kcal/kg/d

EXERCISE(8,9,18)

The women with pregnancy can use arm ergometry or undertake walks as permissible by the obstetrician and such a programme results in lower level of glycaemia than diet alone. Exercise improves both hepatic glucose output and peripheral glucose utilization and is particularly useful in overweight pregnant diabetics. Most advises of exercise in diabetic pregnancies have to be supervised closely. Diet and exercise may obviate the need for insulin treatment in many patients with gestational diabetes mellitus (GDM).

INSULIN(6,7,8)

Insulin therapy is instituted when diet therapy does not achieve a good metabolic control. Due to decrease in insulin sensitivity, the insulin requirement goes up especially during later half of pregnancy. Requirements may range from 0.7 u/kg/day in the first trimester to about 1.0 U/kg/day in the third trimester. A split-mix regimen may be sufficient for few patients while most patients require multiple dose injections (MDI) i.e. intermediate or long acting insulin at bedtime and regular insulin before each meal. Patients of GDM may be controlled with simpler regimens. Human insulin is preferable but there is no teratogenicity with purified animal insulin. There is no transplacental passage of insulin as it degraded by placenta. The dose of insulin is modified as per the results of self monitoring of blood glucose. Use of oral hypoglycemic agents is yet debatable as they cross the placental barrier and may cause severe neonatal hypoglycemia.

Management during labour and postpartum(7,8)

Patients with good metabolic control can be carried to term and a normal vaginal delivery. Patients who did not have good control can be delivered at 36-37 weeks after assessment of fetal well being. It is advisable to deliver insulin dependant diabetics at 38 weeks of gestation as there is little fetal benefit after 38 weeks in utero.(fogsi).The major disadventage is the risk of failure of induction due to unfavourable cervix. Spontaneous vaginal delivery may be contemplated in the absence of other obstetric indicatons and fetal Macrosomia. The risk of shoulder dystocia is 0.07% in vaginal deliveries of infants weighing less than 4000gm and 23% in infants weighing more than 4000gm.

Patients who are to be induced should not receive the morning dose of insulin or 6-10 units of an intermediate acting insulin mey be given subcutaneously. Intravenous line is placed for administering oxytocin and fluids. Generally, Ringer's lactate is administered at 100ml/hour through a controlled infusion pump. Maternal capillary blood sugar should be checked hourly, and if the value is above 120 mg/dl intravenous insulin infusion can be initiated[19] Usually ten units of regular insulin is added to 100 ml of normal daline and infused in a controlled manner. Bolus dose of glucose(5gm/hour of glucose) solution should be avoided. The aim is to maintain a blood glucose around 100 mg/dl.

Prior to elective Cesarean section, approximately one third of the patient's pre-pregnancy dose of insulin is given as intermediate acting insulin in the morning of the day of surgery. Infusion of glucose solutions should be avoided during surgery unless there is a delay between insulin administration and surgery. In the latter event, a glucose infusion drip, as described previously, should be instituted. A neonatal paediatrician should be present to take care of newborn.

Postpartum insulin resistance is decreased and insulin requirement goes down suddenly in pre-gestational diabetes while GDM women may not require insulin at all. The insulin dose should be adjusted accordingly. These patients should be advised to undergo an OGTT at 6 weeks and also counseled regarding recurrence in subsequent pregnancy and increased risk of developing Diabetes mellitus in later life.

The outlook for pre-gestational diabetics who are free of complications has improved considerably with meticulous metabolic control from pre-conception stage and through out the duration of pregnancy.

Management of diabetic complications in pregnancy([6,7])

Pregnancy may worsen renal function in women with diabetic nephropathy. Hence blood pressure must be kept under optimal control. Retinopathy, particularly preproliferative and proliferative may rapidly deteriorate during pregnancy especially once glycaemic control is suddenly improved.[9,10] Prophylactic photocoagulation should be done in such patients before planning pregnancy or early in pregnancy. Coronary heart disease also manifests more frequently in diabetic pregnancies. If known before conception the patient should be advised against pregnancy. If detected during pregnancy appropriate management strategies should be followed.

Management on the infant born from a diabetic pregnancy([6,7,8])

A neonatologist should be actively involved in the management of the infant born to diabetic mothers. Broad outlines of management are summarized in Table-11

Table 11 Management of the infant of diabetic mother

PROBLEM	MANAGEMENT
DAY I	
Congenital malformations	early detection, supportive measures, specific corrective treatment
Birth asphyxia	Supportive measures including ventilator support
Birth trauma	early detection, specific and supportive measures
Macrosomia	Avoid birth trauma
Cardiomyopathy	Confirmation by echocardiography, supportive measures
Hypoglycemia	intravenous glucose, glucagon/epinephrine
RDS	prevention (avoid prematurity, corticosteroids,surfactant therapy) supportive and ventilatory therapy
DAY 2 AND 3	
Hypocalcaemia	calcium and magnesium supplementation
Hyperbilirubinemia	phototherapy, exchange transfusion
Polycythaemia	hydration, partial exchange transfusion
Renal vein thrombosis	supportive measures, heparin (?),
LONG TERM	Increased incidence of DM
	Increased incidence of obesity

Contraception

Diabetic women are encouraged to use copper containing intrauterine devices. The use of oral contraceptive pill is controversial as it may increase the risk of cardiovascular accidents. However, the low dose pills pills can be prescribed to women who do not suffer from microvascular disease. If the woman has completed her family, she should be advises laparoscopic sterilization(19)

Gestational diabetes mellitus(6,7,8,11,12.20)

Gestational diabetes mellitus (GDM) is a heterogenous entity, including carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. GDM may represent an unidentified pre-existing disease, an unmasking of a compensated metabolic abnormality by stress of pregnancy or may be a direct consequence of altered maternal metabolism in pregnancy. The importance of GDM lies in the fact that it not only predisposes to future GDM but it is also associated with a higher risk for future diabetes.

As diabetes mellitus frequently develops after GDM, the auto-immune origin of GDM is an always returning, plausible and current hypothesis.The presence of several auto-antibodies to islet cells (islet cell antibody [ICA], glutamic acid decarboxylase antibody[GADA] and antibody to islet antigen [IA-2A] have been implicated.(20)

Deterioration of glucose tolerance in GDM usually in the 3rd trimester and in the majority of cases glucose regulation will return to normal after delivery. Six weeks or more after pregnancy ends, the woman should be reclassified into one of the following categories: (1) diabetes mellitus, (2) Impaired fasting glucose, *(3*) Impaired glucose tolerance or *(4*) normoglycemia.

Screening for gestational diabetes

Previous recommendations have been that screening for GDM be performed in all pregnancies. However, the ADA does not recommend universal screening for GDM in low risk groups any more These include women who are <25 years of age and of normal body weight, have no family history (i.e., First-degree relative) of diabetes, *and* are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic-american, native american, asian-american, african-american, pacific islander). Pregnant women who fulfill *all* of these criteria need not be screened for GDM.

The optimal time to screen for gestational diabetes in pregnancy is between 24-28 weeks by which time it is manifest in 75% of women who are destined to develop GDM. If there is suspicion of undiagnosed DM or pre-existent DM screening may be done on the first visit itself. The test may be repeated in high risk population at 32 weeks. Screening test consists of a 50-g oral glucose load without regard to meal timing followed by a plasma glucose determination 1 h later. A value of ≥140 mg/dl (7.8 mmol/l) 1 h after the 50-g load indicates the need for a full diagnostic, 100-g, 3-h OGTT performed in the fasting state.(21).The criteria for abnormal glucose tolerance in pregnancy were proposed by o'sullivan and Mahan (After an 100gm OGTT) and revised in 1979 by the NDDG Management(7,8)

Goal of treatment is near euglycaemia. Diet appropriate to the current weight of the pregnant woman is the cornerstone of treatment. Insulin is indicated if FPG>105mg/dl + PPPG >140 mg/dl on >2 occasions within a 2 week period. Dietary interventions to decrease obesity & physical exercise after pregnancy along with an effort to avoid repeated pregnancies can go a long way in preventing GDM.

Glyburide and GDM (20)

The striking paper by Langer et al on gltburide treatment of GDM mothers generated an enormous debate in the literature. In a randomized controlled trial setting they studied 404 women with gestational diabetes that required treatment. The women were randomly assigned to receive either glyburide or insulin, according to an intensified treatment protocol to achieve the desired glycemic control. There were no significant differences between the glyburide and insulin groups in the percentage of macrosomic infants or other investigated outcome parameters including fetal anomalies. The cord serum insulin concentrations were similar in the two groups , and glyburide was not detected in the cord serum of any infant in the glyburide group. Although the authors suggest glyburide as an equivalent substitute for insulin treatment, further confirmatory studies are desirable before a full scale recommendation can be made

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TUBERCULOSIS IN ELDERLY

D. N. Moharana*

"The captain of all the men of death" is an appropriate dictum because of TB taking the lives of the great toll of mankind till the first anti TB drug were discovered in the 1940. The discovery of refampicin and pyrazymide in 1970s further improved the survival of the TB patients. TB including other killer diseases have been controlled because of availability of improved medical care. Increased life expectancy has consequently increased the percentage of freshly diagnosed Pulmonary TB cases from 4% in 1948 to 18% in 1986 in elderly age group as compared to other age groups. Recent study in New Delhi has observed a male to female ratio of 3:1 in elderly, in contrast to 1.4:1 in younger age group.

Over 90% of cases in elderly represent endogenosis tuborculosis i.e reactivation of dormant infection in the lungs or else where in the body and the rest may be exsogenous i.e. acquired from an outside source, usually from a sputum positive case. A substancial reduction in number and percentage of CD4+T-helper lymphocytes in addition to impaired proliferative response has been observed in elderly leading to diminished cell mediated immunity. Inadequate serum levels of vitamin-D has been reported in elderly that could diminish the capacity to inhibit intracellular growth of mycobacteria. Apart from all these mechanisms numerous other factors such as

1. HIV infection, co-morbid diseases such as diabetes mellitus,
2. Silicosis,
3. Malignancies
4. renal diseases
5. immuno-compromised health status
6. immuno-suppresive therapy
7. cigarette smoking
8. alcohol
9. drug abuse
10. Elderly living in migrant camps, homeless shelters & institutions
11. Mental stress and strain and genetic susceptious

HIV infection is very strong risk factor for reactivation of TB. Progressive depletion and dysfunction of CD4+T-helper lymphocytes and also impairs macrophage function including diminished phagocytic capacity, altered cytokine production, decreased elaboration of intermediate oxygen metabolites, and impaired antigen presentation. A study in USA revealed that there is a 30% excess morbidity of TB patients in HIV patients during 1985-1993. However we need to have a study on the precise contribution of HIV in guiding the scnario of TB in elderly.

Diabetes mellitus is a very frequent accompaniment of old age and there more prone for developing TB. Studies in Indian and abroad (Korea) have revealed that the elderly diabetics there is a 3.5 to 44 increase in risk of developing TB and 7 to 8 times higher risk of sputum positivity.

Smokers, alcoholics and drug addicts do have an oxidative damage in the respiratory tree leading to increased secretion, peribronchial fibrosis, repairment of mucocilliary clearance and reduction in T-helper cells.

Migrant camps and homeless shelters are usually associated with over-crowding and poorly ventilated environment that encourages spread of

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infection between inmates. An institutional care for elderly is uncommon in India. However, a French study has shown elderly living in institutions to account for 4 times more TB cases than elderly living at home. Further, mortality, even with treatment, was high and further increased with age. An outbreak of pulmonary tuberculosis, with 27 cases, was recently reported from a nursing home for elderly in Japan, where source of infection was traced to an 82-year-old woman resident.

Clinical features and atypical

Presentation in the elderly

The clinical presentation of tuberculosis in the Elderly is variable.

Primary Infection	Pleurisy with effusion	Reactivation or post-primary form of pulmonarytuberculosis.
It is occasionally observed in old age. Middle and lower lung field infiltrates with progressive primary infection have been reported to occur with this type of tuberculosis in the elderly.(Khan MA,et al	It is more frequent in older individuals. It is caused by rupture of subpleural caseous focus into the pleural space.	It is the most common form of pulmonary tuberculosisin older adults. Failure torecognize this problemearly contributes to an increased morbidity and mortality in the elderly

Comparison of TB in elderly versus younger age patients

Parameters	*Younger group*	*Older group*
The classic symptoms like fever, night sweats, weight loss, sputus production and haemotysis	More common	Less common
Abnormal mentation	Less common	More common
The mortality related to tuberculosis	3%	20%

Diagnosis of TB in elderly

X-Ray findings in Elderly TB

- The chest radiographs in the elderly patients are less likely to have upper lobe infiltration.
- They tend to have more extensive disease involding both lungs, though cavitation was much more common in the younger adults.

Hematological and biochemical abnormalities.

The occurrence of anaemia Hypoalbuminaemia, hyponatraemia, hypokalaemia and deranged liver function tests (LFTs) have been seen much more commonly in the elderly as campared to younger patients eignifying that there may be clinically silent extrapulmonary involvement. (Morris CDW, et al)

Smear and/ or culture of Mycobacterium

Positive smear and/or culture of mycobacteria is thegold standard for the diagnosis of TB. However, many elderly patients are weak and fragile and are unable to produce a good sputum specimen for examination.

Therapeutic difficulties in elederly patients.

- The main cause of failure of treatment in tuberculosis, whatever the age, is kpoor patient compliance.
- Poor memory,poor eyesight and mental confusion may be contributory factors.
- The elederly patients often become apathetic about their treatment and lack of determination required to complete a course of treatment.
- Elderly patients were nearly three times more likely to have adverse reactions to anti-tuberculosis drugs as compared to younger patients.

Tolerability to TB drugs in Elderly.

- The advancing age is an important predictor of hepatotoxicity due to INH and rifampicin. Rifampicin combined with INH has an additive but not synergistic hepatotoxic effect.
- Ethambutol can cause diminution of visual acuity, central scotomas and disturbance of red-green vision attributable to optic neuritis.
- The nephrotoxicity and ototoxicity due to streptomycin is more frequent in patients with pre-existing renal impairment like in elderly and is generally irreversible.

Role of fluoroquinolones for treatment of TB in elderly patients.

- Fluoroquinolones are used for the management of MDR-TB.
- Tuberculous pleurisy with a rapid decrease in pleural effusion is efficiently achieved.
- Fluoroquinolones can be efficiently used as a standard chemotherapy regimen for the treatment of patients with recurrent pulmonary tuberculosis.
- They can be regarded as the second line drugs in therapeutic regimens for MDR-TB
- No significant alteration of either liver function tests, blood tests or any other described side effect is found.
- Newer fluoroquinolones to have higher in vitro activity as compared to older fluoroquinolones.
- They display powerful activities against Mycobacterium Tuberculosis both in vitro and in vivo, which is two times that of older once.
- Levofloxacin at the dose of 300 mg/d shows the same effectiveness and fewer adverse drug reactions in comparison with Ofloxacin at the dose of 600 mg/d in the treatment of pulmonary tuberculosis.
- Newer once are well tolerated and safe as compared to other quinolones.

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MANAGEMENT OF OLEANDER POISONING

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INTRODUCTION :

Yellow oleander (Pila kaner) grown as an ornamental tree in gardens and at religious sites for offerings. It belongs to the family 'Apocynaceae' & species Cascabela thevetia (previously known as (Thevetia peruviana). This plant is native of central & south America, but now is frequently grown in tropical and subtropical regions the other members which belong this species are thevetia abouai, thevetia amazonica, thevetia bicornuta, thevetia guamasi, thevetia avata, thevetia nerifolia, thevetia plumeriaefolia thevetia thevetioides.

Ingestion of oleander seeds and leaves is a common cause of accidental poisoning world wide particularly among children. Case have been reported from places as diverse as Hawaii, the Solomon islands, South Africa, Australia, Europe, the far East and even the United States. It has been used for suicide, homicide, abortion, cattle poison and herbal remedies in India Srilanka Thailand and Brazil because of its easy availability.[1]

Yellow oleander poisoning most commonly occurs in females in the low economic strata in villages and slums in India and Srilanka.[2]

Toxic Principles :

All parts of this plant are highly toxic as they contain cardiac glycosides. The leaves are leathery and narrow to about 16 cm long & 1 to 1.5 cm wide. Flowers are bell shaped to about 7 cm and blooms through out the year. The fleshy fruits which are about the size of an unshelled walnut and seeds are most dangerous. The whole plant also exudes a milk juice which is very poisonous. The kernel of about 10 fruits may be fatal in adults where as even the kernel of a single fruit may be lethal to a child. Yellow oleander contains atleast eight different cardial glycosides including thevbetin A, Thevetin B (cereberoside) thevetoxin, nerefolin. Peruvoside and ruvoside.[3]

Mechanism of Action :

These cardiac glycosides exert a digitalis like effect by inhibiting the transmembrane Na^+/K^+ ATpase pump which is attributable to increased intracellular concentration of cal and Nat. The increased intracellular sodium concentration and the increased serum potassium concentration produce negative chronotropic and positive ionotropic effect. The resulting toxic syndrome resembles. digitalis poisoning with marked hyperkalemia, conduction abnormalities. and ventricular arimythmias.

Acute poisonious :

Yellow oleander poisoning closely resembles digitalis poisoning with local, gastrointestinal, metabolic and cardiac symptoms. Mostly poisoning due to yellow oleander occurs due to ingestion of plant parts particularly kernels and fruits. Sometime it is taken with alcoholic drinks. Children gets accidental poisoning by playing with and tasting bright yellow flowers and conspicuous green fruits. Sap exposure to skin, eyes & mucous membrane may lead to burning sensation irritation. and dryness.

Clinical features :

Following ingestion, local irritation or mucous membrane leads to redness of lips, gums, tongue which is followed by dry mouth nausea, intense vomiting, stomach pain, and diarrhea. Depression, irritability, sweating and fast berthing are commonly observed.

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The main actions of thevetin and other cardiac glycosides are on the heart. In mammalian heart low doses of thevetin have a stimulant action while a large dose will depress or evens stop the heart.

This results in several ECG changes which includes inversion of Twaves, Sinus bradycardia, sino-atrial block, sinus arrest or exit block, first & second degree of heart block, junctional rhythms, AV block AV dissociation, atrial & Ventricular ectopic beats, ventricular tachycardia & fibrillation.

Although the ECG charges is oleander poisoning simulates digoxin poisoning the incidence of Ventricular ectopics and tachycardia are less commonly seen in oleander poisoning than those are seen in digitalis poisoning.[1]

CNS manifestation ranges from mydriasis, drowsiness, coma and occasionally convulsion. Parasthesia and weakness or limbs have been reported in the early phase as apart or peripheral nervous system dysfunction.

The effects of toxin's on autonomic nervous system, skeletal muscles and smooth muscles may result in dilatation of pupil, excessive salivation and stimulation of intestine, bladder, uterus and blood vessels. At times skeletal muscle, was become hypertonic.

Normal oleander glycosides do not have direct effects on respiration, However the respiration can be affected indirectly through shock, metabolic acidosis and CNS affection.

In severe poisoning hypotension & shock can result from severe vomiting and hypovolema, cardiac arrhythmic which in hum may lead to metabolic acidosis including lactic acidosis. Hyperkalemia is also seen is severe poisoning. Occasionally jaundice and acute renal failure may occur.

Diagnosis :

The diagnosis of yellow oleander poisoning should be suspected in a patient presenting with a history of poisoning and ECG findings simulating digoxin toxicity. A digoxin radioimmunoassay confirms the diagnosis.

MANAGEMENT :

General Principle :

Once suspected and / or detected the patient should ideally be shifted to a center equipped for cardiac monitoring as well as for cardiac pacing if possible after taking steps for decontamination including gastric lavage and administration of available drugs for brady or tachyrhythmia. If possible the patient should be accompanied with trained personal with ready stock of atropine, Isoprenaline, Lidocaine, Phenyntoin for emergency use besides cardiac monitor & defibrillator also.

On arrival the patients should ideally be admitted even if asymptomatic for observation, decontamination if not done and cardiovascular monitoring. In severe poisoning admit to an intensive care unit for immediate monitoring.

The treatment should aim at

(a) Gut decontamination by means of emesis or lavage.

(b) Correction of electrolyte imbalance.

(c) Correction of arrhythmias.

Frequent electrocardiograms or continuous cardiac monitoring are mandatory. Electrolytes must be checked regularly particularly serum potassium levels.

Relevant laboratory analyses and other investigation :

(i) Sample collection : Vomitus & plant portions found should be preserved in plastic bag.

(ii) Biomedical analysis :

ECG is valuable for diagnosis, treatment & prognosis.

Electrolytes (especially serum potassium), renal function, hepatic function and Arterial blood gas need to be checked regularly.

(iii) Digoxin immunoassays can be used for diagnosis of available.

Life supportive procedures and symptomatic treatment :

- Ensure adequate airway and ventilation.

- Give adequate oral or IV fluids.

Correct any electrolyte unbalance.

If serum potassium level exceeds 6 mmol/lt administer 50 ml of 50% glucose and 10 units of soluble insulin, Or else use sodium bicarbonate or exchange resins Hemoperfusion may be considered is severe cases. Calcium chloride is contraindicated.[6]

The optimal management is oleander poisoning depends on the occurrence of cardiac effect.

(a) Brady cardia may require atropine. In severe symptomatic bradycardia or in advanced degree of heart block isoprenaline infusion (5-10 μ gram/min) may be started.

If available temporary pacing should be instituted as soon as possible in such cases.

(b) Venticular arrythmias may be controlled with lidocaine or less appropriately phenyntoin. Lidocaine may be administered at a dose of 1 mg/kg IV bolus followed by continuous infusion of 1-4 mg/min. Phenytoin should be infused intravenously slowly is doses of 3.5 to 5 mg/kg at a rate not greater than 50 mg/min to repeat once if necessary,

(c) Shock can effectively be treated with IV fluid if due to hypovolemia. If the shock state persists after correction of hypovolemic state, other pressure agents such as norepinephrine, epinephrine and dopamine may be tried.

Decontamination:

Emesis or gastric lavage are indicated if the patient has not vomited copiously or if no contraindication exist. It should be followed by the administration of activated charcoal, which is highly effective in adsorbing plant toxins and possibly a cathartic.

Elimination :

Forced diuresis, dialysis and hemoperfusion are not helpful in the elimination of cardiac glycosides.

Antidote & Antitoxin Treatment :

The efficacy of Digoxin specific avian Fab antibody fragments have been studied by Eddelstone & Warell (1999)1 and the result have been stated to be encouraging.

Course, Prognosis and mortality :

In severe poisoning, diarrhea, vomiting abdominal pain & bradycardia early feales, hyperkalemia, conduction block ventricular arrhythmia, Lactic acidosis, acute renal failure and seizure indicate serious toxicity. Conduction block & sinus bradycardia may persist for 5 days.

Multiple and varying cardiac rhythms, SA & AV blocks in combination with ventricular excitability & marked depression of ST segments in excess of 2.5 mm have been identified to be poor prognostic indicators. The usual cause or deaths in oleander poisoning is venticular fibrillation, although in some cases advanced degree of AV blocks, shock & renal function may lead to death.[4]

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SLEEP APNEA IN HYPERTENSION

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

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

OSAS is the commonest form of SDB. Recurrent episodes of cessation of respiratory airflow caused by upper airway obstruction and collapse during sleep with consequent decrease in haemoglobin O_2 saturation. Apnea >10 secs. may be assocoiated with significant decrease in systemic O_2 concentrations with consequent myocardial and systemic hypoxaemia. Inspiration against closed glottis in sleep may lead to negative intrathoracic pressure→increased LV afterload & consegquent ↑ transmural pressure thus inducing further cardiac wall stress.

COMMON TERMS USED

SLEEP APNEA (SA): Intermittent cessation of airflow at the nose and mouth during sleep for atleast 10 secs. regardless of O_2 saturation. SLEEP APNEA SYNDROME (SAS): A clinical diorder – recurrent episodes of SA during sleep. HYPOPNEA: One of the three : 30% or more reduction in airflow, Thoracoabdominal excursion with atleast 4% decrease in arterial O_2 saturation, Arousal (EEG)

APNEA-HYPOPNEA INDEX (AHI) : Average no. of apneas and hypopneas that occur / hour of sleep.

AHI > 5 = OSAS , MILD AHI= 5-15; MODERATE AHI =15-30; SEVERE AHI = >30, SLEEP APNEA

EPIDEMIOLOGY & PREVALENCE

Common but under diagnosed problem 80-90% cases undiagnosed in USA (Silent Epidemic).

PREVALENCE : (USA figures)

General population→2% women; 4% men. Children →2 – 3%. 30 to 60 yrs age group → 9% women; 24% men.Similar prevalence estimate in other countries. Prevalence higher in elderly, obese individuals. Racial and ethnic variations.

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RISK FACTORS

Conventional risk factors. Recently implicated risk factors : Menopausal status women, Ethnic origin, Family history, Use of sedatives potentiates effect of all risk factors. Central obesity is the most important risk factors.

A 10% weight loss was associated with a 26 decrease in the AHI in a population based study(Peppard PE; Scheuller M), OBESITY is present in 70-90% of cases.

PATHOGENESIS

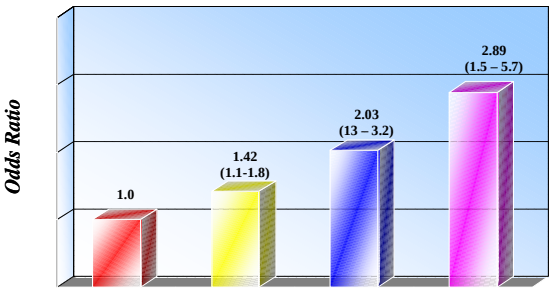
OCCLUSION – Oropharynx –Asphyxia-Arousal ⇒Marked Fragmentation of Sleep. COLLAPSE OF UPPER AIRWAY- due to generation of a critical subatmospheric pressure duing inspiration that exceeds the ability of the airway dilator & abductor muscles to maintain airway stability. Minority-ANATOMIC DISTURBANCES– adenotonsillar hypertrohy, macroglossia etc.

Majority- subtle reduction in airway size “pharyngeal crowding”, ‘FLOPPY’-airway.

CHARACTERSTICS OF HYPERTENSIVE PATIENTS WITH SLEEP APNEA

Although SA is possible in all HTN, index of suspicion should be high in the following :

Elderly male (30 – 60 yrs), Obesity, Daytime somnolence, Nocturnal choking or gasping, H/o – witnessed apneas, Non dipper hypertensive patients, Patients with resistant hypertension



EVIDENCE LINKING OSA to HTN

INITIAL STUDIES - SETBACKS

CAUSE: Inadequate controlling for confounders.

TO OVERCOME: Employed multiple regression modelling techniques to try to unravel independent associations

IN GENERAL: The more the controlling, the less is the independent effect of OSA on BP.

UNAVOIDABLE CONSEQUENCE OF THIS APPROACH: Is that true cause and effect within closely correlated variables such as Obesity, Blood pressure, and OSA are difficult to establish.

1st approach- Employed multiple regression modelling techniques. Lavie et al studied 2677 pts over a 10 yr period – exercise and caffeine consumption were not considered. 2nd approach- to bypass the problems of confounding has been the use of case control studies. Davies et al matched 45 pts with OSA to 45 control subjects without OSA from the communityThematching was difficult as, not suprsingly, many subjects matched to pts. with OSA had degrees of OSA themselves & had to be discarded. 3rd approach is the treatment approach.

Evidence to suggest SDB may be independently associated with high BP was provided mainly from SHHS, WSCS & several other studies. Sleep apnea - ? Independent risk factor for HTN (Nieto et al). The odds of HTN increase with increasing AHI in a dose response fashion. Follow-up for 4 years – threefold increase in the odds ratio of developing NEW HTN if baseline AHI was 15 or more / hour (Pappard PE et al, 2000).

Relationship between OSA & HTN persisted even after adjusting for a variety of confounding variables including age, gender, BMI, tobacco & alcohol use and baseline HTN status. Multiple regression analysis of BP levels of patients not taking AHTs showed that apnoea was a significant predictor of both SBP and DBP

Also, multiple regression showed that each additional apnoeic event / hr of sleep increase the odds of HTN by 1%, whereas each 10% decrease in nocturnal PO_2. increase the odds HTN by 1.3% (Lavie P et al, 2000) > 50% of patients with OSA have systemic hypertension.

EVIDENCE LINKING OSA TO HTN

SUMMARY

Most compelling evidence linking OSA to HTN was recently provided by the Wisconsin Sleep Cohort Study (WSCS) – sample of 709 pts followed for 4 yrs. & the SHHS-sample of 6132 pts.

RESULTS :

The odds of HTN appeared to rise with increasing AHI in a dose-response fashion. Three fold increase in the odds ratio of developing HTN- if baseline AHI was ≥15 events/ hr. A dose response association from baseline & de-novo presence of HTN 4 years later that was independent of other

Changes in blood pressure and other confounding factors with severity of apnoea. Values are mean (SD) unless stated otherwise

Variable	Severity of apnoea*			
	Controls (n=1249)	Mild apnoea (n=755)	Moderate apnoea (n=308)	Severe apnoea (n=363)
Age (years)	45.9 (12.7)	50.0 (12.0)	51.9 (11.9)	50.8 (12.2)
% Males	61.5	78.0	86.4	89.3
Body mass index	28.5 (5.9)	30.6 (6.3)	32.9 (6.9)	35.4 (7.7)
Neck circumference	38.5 (4.1)	40.7 (3.7)	42.5 (3.9)	44.5 (4.2)
Waist:hip ratio	0.92 (0.09)	0.96 (0.07)	0.99 (0.06)	1.01 (0.06)
Pack years of smoking	10.9 (17.7)	13.4 (18.7)	14.4 (19.2)	14.6 (18.9)
Lowest oxygen saturation	86.2 (5.9)	80.2 (9.4)	74.8 (11.2)	62.7 (18.8)
Mean oxygen saturation	93.2 (2.0)	92.2 (2.8)	91.2 (2.9)	86.0 (5.7)
% Time spent below 90% saturation	6.2 (14.8)	14.5 (22.2)	26.4 (25.8)	45.3 (28.6)
% Hypertensive	22.8	36.5	46.0	53.6
% Antihypertensive drug use	13.8	23.0	30.1	29.2
Morning systolic blood pressure	118.1 (16.9)	124.8 (18.4)	128.5 (18.7)	133.4 (18.7)
Morning diastolic blood pressure	70.1 (10.4)	73.6 (10.6)	76.1 (10.7)	78.8 (11.5)

*Controls: non-apnoeic patients (apnoea-hypopnoea index <10); mild apnoea (>10 and <31), moderate apnoea (>30 and <51), and severe apnoea (>50).

Multiple linear regression models for blood pressure measurements only in patients not taking antihypertensive drugs (n=1865)

Independent variables	Systolic blood pressure		Diastolic blood pressure	
	β (95% CI)	P value	β (95% CI)	P value
Apnoea-hypopnoea index (1 apnoeic event)	0.10 (0.07-0.13)	0.0001	0.07 (0.05-0.09)	0.0001
Age (1 year)	0.39 (0.34-0.44)	0.0001	0.21 (0.17-0.24)	0.0001
Sex (male)	-0.70 (-2.50-1.11)	0.45	2.05 (0.86-3.24)	0.0007
Neck circumference (1 cm)	1.01 (0.80-1.21)	0.0001	0.47 (0.33-0.61)	0.0001

risk factors and after adjusting for a variety of confounding variables-age, gender, BMI, tobacco & alcohol use and baseline hypertension status

POTENTIAL MECHANISMS LINKING OSA TO HTN

ACUTE EFFECTS OF OSA

Hypoxaemia, CO_2 retention & marked negative swings in intrathoracic pressure, which increase afterload and myocardial wall stress.

Responses to the apneic events :

Chemoreflex activation with consequent sympathetic activation and increases in BP – which overwhelm the normal cardiovascular physiologic response to sleep. OVERALL during sleep, neither BP nor sympathetic activity decline in severe OSA pts. in contrast to healthy subjects. In OSA pts. high BPs & increased Sympathetic activity during sleep carry over into daytime wakefulness – so that even when Even whenOSA pts. are normoxic, awake & breathing normally, they have a heightned sympathetic drive & higher BPs.

MECHANISMS (PATHOGENESIS)

↑ SYMPATHETIC ACTVITY, RAAS, INLAMMATION, OXIDATIVE STRESS

Some data suggest that Edothelial dysfunction(ED) is present in OSA INDEPENDENT of Obesity.

ED with attenuated NO production in OSA pts. could play a role in OSA related HTN.However,whether ED is impaired in OSA pts is CONTROVERSIAL. RESISTANCE® & CONDUIT©VESSEL IN OSA-for ED. ®→imp. vasodilation or no change & ©→showed endothelial dysfunction. Regarding ® and © vessel- It is imp. to compare healthy SA pts as compared to matched controls not having SA so that confounding variables including obesity can be excluded.

OXIDATIVE STRESS:

Hpoaxaemia and recurrent reoxygenation –> release of potential harmful oxygen free radcals. Excess Anngotensin II- reactive oxygen species(ROS) and ↑ vasoconstrictor activity. In oxidative stress – inactivation of NO, activation of Angiotensin II and thromboaxane receptors increase generation of ENDOTHELIN-1→Vasoconstriction & ED. %Thus, Oxidative Stress may have a role to play.

R A A S

Activated in Obesity as BMI corelates with plasma aldosterone levels Mechanisms: ?

1. activation of SNS. 2. hyperinsulinaemia 3. huperleptinaemia 4. aldosterone-↑ aldosterone levels in urine & low plasma renin activity. 5. angiotesin II levels ↑ in OSA.

Thus-RAAS activation augmented in OSA.

INFLAMMATION

↑ CRP ↑ TNF-Ü INTERLEUKINS-paricularly, I-6 SAA(Serum amyloid A)-acute phase reactant-upregulated by interleukins 1 & 6 OTHERS: Insulin resistance, EDRF, Prostaglandins etc.

SYMPATHETIC NEVOUS SYSTEM & BARORECEPTOR REFLEX

NORMAL INDIVIDUALS (NORMOTENSIVE, NORMOXIC wakefulness) –DURING SLEEP-show ↓HR variability, ↑ BP variability, etc. IN SLEEP APNEA – the sleep stage dependant circulatory control is disrupted. The following mechanisms are involved: hpoxaemia & hypercapnia cause-chemoreceptor mediated activity of the adrenergic

Table 4 Odds ratios for apnoea-hypopnoea index, body mass index, sex, age, and hypertension

Variable	Estimate (Wald 95% CI)	Odds ratio
Intercept	−6.949 (−7.686 to −6.211)	—
Age (10 years)	0.805 (0.718 to 0.892)	2.24
Sex (male)	0.161 (−0.061 to 0.383)	1.17
Body mass index (5 kg/m²)	0.332 (0.256 to 0.409)	1.39
Apnoea-hypopnoea index (10 apnoeic events)	0.116 (0.075 to 0.156)	1.12

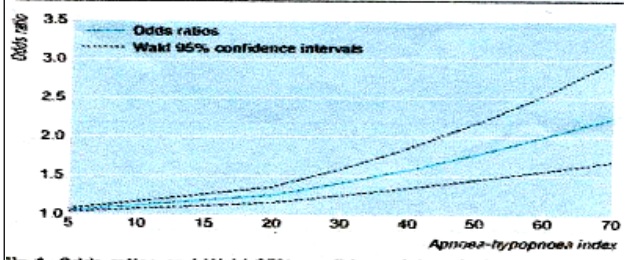


Fig 1 Odds ratios and Wald 95% confidence intervals for hypertension associated with apnoea-hypopnoea index level of 5, 15, 30, 40, 50, 60, and 70 predicted by best fitting multiple logistic (n=2452)

system –> vasoconstriction- ↑ BP. adrenergic stimulation may be augmented by cessation of ventilation resulting in repeated arousals during apneic episodes. Also, the other following mechanisms are involved:

1. Chrnoic periphral activation during hypoxia. 2. Baroreceptor reflex arc dysfunction in OSA. 3. ↑ SNS activity It is in termination of the apnea that HYPERVENTILATION ocurs which increases venous return to heart- ↑ cardiac output. The ↑ cardiac output & peripheral constriction causes high BP.

OSA, OBESITY AND HYPERTENSION

Pts. with HTN – more likely to have OSA than non-HTN. Respiratory disturbances during sleep have been observrd in 22-48% of pts. with essential HTN and prevalance of elavated BP in pts. with sleep apnea is about 30%. OSA prevalance is higher in Obesity which is itself is a factor for development of HTN. Cause: Given the pathophysiological effects of obesity on CVS -it is important to define whether pathophysiological effects of OSA are present independent of obesity. Further-since OSA has emerged recently as a potential risk factor-the corollary is that it is also imp. to ensure that those CV disease mechanisms thought to be secondary to obesity and not in fact primarily a cnsequence of occult OSA in these individuals. Approx. 50% of obese men suffer from OSA & this prevalance of OSA increasese with obesity.

DIAGNOSIS

Clinical Features – HIGH INDEX OF SUSPICION.
Investigations :

"Polysomnography –(a detailed overnight sleep study)

"Electrographic variable (EEG, EOG, Submental emg). Ventilatory variables-(for identification of apneas & their classification as Central or Obstructive. Arterial O_2 saturation (ear or finger OXIMETRY) Heart rate, Continous percutaneous PCO_2 measurements

MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA

GENERAL MEASURES MECHANISMS MILD-MODERATE MODERATE—SEVERE

↑ Upper airway muscle tone	Avoidance-alcohol, sedatives
↑ Upper airway lumen size	Weight reduction UPPP No-supine posture Oral prosthesis
↓ Upper airway subatmospheric pressure	Improved nasal patency Nasal CPAP

BYPASS OCCLUSION - Tracheostomy

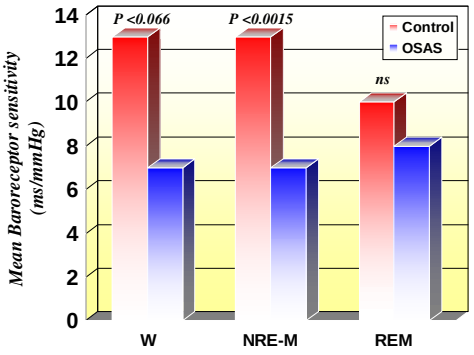
MEDICINES

EFFECTS OF TREATMENTOF SLEEP APNEA ON BLOOD PRESSURE

The effects of treatment of SA by therapeutic doses and subtherapeutic doses of CPAP and APAP appear to be more pronounced in hypertensive patients vis-à-vis normotensive patients

LEARNING POINTS

Large arousal related transient rises in BP occur at the end of each OSA. Daytime HTN is common in OSA but these conditions share many common risk factors and disentangling true cause and effect has been very dificult. Poor quantification of both HTN and OSA will have reduced estimates of any potential correlation. Case control and treatment studies in OSA strongly suggest carryover of HTN into the day, mainly in the morning. Epidemiological studies controlling for as many as possible also strongly suggest that even small amounts of OSA are an independent risk factor for daytime HTN. Potential candidates for provoking daytime HTN in OSA are – nocturnal hypoxia, or hypercapnia, increased ventilatory effort, and sleep fragmentation;the latter seems the least likeley explanation.



☆ ***Decrease in spontaneous baroreceptor sensitivity in patients with OSA syndrome compared with matched controls.***

SUMMARY & CONCLUSION

OSA has been linked to number of CV disorders. PRESENTLY the most compelling evidence suggest that its etiologically associated with HTN. Not only does untreated sleep apnea increase the likelihood of NEW "essential" hypertensions, but also treatment of OSA is accompanied by lower daytime BPs even in patients with relatively mild hypertension. In patients with "resistant" HTN, OSA should be suspected and treated, because treatment of the apnea may improve overall BP control.

If OSA indeed has an etiologic role in events such as stroke, myocardial infarction, heart failure and renal failure, which are all also consequences of HTN, it may well be that treating the OSA may decrease the potential effects of hypertension in leading to these disease conditions. It seems likely, the so called 'essential' / idiopathic hypertension are due to Sleep Apnea.

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EPIDEMIOLOGY, CLINICAL FEATURE & MANAGEMENT OF SNAKEBITE

D.K.Patel, P.K.Mohanty**, L.K. Das*, Shivdutt Padhi***, R.S. Mashon*****

INTRODUCTION

Snakebite is an occupational hazard especially in a tropical country like India. Approximately 20,000 cases of snakebite die in our country annully. We studied the epidemiology and clinical outcome of 32 cases of snakebite in our institute over a period of one year. 31% cases had no local / systemic signs of envenomation. Neurotoxicity was found in 44% of cases. 13% of snakebites resulted in death. Antivenom treatment was the mainstay of treatment with only one case developing hypersensitivity. Although snakebite is common problem in this part of Orissa proper management results in significant reduction of morbidity & mortality.

Snake bite is a common problem in the tropics in view of the occupation, weather and climatic conditions. The paramount fact about bites of man by poisonous snakes is that more than one-half of the victims will have minimal or no poisoning. Only about one quarter will develop systemic poisoning. Hence poisonous snakebite is not synonymous with snakebite poisoning.

CLASSIFICATION

There are two important groups (families) of venomous snakes in South-East Asia namely Elapidae & Viperidae1. Elapidae have short permanently erect fangs. This family includes the cobras, king cobra, kraits, coral snakes and the sea snakes. Viperidae have long fangs which are normally folded up against the upper jaw but, when the snake strikes, are erected. There are two subgroups, the typical vipers (Viperinae) and the pit vipers (Crotalinae). The Crotalinae have a special sense organ, the pit organ, to detect their warm-blooded prey. This is situated between the nostril and the eye. The most important species of snakes from a medical point of view include the following :

A. Elapidae

1.Cobras:	Common Cobra	*N naja*	Common spectacled Indian cobra
		N oxiana	North Indian or Oxus cobra
	king cobra	*Ophiophagus hannah*	
2. Kraits:	Common krait Banded krait	Bungarus caeruleus Bungarus fasciatus	
3. Sea snakes		Enhydrina, Lapemis and Hydrophis	

B. **Viperidae**	
1. Typical vipers	*Daboia russelii (*Russell's vipers) *Echis carinatus (*Saw-scaled vipers)
2.Pit vipers	*Calloselasma rhodostoma* Malayan pit viper

B. Viperidae

1. Typical vipers Daboia russelii (Russell's vipers) Echis carinatus (Saw-scaled vipers)
2. Pit vipers Calloselasma rhodostoma Malayan pit viper

Epidemiology

It is difficult to study the incidence of snake bite because many snake bites and even deaths from snake bite are not recorded. One reason is that many snake bite victims are treated not in hospitals but by traditional healers.

In India the approximate yearly incidence is 200,000 bites with 35-50,000 deaths per year. In 1981, a thousand deaths were reported in Maharashtra State. In the Burdwan district of West Bengal 29,489 people were bitten in one year with 1,301 deaths 2,3. It is an occupational disease with death reported amongst farmers, plantation workers (rubber, coffee), herdsmen, hunters, Snake handlers, fishermen, fish farmers and sea snake catchers (for sea snake skins, leather).

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The epidemiology of snakebite in various countries is as follows:

Country	No. Bites per year	No. deaths per year
India	200,000	20,000
Brazil	51,026	1,153
USA	7,000	15
Australia	2,000	2
SriLanka	-	900
Burma	-	2,000
VSSMC, Burla	32	4

At V.S.S. Medical College, Burla 32 cases of snake bite were admitted in one year and the present study was undertaken in these patients.

Age & sex distribution of snakebite in one year at V.S.S. Medical College, Burla

Age group	Male	Female	Total	%
<20	3	1	4	12.5
21-30	9	4	13	40.6
31-40	7	5	12	37.5
>40	3	0	3	9.4
Total	**22**	**10**	**32**	**100%**

Maximum cases were in age group of 21-40 years. Commonest occupation was farmer. Commonest site of bite was lower limbs (76%).

Venom composition [4]:

Most complex of all poisons: More than 20 components

Dry poison contains 90% proteins (polypeptide toxin/ enzyme)

Elapidae & Hydrophidae Poison

- ***Neurotoxin:***
  - Cobrotoxin (60AA) like alpha bungaro toxin is a curare like substance which acts on post junctional Ach (Acetyl Choline) receptors blockade. The action is slow but irreversible.
  - Beta bungarotoxin (crototoxin, talpoxin 120AA) causes decreased pre synaptic release of acetylcholine.
  - Cholinestrase- Leads to accelerated ACh breakdown.
  - Beta RTX (Receptor active protein) Release of endogenous opioids leading to sedation.
- ***Cardiotoxin*** – Cardiac asystole due to direct action on heart.
- ***Local toxin:*** Hyaluronidase – Helps spread of necrosis & oedema.
  Hydrolases – Increased permeability
- ***Hemolysin-***
  - Lecithinase (phospholipase A): Direct/ Indirect hemolysis leading to massive intravascular hemolysis & acute renal failure.
  - Cobra C_3b- Activation of complement by alternate pathway leading to DIC.

Viperidae poison

- ***Daboia russelii (Russell's vipers)***
  Toxin with clotting disturbances-
  - RVV-X: A glucoprotein which causes DIC leading to defibrination, diffuse bleeding, acute renal failure & anemia.
  - RVV-V (Arginine ester hydrolase) Caused activation of coagulation cascade leading to DIC
- ***Echis carinatus (Saw-scaled vipers)***
  - Ecarin (Zinc metalloprotein) - Causes activation of prothrombin.
  - Phospholipase A2- Damages RBC, WBC, Plasma, endothelium & mitochondria
  - Autopharmacological release of histamine.

Clinical features:

Poisonous snakebite is not equivalent to snakebite poisoning. 50% of snakebites with poisonous snakes bears no signs of poisoning because snake bite in man is a defensive reaction with rare injection of much venom. Bite by non poisonous snakes is not common.

Symptoms:

Commonest is fright , fear of impending death. Emotional reaction within minutes causes semi consciousness, cold skin, feeble pulse, rapid breathing causes pins & needle sensation. In our study of 32 cases 10 cases (31%) had no local or systemic sign of envenomation.

Local pain is mild to severe in cobra and viper envenomation. Swelling occurs because of phospholipase polypeptide toxin, hyaluronidase, autocoids (histamine , kinin, 5HT). However local swelling is not seen in krait and sea snake[5].

Local finding in Cobra & Viper bites:

Local swelling	**Cobra**	**Viper**
Onset	1-3 hrs	within minutes
Maximum	48hrs	12hrs
Necrosis	Rule	Depends upon the de gree of envenomation.

Nature of snakebite in 32 cases

Nature of snakebite	***No***	***%***
No envenomation (local/ systemic)	10	31
Neurotoxic cobra/ krait	14	44
Vasculotoxic (Viperidae)	8	25
Total	**32**	**100**

In the present study the local signs of envenomation were as follows:

- Of the 7 cases of Krait bite one case had mild swelling.
- Of the 7 cases of Cobra bite all had local swelling, 1 had necrosis.
- Of the 8 cases of Viper bite 1 had extensive necrosis or blister formation; 5 had mild local reaction.

Systemic signs:

a. Neurological: Elapidae [6]:

Early symptoms	**Early Signs**
• Vomitting	• Ptosis
• Drowsiness	• Contracted frontalis
• Blurred vision	• Goose flesh
• Hyperaccusis	• Neuropalsy
• Ptosis	• Respiratory paralysis
• Difficulty in swallowing	• Coma (due to respiratory failure)
• Neck weakness	• Convulsion
• Respiratory palsy	

a. Hematological (Viperidae) [7]

- Bleeding from fang mark or injection site
- Gingival bleeding, hemoptysis on deep coughing , hematuria or subconjunctival bleeding.
- Rarely patient may develop visceral, intra cranial bleed or peritoneal bleeding.
- Blood becomes uncoagulable

b. Intravascular hemolysis due to cobra & some viper toxins

c. ARF common in Russel viper bite [8].

- This may be caused by DIC, hypotension, hemoglobinuria & myoglobunuria.

d. Hypotension & shock [6]

- Russel viper causes auto pharmacological syndromes due to release of histamine, bradykinin.
- Oligo peptides are released which have ACE inhibitor like action.
- The other reason could be hypersensitivity to snake venom especially in snake charmers.

Time of death:

- Elapidae : 1-12 hrs
- Sea snake : 12 -24 hrs
- Viperidae : 2-7 days

Clinical feature & outcome of snakebite in 32 cases

Clinical feature	No cases	%
Local swelling	16	50
Neurotoxicity	14	44
Intravascular hemolysis	5	16
ARF	4	13
Hypotension & shock	2	6
Death	4	13

Local swelling was seen in 50% of the cases. The commonest systemic symptoms was neurotoxicity found in 44% cases. 28 (87.5%) patients out of 32 recovered completely. Four cases (12.5%) died. All the deaths occurred in patients with neurotoxic (Elapidae) envenomation.

Investigations:

1. Routine hematological tests

Haemoglobin concentration/haematocrit: a transient increase indicates haemoconcentration resulting from a generalised increase in capillary permeability (eg in Russell's viper bite). More often, there is a decrease reflecting blood loss or, in the case of Indian and Sri Lankan Russell's viper bite, intravascular haemolysis.

Platelet count: this may be decreased in victims of viper bites.

White blood cell count: an early neutrophil leucocytosis is evidence of systemic envenoming from any species.

Blood film: fragmented red cells ("helmet cell", schistocytes) are seen when there is microangiopathic haemolysis.

Plasma/serum may be pinkish or brownish if there is gross haemoglobinaemia or myoglobinaemia.

2. 20 minute whole blood clotting test (20WBCT) [9]

This very useful and informative bedside test requires very little skill and only one piece of apparatus - a new, clean, dry, glass vessel (tube or bottle). Place a few mls of freshly sampled venous blood in a small glass vessel.

- Leave undisturbed for 20 minutes at ambient temperature
- Tip the vessel once.
- ?If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenaemia ("incoagulable blood") as a result of venom-induced consumption coagulopathy
- Incoagulable blood is diagnostic of a viper bite and rules out an Elapidae bite.

3. Bleeding & Clotting time: Increased in patients with DIC

4. Urine examination: The urine should be tested by dipsticks for blood/ haemoglobin/myoglobin. Standard dipsticks do not distinguish blood, haemoglobin and myoglobin. Haemoglobin and myoglobin can be separated by immunoassays but there is no easy or reliable test. Microscopy will confirm whether there are erythrocytes in the urine. Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalised increase in capillary permeability in Russell's viper envenoming [10].

5. Fibrin degradation product (FDP) - Increased more than 80mg/ml in Viperideae bite (Kit- Latex agglutination).

6. Liver function test (LFT): Mild hepatic dysfunction is reflected in slight increases in aminotransferases. Bilirubin is elevated following massive extravasation of blood.

7. Renal function test: Creatinine, urea or blood urea nitrogen levels are raised in the renal failure of Russell's viper and saw-scaled viper bites and sea snake bites.

8. Electrolyte: Early hyperkalaemia may be seen following extensive rhabdomyolysis in sea snake bites. Bicarbonate will be low in metabolic acidosis (eg enal failure).

9. Radiological examination of the chest & electrocardiography: In cobra bite there could be myocardial necrosis leading to ST elevation raised cardiac markers & pulmonary oedema.

10. Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidaemia (respiratory or metabolic acidosis). Arterial oxygen desaturation can be assessed non-invasively in patients with respiratory failure or shock using a finger oximeter.

Treatment:

A. Reassurance: Many patients develop acute psychological symptoms to snake bite without envenomation these patients need reasuurance & emotional support.

B. Local treatment [5, 11]:

1. The bitten limb, which may be painful and swollen, should be nursed in the most comfortable position, preferably slightly elevated, to encourage reabsorption of oedema fluid. Bullae may be large and tense but they should be aspirated only if they seem likely to rupture.
2. Bacterial infections: Infection at the time of the bite with organisms from the snake's venom and buccal cavity can be treated by injectable penicillin G sodium 6 lakh units 6 hourly & gentamycin. Immunisation for tetanus with toxoid is recommended. Interference with the wound (incisions made with an unsterilised razor blade/knife etc) creates a risk of secondary bacterial infection and justifies the use of broad spectrum antibiotics (eg amoxicillin or a cephalosporin plus a single dose of gentamicin plus metronidazole).
3. Compartmental syndromes and fasciotomy: The appearance of an immobile, tensely-swollen, cold and apparently pulseless snakebitten limb may suggest the possibility of increased intracompartmental pressure, especially if the digital pulp spaces or the anterior tibial compartment are involved. Swelling of envenomed muscle within such tight fascial compartments could result in an increase in tissue pressure above the venous pressure, resulting in ischaemia. This is evidenced by disproportionately severe pain, weakness of intracompartmental muscles, pain on passive stretching of intracompartmental muscles, hypoaesthesia of areas of skin supplied by nerves running through the compartment & obvious tenseness of the compartment on palpation.
4. Detection of arterial pulses by palpation or doppler ultrasound probes, does not exclude intracompartmental ischaemia. Intracompartmental pressure can be measured directly through a cannula introduced into the compartment and connected to a pressure transducer or manometer. Intracompartmental pressures exceeding 40 mmHg may carry a risk of ischaemic necrosis (eg Volkmann's ischaemia or anterior tibial compartment syndrome). However, fasciotomy should not be contemplated until haemostatic abnormalities have been corrected, otherwise the patient may bleed to death. Animal studies have suggested that muscle sufficiently envenomed and swollen to cause intracompartmental syndromes, may already be irreversibly damaged by the direct effects of the venom. Early treatment with antivenom remains the best way of preventing irreversible muscle damage. Intracompartmental syndrome may need fasciotomy. This can be carried out in patients in whom haemostatic abnormalities have been corrected & intracompartmental pressure exceeds 40 mmHg.

C. Antivenom treatment

Antivenom is the only specific antidote to snake venom. A most important decision in the management of a snake bite victim is whether or not to give antivenom.

Antivenom is immunoglobulin (usually the enzyme refined F(ab)2 fragment of IgG) purified from the serum or plasma of a horse or sheep that has been immunised with the venoms of one or more species of snake. "Specific" antivenom, implies that the antivenom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain specific antibody that will neutralise that particular venom. Monovalent or monospecific antivenom neutralises the venom of only one species of snake. Polyvalent or polyspecific antivenom neutralises the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area. In Haffkine Institute, Kasauli & Serum Institute of India and Bengal "polyvalent anti-snake venom serum" is raised in horses using the

venoms of the four most important venomous snakes in India (Indian cobra, *Naja naja*; Indian krait, *Bungarus caeruleus*; Russell's viper, *Daboia russelii*; saw-scaled viper, *Echis carinatus*). Antibodies raised against the venom ofone species may have cross-neutralising activity against other venoms, usually from closely related species. This is known as paraspecific activity. The manufacturers of Haffkine polyvalent anti-snake venom serum claim that this antivenom also neutralises venoms of two Trimeresurus species [12].

Indications for antivenom treatment: Antivenom treatment carries a risk of severe adverse reactions and in most countries it is costly and may be in limited supply. It should therefore be used only in patients in whom the benefits of antivenom treatment are considered to exceed the risks. Antivenom treatment is recommended if and when a patient with proven or suspected snake develops one or more of the following signs of systemic or local envenoming :

1. Haemostatic abnormalities: spontaneous systemic bleeding, coagulopathy or thrombocytopenia (<100 x 109/litre).
2. Neurotoxic signs: ptosis, external ophthalmoplegia, paralysis.
3. Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia, abnormal ECG
4. Acute renal failure: oliguria/anuria , rising blood creatinine/ urea.
5. (Haemoglobin-/myoglobin-urea:) dark brown urine , urine dipsticks, other evidence of intravascular haemolysis or generalised rhabdomyolysis (muscle aches and pains, hyperkalaemia).

Local envenoming

- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet). Swelling after bites on the digits (toes and especially fingers)
- Rapid extension of swelling (for example beyond the wrist or ankle within a few hours of bites on the hands or feet)
- Development of an enlarged tender lymph node draining the bitten limb

How long after the bite can antivenom be expected to be effective?

Antivenom treatment should be given as soon as it is indicated. It may reverse systemic envenoming even when this has persisted for several days or, in the case of haemostatic abnormalities, for two or more weeks. However, when there are signs of local envenoming, without systemic envenoming, antivenom will be effective only if it can be given within the first few hours after the bite.

Prediction of antivenom reactions

Skin and conjunctival "hypersensitivity" tests may reveal IgE mediated Type I hypersensitivity to horse or sheep proteins but do not predict the large majority of early (anaphylactic) or late (serum sickness type) antivenom reactions. Since they may delay treatment and can in themselves be sensitizing, these tests should not be used [12].

Contraindications to antivenom

There is no absolute contraindication to antivenom treatment, but patients who have reacted to horse (equine) or sheep (ovine) serum in the past (for example after treatment with equine anti-tetanus serum, equine anti-rabies serum or equine or ovine antivenom) and those with a strong history of atopic diseases (especially severe asthma) should be given antivenom only if they have signs of systemic envenoming.

Prophylaxis for antivenom hypersensitivity in high risk patients

In the absence of any prophylactic regimen that has proved effective in clinical trials, these high risk patients may be pre-treated empirically with subcutaneous epinephrine (adrenaline), intravenous antihistamines (both anti-H1, such as promethazine or chloramphenicol; and anti- H2, such as cimetidine or ranitidine) and corticosteroid. [12].

In asthmatic patients, prophylactic use of an inhaled adrenergic "2 agonist such as salbutamol may prevent bronchospasm.

Selection of antivenom

Antivenom should be given only if its stated range of specificity includes the species known or thought to have been responsible for the bite. Liquid antivenoms that have become opaque should not be used as precipitation of protein indicates loss of activity and an increased risk of reactions.

If the biting species is known, the ideal treatment is with a monospecific/ monovalent antivenom, as this involves administration of a lower dose of antivenom protein than with a polyspecific/ polyvalent antivenoms. Polyspecific/ polyvalent antivenoms are preferred in many countries because of the difficulty in identifying species responsible for bites. Polyspecific antivenoms can be just as effective as monospecific ones, but since they contain specific antibodies against several different venoms, a larger dose of antivenom protein must be administered to neutralise a particular venom.

Administration of antivenom [13]

- Epinephrine (adrenaline) should always be drawn up in readiness before antivenom is administered.
- Antivenom should be given by the intravenous route whenever possible.

Freeze-dried (lyophilised) antivenoms are reconstituted, usually with 10 ml of sterile water for injection per ampoule. The freeze-dried protein may be difficult to dissolve.

Two methods of administration are recommended:

(1) Intravenous "push" injection: reconstituted freeze-dried antivenom or neat liquid antivenom is given by slow intravenous injection (not more than 2 ml/minute). This method has the advantage that the doctor/nurse/ dispenser giving the antivenom must remain with the patient during the time when some early reactions may develop. It is also economical, saving the use of intravenous fluids, giving sets, cannulae etc.

(2) Intravenous infusion: reconstituted freeze-dried or neat liquid antivenom is diluted in approximately 5-10 ml of isotonic fluid per kg body weight (ie 250-500 ml of isotonic saline or 5% dextrose in the case of an adult patient) and is infused at a constant rate over a period of about one hour.

Local administration of antivenom at the site of the bite is not recommended!

Antivenom must never be given by the intramuscular route if it could be given intravenously.

Dose of antivenom

Snakes inject the same dose of venom into children and adults. Children must therefore be given exactly the same dose of antivenom as adults.

Manufacturers' recommendations are usually based on inappropriate animal tests in which venom and antivenom are incubated before being injected into the test animal.

The recommended dose is often the amount of antivenom required to neutralise the average venom yield when captive snakes are milked of their venom. In practice, the choice of an initial dose of antivenom is usually empirical.

Antivenom manufacturers, health institutions and medical research organizations should encourage and promote the proper clinical testing of antivenoms as with other therapeutic agents. This is the only reliable guide to the initial dose (and safety) of an antivenom [14].

Since the neutralising power of antivenoms varies from batch to batch, the results of a particular clinical trial may soon become obsolete if the manufacturers change the strength of the antivenom.

In a study it was found that low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenoming [12].

Since the neutralising power of antivenoms varies from batch to batch, the results of a particular clinical trial may soon become obsolete if the manufacturers change the strength of the antivenom.

Antivenom reactions

A proportion of patients, usually more than 20%, develop a reaction either early (within a few hours) or late (5 days or more) after being given antivenom.

Early anaphylactic reactions: usually within 10-180 minutes of starting antivenom, the patient begins to itch (often over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. A minority of these patients may develop severe life-threatening anaphylaxis: hypotension, bronchospasm and angio-oedema. Fatal reactions have probably been under-reported as death after snake bite is usually attributed to the venom [12].

In most cases, these reactions are not truly "allergic". They are not IgE-mediated type I hypersensitivity reactions to horse or sheep proteins as there is no evidence of specific IgE, either by skin testing or radioallergosorbent tests (RAST). Complement activation by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by antivenom protein are more likely mechanisms for these reactions.

Pyrogenic (endotoxin) reactions usually develop 1-2 hours after treatment. Symptoms include shaking chills (rigors), fever, vasodilatation and a fall in blood pressure. Febrile convulsions may be precipitated in children. These reactions are caused by pyrogen contamination during the manufacturing process. They are commonly reported.

Late (serum sickness type) reactions develop 1-12 (mean 7) days after treatment.

Clinical features include fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and rarely encephalopathy. Patients who suffer early reactions and are treated with antihistamines and corticosteroid are less likely to develop late reactions.

Treatment of early anaphylactic and pyrogenic antivenom reactions

Epinephrine (adrenaline) is given intramuscularly (into the deltoid muscle or the upper lateral thigh) in an initial dose of 0.5 mg for adults, 0.01 mg/kg body weight for children. Severe, life-threatening anaphylaxis can evolve very rapidly and so epinephrine (adrenaline) should be given at the very first sign of a reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia or restlessness. The dose can be repeated every 5-10 minutes if the patient's condition is deteriorating [11].

At the earliest sign of a reaction:

- Antivenom administration must be temporarily suspended
- Epinephrine (adrenaline) (0.1% solution, 1 in 1,000, 1 mg/ml) is the effective treatment for early anaphylactic and pyrogenic antivenom reactions

In the present study the amount of antivenom required for recovery varied from 5 – 24 vials with a mean of 12.4 vials per patient. Only 1 patient developed mild hypersensitivity which responded to anti histamine and steroid injections.

D. Treatment of hypotension and shock

This is usually the result of hypovolaemia (from loss of circulating volume into the swollen limb, or internal/external haemorrhage), venom-induced vasodilatation or direct myocardial effects with or without arrhythmias. Ideally, treatment with plasma expanders (colloids or crystalloid) should be controlled by observation of the central venous pressure (jugular venous pressure or direct measurement of pressure in the superior vena cava via a catheter connected to a saline manometer, see Annex 4).

Excessive volume replacement may cause pulmonaryoedema when plasma extravasated in the bitten limb and elsewhere is reabsorbed into the circulation. In patients with evidence of a generalised

increase in capillary permeability, a selective vasoconstrictor such as dopamine may be given by intravenous infusion, preferably into a central vein (starting dose 2.5-5 ìg/kg/minute).

In victims of Russell's viper bites in Myanmar and South India, acute pituitary adrenal insufficiency resulting from haemorrhagic infarction of the anterior pituitary may contribute to shock. Hydrocortisone is effective in these cases.

Two of the cases in the present study had hypotension and shock of which one died inspite of aggressive treatment.

E. Acute renal failure

Oliguric phase of renal failure

Most, but not all, patients with acute renal failure are oliguric, defined as a urine output of less than 400 ml/day or less than 20 ml/hour. Conservative management may tide the patient over, avoiding the need for dialysis. If the patient is hypovolaemic, fluid challenge: depending on the initial state of hydration/ dehydration, an adult patient can be given two litres of isotonic saline over one hour or, until the jugular venous pressure/central venous pressure has risen to 8-10 cm above the sternal angle (with the patient propped up at 45o). The patient must be closely observed while this is being done. The fluid challenge must be stopped immediately if pulmonary oedema develops. If the urine output does not improve, try furosamide challenge. Furosamide (frusemide) challenge: 100 mg of furosamide is injected slowly (4-5 mg/minute). If this does not induce a urine output of 40 ml/hour, give a second dose of furosamide, 200 mg. If urine output does not improve, try mannitol challenge. Mannitol challenge: 200 ml of 20% mannitol may be infused intravenously over 20 minutes but this must not be repeated as there is a danger of inducing dangerous fluid and electrolyte imbalance. An improvement in urine output to more than 40 ml/hr or more than 1 lit/day is considered satisfactory [12].

Serum potassium, urea, creatinine and, if possible, pH, bicarbonate, calcium and phosphate should be monitored frequently. Electrocardiogram (ECG) should be examined for evidence of hyperkalaemia, especially following bites by sea snakes, or Sri Lankan or South Indian Russell's vipers or if the patient is passing dark brown urine, indicating rhabdomyolysis or intravascular haemolysis.

ECG evidence of hyperkalaemia: tall peaked T waves, prolonged P-R interval, absent P waves, wide QRS complexes.

Emergency treatment of hyperkalaemia (S. potassium >6.5 mmol/l or ECG changes)

Give 10 ml of 10% calcium gluconate intravenously over 2 minutes (with ECG monitoring if possible) repeated up to three times give 50 ml of 50% dextrose with 10 units of soluble insulin intravenously. Sodium bicarbonate (40 ml of 8.4%) by slow intravenous infusion and a â2 agonist aerosol by inhaler (eg salbutamol – "Ventolin" 5-10 mg) may also be used. These emergency treatments will control hyperkalaemia for 3-6 hours only. If the patient is hypotensive and profoundly acidotic (deep sighing "Kussmaul" respirations, very low plasma bicarbonate concentration or very low pH - <7.10), 40 ml of 8.4% sodium bicarbonate (1 mmol/ml) may be infused intravenously over 30 minutes. If this leads to circulatory improvement, the dose can be repeated.

Dialysis: Indications for dialysis

- Clinical uraemia
- Fluid overload
- Blood biochemistry – one or more of the following creatinine >6 mg/dl (500 ìmol/l); urea >200 mg/dl (400 mmol/l); potassium >7 mmol/l (or hyperkalaemic ECG changes)
- symptomatic acidosis

Prevention of renal damage in patients with myoglobinuria or haemoglobinuria

To minimise the risk of renal damage from excreted myoglobin and/ or haemoglobin:

- Correct hypovolaemia (see above) and maintain saline diuresis (if possible)
- Correct severe acidosis with bicarbonate ?give a single infusion of mannitol (200 ml of 20% solution over 20 minutes)

Diuretic phase of renal failure

Urine output increases following the period of anuria. The patient may become polyuric and volume depleted so that salt and water must be carefully replaced. Hypokalaemia may develop, in which case a diet rich in potassium (fruit and fruit juices) is recommended.

Four of the 32 cases (13%) developed renal failure. All of them recovered by conservative treatment.

F. Haemostatic disturbances

Bleeding and clotting disturbances usually respond satisfactorily to treatment with specific antivenom, but the dose may need to be repeated several times, at six hourly intervals, before blood coagulability (assessed by the 20WBCT) is finally and permanently restored.

In exceptional circumstances, such as severe bleeding or imminent urgent surgery, once specific antivenom has been given to neutralise venom procoagulants and other antihaemostatic toxins, restoration of coagulability and platelet function can be accelerated by giving fresh frozen plasma, cryoprecipitate (fibrinogen, factor VIII),d electrolyte replacement may be needed infresh whole blood or platelet concentrates these patients. Heparin is ineffective against venom-induced thrombin and may cause bleeding on its own account. It should never be used in cases of snake bite. Antifibrinolytic agents are not effective and should not be used in victims of snake bite.

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Current Concept

ROLE OF STATINS IN HEART FAILURE

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ABSTRACT

The prognosis of heart failure remains grim even after improvement of heart failure treatment with combination of angiotensin-converting enzyme inhibitors, diuretics, beta blockers and digitalis. Half of patients with a diagnosis of heart failure will die within 4 years, and of those in severe heart failure, 50% will die within 1 year. In view of this bleak scenario, any new addition of drugs to existing therapeutic armamentarium for treatment of heart failure is always welcome. Statins have been shown to lower morbidity and mortality in coronary artery disease and other atherosclerotic vascular diseases. Analyses of these trials have shown statin therapy reduces the risk of developing heart failure. Statins have therapeutic properties that are of potential benefit to patients with heart failure of both ischemic and non-ischemic aetiologies, irrespective of lipid levels. Some concern has been raised regarding the potential adverse effects of statins in heart failure. Low blood cholesterol levels are associated with poor outcomes in advanced heart failure. However, current observational data strongly support the use of statins in appropriate patients. Ongoing trials like CORONA and GISSI-HF are expected to provide more robust evidence for the therapeutic role of statins in the treatment of heart failure.

Key Words : Statins, Heart Failure, Pleiotropic effects.

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INTRODUCTION

Although mortality from coronary artery disease is declining, the incidence and health burden due to heart failure are rising. In the United State of America alone, approximately 5 million persons have heart failure (HF) and 550,000 new cases are diagnosed annually; HF is the most common cause of hospitalisation among persons aged e”65 years and health care costs for HF exceed $20 billion annually.[1] Unfortunately no data exists regarding the incidence of HF in India. Patients with HF having severely reduced left ventricular function and severe symptoms are at particular risk with mortality rates approaching 30% per year.[2] Current therapy for patients with chronic heart failure includes angiotensin converting enzyme inhibitors, â-adrenergic receptor blockers, diuretics and digitalis. However, despite aggressive medical therapy, HF is major cause of morbidity and mortality worldwide. Half of patients with diagnosis of HF will die within 4 years, and those in severe HF, 80% will die within 1 year.[3]

The 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins) are among the most frequently prescribed medications in clinical practice used for treating hypercholesterolemia and coronary artery disease (CAD). However, clinical trials for primary and secondary prevention of CAD have routinely excluded patients with HF. Despite the frequent intersection of CAD with HF, the relationship of statin therapy to outcomes in HF is not well established.[2] Additionally, many patients with HF do not have significant CAD, and the appropriateness of therapy with statins is unclear. In the present article, we shall review the evidence for and against

the use of these agents in patients with HF and whether they are indicated at all in patients with non-ischemic HF.

Role of Statins in Ischemic Heart Failure

Statins are of proven clinical benefit in patients with CAD, at least in those who do not have HF.[4] Consequently, the greatest potential benefit of studies in HF is probably in those patients with CAD. It is highly likely that the proportion assumed to have CAD is actually an underestimate, as patients with HF thought not to have CAD are often found to have CAD, if invasive investigation is undertaken.[5]

Current Evidences

Fundamental to the proposition that statins may reduce the progression of HF is the belief that acute coronary events (which statins reduce) contribute to this progression. There is good evidence that this is, indeed, the case.

In the Studies of Left Ventricular Dysfunction (SOLVD), interim myocardial infarction (MI) and unstable angina (UA) increased the risk of death and hospitalisation for HF.[5] MI had a particularly powerful effect, more than doubling the one-year risk of HF hospitalisation from 8.6% to 20.5% (relative risk : 2.1, 95% confidence interval : 1.6 – 2.6).

A similar insight can be gained from the Scandinavian Simvastatin survival study.[4] In the placebo group of 4S, 52% of patients developing HF had a preceding, post-randomisation, MI (i.e., in many, if not most, patients a recurrent infarction). Of those not developing heart failure, the proportion having interim infarction was only 16%.

Limitation of Present Data

However, recognised MIs are uncommon in HF trials.[7] This may be because infarction is more commonly fatal in patients with HF, and death is then classified as sudden death rather than due to MI.[8] It is also possible however, that CAD becomes burnt out as HF worsens. Thus, new coronary events are uncommon, and progression of disease occurs in other ways. Review of data from HF trials and registers also suggests that angina may be more common in milder HF and less so in patients with more advanced HF.[9] Overall, therefore it is likely that acute coronary events are probably a more important mechanism of progression in patients with lesser degrees of HF and LV systolic dysfunction.

Even in such patients, there is evidence that statins retain their efficacy in preventing acute ischemic events. In the Cholesterol and Reduction of Events (CARE) study, 706 patients with an LV ejection fraction (EF) of > 0.25 and < 0.40 were randomised.[10] Pravastatin was equally effective in reducing coronary events in these patients as in patients with an EF of >0.40 (Fig. 1).

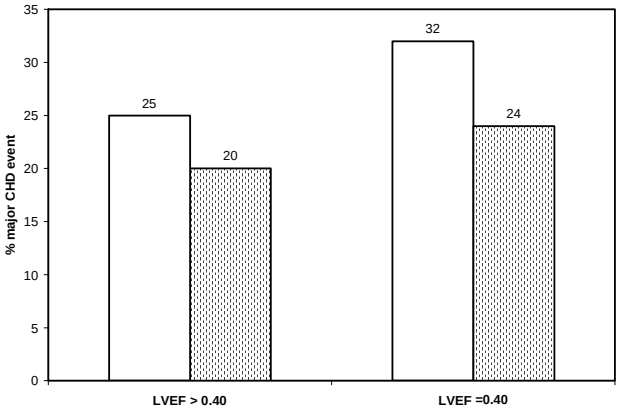

Fig. 1: Effect of pravastatin on coronary events in patients with coronary artery disease and a left ventricular ejection fraction (LVEF) of >0.40 enrolled in the Cholesterol and Recurrent events trial.[10] CHD = coronary heart disease. White bar =placebo, Dotted bar = pravastatin.

Ongoing Definitive Trials of Statins in Heart Failure

Several large scale trials are currently underway to examine the efficacy of statins on clinical outcomes in HF patients. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) is currently enrolling 4950 patients with ischemic cardiomyopathy and symptomatic HF (NYHA functional class III or IV) and a EF of 40% or less or NYHA functional Class II and IV of 35% or less.[34] The primary objective of this study is to

examine the effect of rosuvastatin (10 mg daily) versus placebo on the composite end point of cardiovascular death, nonfatal MI or nonfatal stroke.

GISSI – HF is another ongoing project which is a placebo controlled multicentre clinical trial.[35] This trial is evaluating the effects of N-3 polyunsaturated fatty acids (PUFAs) and rosuvastatin in patients with symptomatic HF (NYHA functional Class II-IV) of both ischemic and non-ischemic origin. Approximately 7000 patients will be randomised to n-3 PUFAs (1g daily) or placebo and to rosuvastatin (10 mg daily) or placebo, with co-primary end points consisting of, first all cause mortality, and second all cause mortality or cardiovascular hospitalisations. Both trials are expected to be completed within next few years and should provide strong evidence for the therapeutic role of statins in the treatment of HF.

Evidences for Role of statins in Ischemic Heart Failure

Lowering cholesterol levels with statins results in significant reduction in mortality and cardiovascular end points in comparison with placebo in patients with relatively preserved left ventricular function and both normal and high levels of plasma cholesterol and proven CAD.[4] Retrospective, non-randomised subset, analyses suggest a possible benefit of statins in HF patients.

Retrospective Studies

In the 4S study, the mortality rate in patients developing HF was 25.5% in the simvastatin group compared with 31.9% in the placebo group.[4] Among those who developed HF, simvastatin conferred a 6.1% absolute risk reduction for mortality, compared with 2.6% absolute risk reduction in patients without HF.

Similar results were noted in a retrospective analysis of Losartan Heart Failure Survival Study (ELITE II).[11] In this study 3152 HF patients were randomly assigned to either losartan or captopril. While only 11% of the study cohort were on statin therapy, those individuals receiving statin had a significantly lower all cause mortality (10.6%) compared with that not taking statin (17.6%).

These results were validated by a study of 551 patients with advanced systolic HF of various aetiologies referred to cardiomyopathy clinic for HF management and transplant evaluation.[12] Patients had a mean EF of 25% and nearly half had CAD. Forty-five percent of patients in the study cohort received statins. As expected, patients on statins were more likely to have known CAD, or known atherosclerotic risk factors including hypertension, diabetes, and a history of tobacco use. The blood cholesterol levels were nearly similar in all the patients, irrespective of statin use. After adjustments for age, gender, presence of CAD, cholesterol levels, diabetes, medication use, haemoglobin, creatinine and New York Heart Association (NYHA) functional class, statin use was associated with a 14% absolute risk reduction in mortality or necessity for urgent heart transplantation at one year. Although reduction in mortality associated with statin use was substantial, the findings should be cautiously interpreted in light of the retrospective and nonrandomised nature of the study.

Prospective Studies

Mozaffarian et al have prospectively evaluated the relationship between statin use and clinical outcomes in patients with HF.[13] Using data from Prospective Randomised Amlodipine Survival Evaluation (PRAISE) trial, they examined the effects of statin on overall mortality in 1153 patients with advanced systolic HF and NYHA Class III B or IV symptoms. The PRAISE trial was a randomised study of amlodipine versus placebo in HF patients. Approximately 12% patients received a statin during the study period. Over a mean follow up of 1.3 years, statin use was associated with a 62% reduced incidence of death. The association persisted even after adjustment for differences in clinical characteristics and serum cholesterol levels among statin and non-statin treated groups and after propensity score analysis.

Observational Studies

Ray et al have done largest observational study of statin use in HF.[14] They carried out a population based retrospective cohort study of 28828 patients, aged 66-85 years, who survived at least 90 days following hospitalisation for HF. Using administrative data from the province of Ontario, Canada, the authors reported that, during the 7 years study period, patients who were newly dispensed statins (n=1140) had a statistically significant 28% reduction in the incidence of death, MI, or stroke (13.6 per 1000 person years) compared with patients who were not dispensed statins (n=27692; 21.8 per 1000 person years). The benefit from statins in the study was mostly related to reduction in all cause mortality. Several important limitations of this study should be considered. Confounding the results are higher rates of previous angina, acute MI or revascularisation procedures and greater co-morbid conditions, including hypertension, dyslipidemia, and diabetes, among those patients prescribed statins at discharge. Consequently, these individuals were more likely to be prescribed ACE inhibitor, angiotensin II receptor antagonists, aldosterone antagonists, and aspirin, all of which are known to improve outcomes in HF patient.

Evidences for role of statins in non-ischemic Heart Failure

While CAD is a common cause of HF, question arises whether patients with nonischemic HF can benefit from statins. Very little is known about the benefit of statins in this group of patients.

Node et al have examine the effects of short-term statin therapy in patients with non-ischemic, symptomatic HF.[15] Sixty three patients with NYHA class II-III HF were randomise to simvastatin (10 mg/day) or placebo. After 14 weeks, the statin group had lower NYHA functional classification (2.04 Vs. 2.32, $P < 0.01$) and significantly lower plasma concentration of tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), and brain natriuretic peptide (BNP) compared with the control group. In addition, statin treated patients had improved EF at 14 weeks (34% to 41%, $P < 0.05$) compared with baseline. This effect was not seen in the placebo group. These results do provide initial evidence for the beneficial effects of statin therapy in patients with non-ischemic HF.

Role of Statins in diastolic heart failure (DHF)

In a hypothesis - generating preliminary study, Fukuta et al examined 137 consecutive HF patients with an EF of at least 50% who were being evaluated at an academic medical centre.[16] During a follow up of 21 ± 12 months, 20 deaths were observed. Treatment with an ACE inhibitor or receptor blocker, β-blocker, or calcium blocker had no significant effect on survival. In contrast, treatment with statin was associated with a substantial improvement in survival (relative risk of death [95% CI] 0.22 [0.07 to 0.64]; $p = 0.006$). After adjustments for differences in baseline clinical variables between groups (hypertension, diabetes, CAD and serum creatinine), statin therapy was associated with lower mortality (adjusted relative risk of death [95% CI] 0.20 [0.06 to 0.62]; $P = 0.005$). The authors concluded that statin therapy may be associated with improved survival in patients with heart failure. The study was not a definitively large, multicentre, double blind, randomised, placebo controlled, clinical study but rather a hypothesis generating preliminary study. However the authors used a state-of-the-art analytic method (propensity matching) in an effort to correct for the bias inherent in the non-randomised treatment assignment.

Mechanisms of beneficial effects of Statins in Heat Failure

The beneficial effects of statin therapy can be divided into those effects that relate to its lipid-lowering effects (lipid dependent) and those effects that may be independent of its lipid-lowering effects (lipid independent; Table-1).

Table-1

Pleiotropic Effects of Statins

- Lipid dependent
  - Decrease vascular atherosclerosis
  - Decrease myocardial infarction
  - Decrease cerebral vascular accident
  - Decrease peripheral vascular disease
- Lipid independent
  - Decrease LV mass
    - Inhibit angiotensin I-mediated cardiomyocyte hypertrophy
    - After intercellular signaling molecules that affect growth regulation
      - Decrease extracellular signal-related kinase (ERK ½) activity
      - Decrease ERK, phosphorylation
      - Decrease RAS membrane targeting and activation
    - Antihypertensive
  - Decrease LV fibrosis
    - Decrease inflammation (decreased C-reactive protein, interleukin-6)
    - Decrease immune activation
    - Alter matrix metalloproteinase activity
    - Decrease oxidative stress, decrease oxygen free radicals
  - Increase arterial compliance
    - Decrease vascular atherosclerosis
    - Improve endothelial function
    - Decrease endothelin synthesis
    - Increase nitric oxide
- Decrease morbidity and mortality in patients with diabetes and renal insufficiency
- Decrease thrombosis

HF is a complex syndrome characterised by haemodynamic, metabolic and neurohormonal alterations including elevation of inflammatory markers, endothelial dysfunction, and neurohormonal imbalance with increased levels of catecholamines, cytokines, renin, angiotensin, and aldosterone.[17].

Antithrombotic Effects and Statins

The potential efficacy of statin in patients with ischemic HF is related to its antithrombotic effects. Autopsy data reveal that a large percentage of mortality in patients with impaired left ventricular function results from acute coronary syndrome precipitated by atherosclerotic plaque rupture.[19] The benefits of statin-induced alteration in lipid profiles have been shown in a variety of population resulting in reduced incidence of vascular disease, vascular events (eg. myocardial infarction and cerebrovascular accident), and cardiovascular morbidity and mortality, which result from vascular disease.[4,19] Whether these lipid-dependent benefits can be realised in patients with chronic HF remains an open question because in most published studies, patients with HF were excluded. However, recent studies have thrown light on this aspect and have demonstrated that addition of statin does indeed reduce morbidity and mortality in patients with HF.[12]

Cardiac Hypertrophy and Statins

The efficacy of statins is mostly due to plaque stabilisation. Statins also significantly preserve viable myocardium resulting in improved ventricular function.[20] In animal models of LV hypertrophy, statins have been shown to reduce LV mass and fibrosis.[21] This lipid-independent effect may result from statin-induced reduction of blood pressure, alterations in myocardial growth regulatory signal transduction pathways, changes in inflammatory and immune-mediated systems or increased arterial compliance.[22]

Inflammation, Oxidative Stress and Statins

Inflammatory mediators play an important role in the development and progression of HF. These mediators or cytokines, are generally pharmacologically active proteins that are secreted by various cell types in response to a variety of stimuli. Among the cytokines, TNF-á plays an important role in the progression of HF. TNF-á has been implicated in the development of LV dysfunction, increased cardiac myocyte apoptosis, and the development of anorexia and cachexia, among other effects.[23] Other cytokines, such as IL-6, are involved in myocyte hypertrophy, myocardial dysfunction, and muscle wasting. Higher levels of IL-6, as well as the inflammatory marker C-reactive protein (CRP), are associated with a poor prognosis in HF patients.

Statins have important anti-inflammatory effects. They down regulate CRP and inflammatory cytokines, which are activated in HF of any aetiology.[24] Recent data have shown a significant reduction in serum levels of hs CRP as well as TNF-á R II and IL-6 in patients with HF treated with statins.[25] In addition, statin treatment was associated with an increase in superoxide dismutase (SOD) activity, suggesting that statins also have anti-oxidant activity in this patient population. These anti-inflammatory and antioxidant effects of statins may account for the beneficial effects of statins in patients with HF.

Endothelial function and statins

The overall effects of statins on endothelial functions merit special attention. Recent research has provided insights into the profound effects of statin on endothelial cell function. The induction of nitric oxide gene transcription, which yields an increased production of the vasodilating molecule nitric oxide, is one among a number of mechanisms contributing to an improvement in endothelial function.[26] Statins also down-regulate the production of reactive oxygen species, which are known to inhibit nitric oxide activity.[27]

Tousoulis et al carried out a prospective, randomised, placebo controlled study on the effects of four weeks of treatment with atorvastatin (10 mg/day) in patients with chronic HF.[28] Atorvastatin treatment affected the coagulation and fibrinolytic system in that it decreased the plasma concentrations of antithrombin III, protein C, coagulation factor V, tissue plasminogen activator, and plasminogen activator inhibitor type-I. Statins interfere with coagulation factors independently of where the production site is located.

Neuroendocrine activation and statins

Statins also normalise sympathetic outflow and autonomic function.[17] Strey et al report that treatment with statin versus placebo is associated with lower concentrations of all measured cardioendocrine hormones, although the difference is significant only for atrial natriuretic peptide (ANP).[29] Given the problems with cardioendocrine hormone measurement and the small patient population (n=23) examined, the data are only suggestive of statin derived benefits for the HF typical neurohormonal imbalance. It is uncertain whether the stabilisation of neurohomonal imbalance is secondary to improvement in endothelial dysfunction or to other statin effects having the potential to delay HF progression. Such effects include the induction of neoangiogenesis, the downregulation of angiotensin II type 1 receptors, the restoration of autonomic dysfunction, and the inhibition of proinflammatory cytokines.[9] However, endothelium-ameliorating and other cardioprotective statin effects probably act synergistically.

Potential drawbacks to statin therapy in Heart Failure

1) Cholesterol Hypothesis

So far it has been argued that the cholesterol lowering and other actions of statins are beneficial in HF patients. However, one should not lose site of the studies that report a survival disadvantage in HF patients with low serum cholesterol levels.[30,31] Rauchhaus et al reported that, in patients with either ischemic or non-ischemic cardiomyopathy, low serum total cholesterol (d” 201 mg/dl) predicted increased mortality at 12 months independently of other risk factors[31]. This inverse relationship between cholesterol level and mortality has been corroborated

by Mozaffarian et al.[2] They further observed that, in patients with severe HF, the highest mortality was noted in the group of patients with the lowest quartile of cholesterol (<172 mg/dl).

2) Ubiquinone Hypothesis

The adverse effects of statins may be due to increased blood endotoxin levels and decreased levels of the antioxidant ubiquinone, both of which may contribute to HF progression.[17] It has been postulated that higher levels of total cholesterol may be beneficial in HF due to the ability of cholesterol-rich lipoproteins to bind and neutralise the effects of bacterial lipopolysaccharide. Lipopolysaccharide is translocated across the gut wall in patients with advanced HF and is an important stimulus of proinflammatory cytokine production.[32] Ubiquinone, or coenzyme Q10, is a lipid soluble micronutrient that acts as a conenzyme in mitrochondrial oxidative phosphorylation and is believed to be an important endogenous antioxidant. Statin therapy has been shown to be associated with a dose related decrease in serum ubiquinone levels, which may in turn have an adverse effect in HF patients.[33]

3) Endotoxin hypothesis

Lipoprotein in plasma can bind and detoxify endotooxins such as lipopolysaccharide entering the circulation via the gut. In the setting of HF, endotoxin may be an important mediator of HF disease progression via activation of proinflammatory cytokines such as tumour necrosis factor- alpha. It is, therefore, argued that lipid-lowering with statin therapy may enhance endotoxemia by reducing plasma levels of lipoproteins. This may, in turn, result in further elevation of plasma levels of proinflammatory cytokines, levels of which are strongly linked to adverse prognosis in HF. In support of this hypothesis, plasma levels of lipopolysaccharide have been shown to be elevated in patients with HF, although the impact of statin therapy on this parameter has not been examined in this setting.

In spite of the findings from this small observational studies and the theoretical concern that reducing plasma lipoproteins too much may be deleterious in HF, it remains unclear whether low cholesterol levels are directly responsible for the increased risk observed or whether they are merely markers of disease severity, poor nutritional status, hepatic dysfunction, or other surrogates of worse prognosis. Table-2 shows the potential disadvantages of statin therapy in heart failure.

Table-2
Potential Disadvantages of Statin Therapy in Heart Failure

1)	Higher mortality rate with low serum cholesterol levels.
2)	Decrease in blood levels of ubiquinone, an antioxidant.
3)	Increase in blood levels of endotoxin resulting in elevation of pro-inflammatory cytokines.

SUMMARY AND CONCLUSION

Statin therapy lowers morbidity and mortality in coronary artery disease and other atherosclerotic vascular disease, as evidenced by multiple large scale clinical trials. Additional analyses of these trials have shown that use of statins also reduces the risk of developing HF. A reduction in cardiovascular events with statins have been demonstrated irrespective of baseline low-density lipoprotein (LDL) cholesterol. Yet, the impact of statin therapy on HF has not been well studied. So far, the major clinical trials of statin therapy have tended to exclude patients with symptomatic severe HF.

Statins have therapeutic properties which are of potential benefits to patients with HF of ischemic and non-ischemic aetiologies, irrespective of lipid levels. Statins improve endothelial function, inhibit inflammatory cytokines, potentiate nitric oxide synthesis, restore impaired autonomic function, and reverse pathologic myocardial remodelling.

Current observational data strongly support the use of statins in patients with both ischemic and non-ischemic HF. A recent randomised clinical trial has demonstrated significant mortality benefit with statin therapy in patients with diastolic HF. These data strongly support the use of statins in appropriate HF patients. Reinforcement regarding the statin use may well come after the results of CORONA and GISSI-HF trial are published.

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TOXICITY OF STATINS AND ITS MANAGEMENT

S. Mohapatra

Aspirin has remained the single most important agent for treatment of CAD for last four decades. Many other agents have come and gone. Statins (HMG Co-enzyme reductase inhibitors) are the next best agents which have appeared in the treatment armamentarium for CAD. It is effective and the best tolerated drugs for treating dyslipidaemia and are in use in our clinical practice for more than two decades. Volumes have been written about the efficacy and pleotropic effects of statins while there is no doubt that this class of drug is the best thing to have happened in reducing cardio-vascular and cerebro-vascular morbidity and mortality and is comparable only to aspirin.Statins were isolated from a mold known as penicillium citrinum and were identified as inhibitors of cholesterol biosynthesis in 1976 by Endo and his colleagues.Browne and Goldstein[1] established the mechanism of action of the statins that they act by inhibiting the action of HMG Co-enzyme reductase.

The first statin used in humans was compactine, renamed Mevastatin later.

But the first ever statin approved for human use was Lovastatin which was derived from Aspergillus Ferrius which was derived by Alberts and his colleagues at Merck.

Pravastatin and Simvastatin are chemically modified derivatives of Lovastatin while Atorvastatin, Fluvastatin and Rosuvastatin are structurally distinct compounds.Statins exert their major effect i.e. reduction of LDL level through Mevalonic Acid like Moiety that competitively inhibits HMG co-enzyme reductase. By reducing the conversion of HMG co-enzyme A to Mevalonate, Statins inhibit an early and rate limiting step in cholesterol biosynthesis.

A large of well-controlled clinical trials have documented the efficacy and safety of Simvastatin,Pravastatin, Lovastatin and Atorvastatin in reducing fatal and non-fatal CHD events,Strokes and total mortality[2].

Table 1 :

Changes in blood pressure and other confounding factors with severity of apnoea. Values are mean (SD) unless stated otherwise

Variable	Severity of apnoea*			
	Controls (n=1249)	Mild apnoea (n=756)	Moderate apnoea (n=398)	Severe apnoea (n=363)
Age (years)	45.9 (12.7)	50.0 (12.0)	51.9 (11.9)	50.8 (12.2)
% Males	61.5	78.0	86.4	89.3
Body mass index	28.5 (5.9)	30.6 (6.3)	32.9 (6.9)	35.4 (7.7)
Neck circumference	38.5 (4.1)	40.7 (3.7)	42.5 (3.9)	44.5 (4.2)
Waist:hip ratio	0.92 (0.09)	0.96 (0.07)	0.99 (0.06)	1.01 (0.06)
Pack years of smoking	10.9 (17.7)	13.4 (18.7)	14.4 (19.2)	14.6 (18.9)
Lowest oxygen saturation	86.2 (5.9)	80.2 (9.4)	74.8 (11.2)	62.7 (18.8)
Mean oxygen saturation	93.2 (2.0)	92.2 (2.8)	91.2 (2.9)	86.0 (5.7)
% Time spent below 90% saturation	6.2 (14.8)	14.5 (22.2)	26.4 (25.8)	45.3 (28.6)
% Hypertensive	22.8	36.5	46.0	53.6
% Antihypertensive drug use	13.8	23.0	30.1	29.2
Morning systolic blood pressure	118.1 (16.9)	124.8 (18.4)	128.5 (18.7)	133.4 (18.7)
Morning diastolic blood pressure	70.1 (10.4)	73.6 (10.6)	76.1 (10.7)	75.8 (11.5)

*Controls, non-apnoeic patients (apnoea-hypopnoea index <10); mild apnoea (>10 and <31), moderate apnoea (>30 and <51), and severe apnoea (>50).

Multiple linear regression models for blood pressure measurements only in patients not taking antihypertensive drugs (n=1865)

Independent variables	Systolic blood pressure		Diastolic blood pressure	
	β (95% CI)	P value	β (95% CI)	P value
Apnoea-hypopnoea index (1 apnoeic event)	0.10 (0.07-0.13)	0.0001	0.07 (0.05-0.09)	0.0001
Age (1 year)	0.39 (0.34-0.44)	0.0001	0.21 (0.17-0.24)	0.0001

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ADVERSE EFFECTS OF STATINS AND THEIR INTERACTION WITH OTHER DRUGS

After introduction of statins in the market there were several reports of hepatotoxicity in the form of a three-fold rise in trans-aminase level. Cerivastatin introduced in 1998 was withdrawn in 2001 because of unacceptable incidence of Rhabdomyolysis. However,in a large multi-centric trials of statins with Placebo-control where 10-40 mg of Symvastin, Lovastatin, Fluvastatin,Atorvastatin or Pravastatin were used, it was found that in the active treatment group or three-fold increase of ALT was in 1-3 % whereas the same three-fold increase was also seen in 1.1% patients in the placebo group[3]. It is therefore recommended that measurement of ALT should be done at the beginning of initiation of Statins and thereafter whenever it would be clinically recommended.

Patients taking 80 mg of Atorvastatin or 40 mg of Rosuvastatin should have a measurement of ALT at the baseline and then after 3 months.If the ALT values remain normal,then there is no necessity to repeat ALT measurement unless there is clinical compulsion.Standard dose of reduction of cholesterol by 30-40 % by Atorvastatin is 10-20 mg,by Fluvastatin 40-80 mg,by Lovastatin 40 mg,by Pravastatin 40 mg,By Rosuvastatin 10 mg and by Simvastatin,it is 20-40 mg.

Estimation of Creatinine Kinase is recommended at baseline if statins are combined with fibrates.It is recommended that CK estimation should be carried out thereafter whenever there is clinical indication like Myalgia. Routine estimation at every 3-6 month interval is hardly of any benefit as Myopathy may occur after years of combination therapy.

Myopathy is the major adverse effect which occurs with statin therapy and this has got clinical significance.FDA recorded 42 deaths from Rabdomyolysis attributed to use of statins between 1987-2001. Incidence of ten-fold increase of CK level from baseline occurred in 0.17% of patients in active drug group versus 0.13% in patients of placebo group which was not statistically significant.With ten-fold increase in CK,only 25% patients complained of Myalgia versus 10% patients in placebo group[1].

Incidence of overall myopathy in various statin-treared group is low,but the risk of Myopathy and Rhabdomyolysis increases in proportion to plasma statin concentration.[4]

FACTORS ASSOCIATED WITH INCREASED RISK OF MYOPATHY

1. Advanced age.
2. Hepatic dysfunction
3. Renal dysfunction
4. Peri-operative period5. Multi-system disease associated with diabetes
6. Small body surface
7. Untreated hypothyroidism[5]
8. Concomitant use of drugs that decrease catabolism of statins[6]

The drugs are : Fibrates, Cyclosporin, Digoxin, Warfarin,Macrolides, anti-fungals, Niacin, HIV protease inhibitors and Aneodaron.

EFFICACY AND SAFETY OF INDIVIDUAL STATINS

Table 2:

PHARMACO-KINETIC MECHANISM BY WHICH COMBINATION OF STATIN WITH OTHER DRUGS INDUCE MYOPATHY.

	Licensed dose range (% LDL cholesterol reduction)*	Metabolism	Most important drug interactions increasing myopathy risk†
Lovastatin	20–80 mg daily (30% with 40 mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4‡,
Simvastatin	10–80 mg (41% with 40 mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4
Pravastatin	20–80 mg daily (34% with 40 mg)	Sulphation, biliary, and urinary excretion	
Fluvastatin	40–80 mg daily (23% with 40 mg)	CYP2C9 (some CYP2C8 and CYP3A4)	Inhibitors of CYP2C9
Atorvastatin	10–80 mg daily (38% with 10 mg)	CYP3A4	Potent inhibitors of CYP3A4
Rosuvastatin	5–40 mg daily (45% with 10 mg)	Minimal metabolism (via CYP2CP and some CYP2C19) and biliary excretion	
Pitavastatin	2–4 mg daily (42% with 2 mg)	Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation, and bilary excretion	Unclear

Combination with Gemi-fibrozil(commonest cause of statin induced Myopathy)

Inhibition of both uptake of the active hydroxyl acid forms of Statins into hepatocytes is by OATP 2 and interference with transformation of most statins is by CYPs Glucuronidases. Primarily because of inhibition of OATP 2 mediated hepatic uptake co-administration of Gemifibrozil nearly doubles the plasma concentration of Rosuvastatin(endnote 6).This occurs despite the fact that gemifibrozil has no effect on Rosuvastatin Glucuronodation or oxidation which are the basic pathways of catabolism of other statins[7].However, concomitant therapy of Simvastin 10 mg with Fenofibrate 160 mg had no significant pharamacokinetic alterations[8]. This was also supported by Rosuvastatin and Fenofibrate study[9]. When there was concomitant use of Statins with Niacin, myopathy was due to an enhanced inhibition of skeletal muscle cholesterol synthesis[10]

Combination of other drugs which interfere with Statin metabolism

Primarily by CYP3A4 :

Macrolytes like erythromycin, clindamycin

Azole anti-fungals like Itraconazole

Cyclosporin

HIV Protease inhibitors[11] [12].

The pharmacokinetic interactions are associated with increased plasma concentration of statins and their active metabolites.Statins those are primarily metbolised by CYP3A4 are Atorvastatin, Lovastatin and Simvastatin.

Fluvastatin is mostly metabolized by CYP2C9.Pravastatin is the only exception and is not metabolized by CYP system[13]. Pravastatin and Fluvastatin are not extensively metabolized by CYP3A4. However, myopathy has been reported by using these agents.

THE MYOPATHY SYNDROME

Myopathy is characterized by intense Myalgia as in flu,first in the limbs and then in the entire body.Patients complain of weakness and easy

fatiguability.If the patients continue to take these agents,Myoglobinuria, Renal failure and death have been reported[14]. If one suspects ensuing Myopathy,there should not be any hesitation in estimating Creatin Kinase (CK) which is usually more than ten-fold of the normal value.If there is no ten-fold rise in the CK Level, it is wiser to wait for sometime before discontinuing Statin therapy so that the patients are not denied of the benefits of Statins.If myalgia persists for some weeks,it is better to discontinue Statins and any other agent suspected of causing myopathy. Rhabdomyolysis should be excluded and renal function must be monitored in all these cases.

Statins used alone rarely cause myopathy. However,it is safer to have one basal estimation of CK at the beginning of the treatment and if it is combined with either Niacin or Fibrate, then it should be monitored once in six months. This procedure may not be a full-proof method of protecting patients from myopathy which can occur after months to years of initiation of the therapy.As a rule,if the Statins are used at a dose of 25% of its maximal dose,then there is very little chance of patients developing myopathy[15].

Early concern about toxicity of Statins in causing eye pathology has not been substantiated[16].Similarly, speculation that lipid soluble statins might penetrate CNS and cause damage was found to be unfounded apprehension and the difference in the lipid solubility of Statins does not appear to be clinically relevant.

USE OF STATINS DURING PREGNANCY

The safety of Statins during pregnancy has not been evaluated properly and hence Statins should not be used during pregnancy. Women wishing to conceive should desist from taking Statins and women in child-bearing age wishing to avoid pregnancy should take highly effective contraceptives. Nursing mothers should avoid Statins.

USE OF STATINS WITH WARFARIN

Some Statins like Simvastin,Fluvastatin and Rosuvastatin potentiates the effect of Coumarin anticoagulants such as Warfarin.The usual recommendation is to check the INR when Statin treatment is initiated,modified or stopped.It is better to keep the INR Level with control at a ratio of 2-3:1.

USE OF STATINS IN CHILDREN

When there is a need for using Statins in younger children particularly suffering from heterozygous familial hyper-cholesterolaemia may take Atorvastatin,Simvastatin if they are 11 years or older and Pravastatin if 8 years older.

STATINS IN ELDERLY

No adverse effects of Statins have been observed by using standard dose of Statins in elderly upto 80 years who were included in various studies and there was no need for dose adjustment[17].

STATINS IN ALCOHOLICS

There is no clearcut evidence that Statins prescribed in alcoholics (Patients taking more than 21 units of alcohol per week) would cause Hepatic damage or Myopathy though theoretically it was proposed that Statins in Alcoholics might induce Myopathy by pressure necrosis[18].

In heart-protection study, over 2000 participants whose baseline alcoholic intake was more than 21 units per week did not show any incidence of greater risk of Myopathy nor raised transaminase level.

STATINS IN RENAL FAILURE

There is ample evidence that Statins are beneficial in patients having mild to moderate renal failure (1.5-2 times of upper limit of Creatinine level or ½ to 1/3 rate of glomerular filtration) as these agents lower the cholesterol / LDL level,thereby decreasing the risk of cardiovascular morbidity and mortality[19]. One trial which compared Statins with Placebo in 1250 patients undergoing Haemodialysis

did not show significant cardiovascular benefit.Rosuvastatin has been associated with increased risk of proteinuria particularly at higher dose[20]. But the fact remains that the role of Statins in patients of chronic renal failure in reducing cardiovascular morbidity and mortality remains unclear.

STATINS IN HEART FAILURE

Concern was raised that Statins by lowering cholesterol level could worsen heart failure as low cholesterol level was associated with poor outcome in patients with heart failure[21].But many more randomized studies reveal that patients with heart failure who had high level of N-BMP derived as much benefit from Statins as patients on Statins without heart failure.

OTHER POSSIBLE HAZARDS OF STATINS

There has been concern about possible hazards of statins in the form of sleep disturbance, mood disorders,Psychosis,dementia, increased incidence of cerebro-vascular accidents and peripheral neuropathy[22]. But data from controlled randomized

comparison did not show any such adverse effect of statins[23]. Although some studies advocated use of Statins to prevent fracture of bones claiming that Statins had effect on bone mineral density[24], and claims that it would delay / prevent dementia by effects on cognkitive function and would prevent macular degeneration were not supported by evidence from randomized trials[25].

TABLE 3:

SAFETY RESULTS OF STATINS USED IN LARGE RANDOMIZED TRIALS

	Statin comparison higher vs lower	Medical condition of participants	Alanine transaminase three times upper limit of normal higher vs lower
PROVE-IT (4162)[7,32]	A 80 mg vs P 40 mg	Acute coronary syndromes	69 (3·3%) vs 23 (1·1%)
Phase Z of the A to Z trial* (4497)[16]	S 80 mg vs S 20 mg	Acute coronary syndromes	19 (0·9%) vs 8 (0·4%)
TNT* (10 001)[5,38]	A 80 mg vs A10 mg	Stable CHD	60 (1·2%) vs 9 (0·2%)
IDEAL (8888)[6]	A 80 mg vs S 20–40 mg	Stable CHD	43 (0·97%) vs 5 (0·11%)
SPARCL* (4731)[39]	A 80 mg vs placebo	Post stroke or TIA (no CHD%)	51 (2·2%) vs 11 (0·5%)

	Statin comparison higher vs lower	Creatine kinase ten times upper limit of normal, or myopathy higher vs lower	Rhabdomyolysis higher vs lower	Non-vascular death higher vs lower
PROVE-IT (4162)[7,32]	A 80 mg vs P 40 mg	2 (0·1%) vs 3 (0·15%)	0 (0%) vs 0 (0%)	17 (0·8%) vs 27 (1·3%)
Phase Z of the A to Z trial* (4497)[16]	S 80 mg vs S 20 mg	9 (0·4%) vs 1 (0·04%)	3 (0·1%) vs 0 (0%)	21 (0·9%) vs 21 (0·9%)
TNT* (10 001)[5,38]	A 80 mg vs A10 mg	(0·0%) vs (0·0%)	2 (0·04%) vs 3 (0·06%)	158 (3·2%) vs 127 (2·5%)
IDEAL (8888)[6]	A 80 mg vs S 20–40 mg	6 (0·14%) vs 11 (0·25%)	2 (0·05%) vs 3 (0·07%)	143 (3·2%) vs 156 (3·5%)
SPARCL* (4731)[39]	A 80 mg vs placebo	7 (0·3%) vs 7 (0·3%)	2 (0·1%) vs 3 (0·1%)	117 (4·9%) vs 94 (3·9%)

CHD=coronary heart disease. TIA=transient ischaemic attack. A=atorvastatin. P=pravastatin. S=simvastatin.

MANAGEMENT OF MYOPATHY

If CK level is 10,000 international units/ l or more,then statins should be stopped immediately to minimize the risk of renal impairment. High fluid intake is mandatory to minimize the damage to renal function.If CK level is moderately raised,then it is better to lower the dose of statins and re-assess CK to see whether there is a fall in the level.If so,then the Statin may be used in full doses again. It is recommended in all such cases of raised CK level, thyroid function to be estimated as both hypothyroidism and hyperthyroidism can adversely affect the muscles[26].

MANAGEMENT OF RAISED TRANSAMINASE LEVEL

If ALT level is more than three times of the upper limit of the normal value,it is better to repeat the enzyme level after one week interval and if the level remains still high, then to be on the safer side,Statins should be discontinued and treatment may be retried with another agent while monitoring ALT.Non-alcoholic steato hepatitis and biliary cirrhosis improved with statin therapy even though there is raised ALT[27]. Similarly,in patients of Hepatitis B,statins have no adverse effect in spite of raised ALT level.

CONCLUSION

Statins have been studied and used extensively during the past twenty years and benefits derived by using this group of drugs for prevention of cardiovascular morbidity and mortality is widely accepted.Statins seem to be remarkably safe while used at their regular dose.The hazards of myopathy and Rhabdomyolysis should be kept in mind while these agents are used at higher doses.Myalgia experienced in middle –aged female might be due to apprehension but nevertheless Myopathy should be kept in the mind.Baseline measurement of CK,ALT should be routine tests and be repeated whenever clinical suspicion of Myopathy or Hepatitis arises. When other drugs are concomitantly used,potential drug interaction should be kept in mind.

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Case Report

SLE PRESENTING AS PSEUDOTUMOUR CEREBRI

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ABSTRACT

Pseudotumour cerebri (PC) is an uncommon neuropsychiatric manifestation of systemic lupus erythematosus (SLE). PC as presenting manifestation of SLE is very rare and only few such cases have been reported in the literature. We report here a patient of SLE who presented with PC and responded to oral prednisolone and acetazolamide.

KEY WORDS

SLE, Pseudotumour cerebri, Benign intracranial hypertension.

INTRODUCTION

There is a wide range of neuropsychiatric involvement in SLE like cognitive disorder, psychosis, cranial neuropathies, movement disorders, aseptic meningitis, stroke, myelopathy etc. PC is one of the rare manifestation of SLE. A number of sporadic cases of PC in SLE have been reported following the first report by Bettman et al,in 1961[1] . Here we report a case of SLE whose presenting manifestation was PC which is extremely rare.

CASE REPORT

A female of 35 years presented with severe generalized headache and vomiting for one month. There was no history of fever or convulsion, or aural discharge or intake of drugs like vitamin A, oral contraceptive pill or steroid. She had past history of arthralgia involving both knee, elbow, wrist, and metacarpophalangeal joints three years back which lasted for six months and subsided with NSAID.

On examination she was found to have moderate pallor, BP 110/70 mmHg, temperature of 98^0F, oral ulcer but no skin lesion or lymphadenopathy. Neurological examination revealed bilateral papilloedema and no focal neurological deficit or meningeal signs. Laboratory investigation revealed haemoglobin 8gm/dl, TPC – 2,00,000 /mm^3, TLC – 6,000/mm^3, DC – N68 L28 E4, ESR – 60 mm in first hour, reticulo cyte count 3%, direct coombs test positive, ANA was positive (1:40, speckled pattern), ds DNA antibody positive (110 IU /ml) and smith antibody was also positive, rheumatoid factor was negative, urine analysis was normal. Tests for anticardiolipin antibody and lupus anticoagulant were negative. Contrast enhanced CT of cranium and MR venography was normal. On lumbar puncture, opening pressure of CSF was very high and CSF was acellular with normal protein (25mg/dl) and normal glucose (42mg/dl). Serum cortisol, FT3, FT4 and TSH were within normal limit.

Thus it was diagnosed as a case of SLE with pseudotumour cerebri. Patient was put on prednisolone 60 mg/day and acetazolamide 250 mg twice daily for one month and the dose of prednisolone was gradually tapered over a period of two months. Headache and vomiting subsided after two months and there was complete regression of papilloedema at the end of two motnhs.

DISCUSSION

The diagnosis of SLE was confirmed in this patient as per the revised American College of Rheumatology criteria[2], as the patient had oral ulcer,

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autoimmune haemolytic anaemia, positive result for ANA, anti-ds DNA and anti Sm. The patient also fulfilled the modified Dandy criteria for diagnosis of PC[3] as there were signs and symptoms of increased intracranial tension (headache, and papilloedema), no focal neurological deficit, normal CT of cranium and MR venography with normal composition of CSF. PC cases have been reported in association with a variety of medical condition like cushing's syndrome, adrenal insufficiency, hypothyroidism, hyperthyroidism, hypoparathyroidism, pregnancy, obesity, use of drugs like Vitamin A, tetracycline, lithium, oral contraceptive, nalidixic acid, phenytoin, indomethacin, etc. but our patient did not have any such association. So it is reasonable to think that PC was due to SLE. The peculiarity of this patient was that PC was the presenting manifestation of SLE and only few such cases have been reported in the literature[4,5]

The pathophysiologic mechanism of PC in SLE is not exactly known. Immune mediated injury within the arachnoid villi and the resultant decrease in CSF absorption[6-] and/or thrombotic obliteration of cerebral arteriolar and venous systems due to a hypercoagulable state are the most probable mechanisms. Corticosteroid is currently the main stay of treatment of PC in patients with SLE and other useful agents are accetazolamide, mannitol, frusemide etc.

Thus it is concluded that though there are many causes of headache in SLE like migraine ,stress, meningitis, lupus flare etc., the possibility of PC must be considered in any patient of SLE having headache and though rare it can be a presenting manifestation of SLE.

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PERICARDIAL EFFUSION IN SYSTEMIC SCLEROSIS

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ABSTRACT

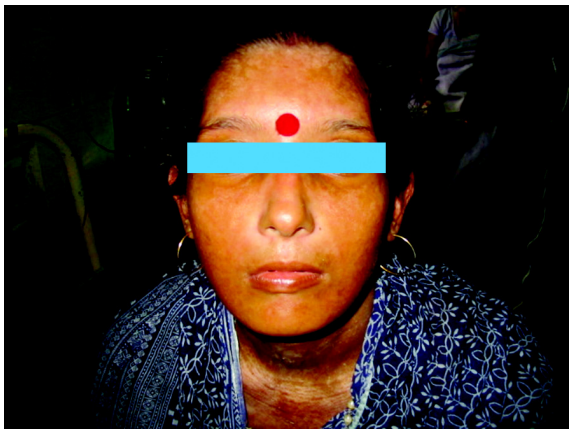
Pathologically myocardium, coronary vessels and pericardium are involved in majority of patients with diffuse scleroderma but clinical evidence is either subtle or absent. Most patients with cardiac involvement remain asymptomatic until heart failure or serious arhythmics occur. Pericardial effusion may occur, causing symptoms and rarely, tamponade[1]. A large pericardial effusion is a poor prognostic sign.

INTRODUCTION

Pathologically myocardium, coronary vessels and pericardium are involved in majority of patients with diffuse scleroderma. The characteristic arteriolor lesions of intimal proliferation and luminal narrowing are accompanied by contraction band necrosis, reflecting Ischemic-reperfusion injury, and patchy myocardial fibrosis that may also involve the conduction system. So cardiac involvement is manifested by myocardial and pericardial disease and conduction system abnormalities. Pericardial effusions may occur, causing symptoms and, rarely tamponade. A large pericardial effusion is a poor prognostic sign. Here we are going to present a case of rapdily progressing PSS-dc with large pericardial effusion with temponede with a diagnostic dilema.

CASE REPORT

A 33 year old Hindu female from Balugaon, Khurda presented to the OPD of Division of Immunology & Rheumatology on 8.8.2008 with complaint of fever - 1½ years; polyarthritis, Alopecia



and thickening of skin - 10 months and difficulty in swolling with breathlessness at rest for 2 months.

Patient had developed fever 1½ years back, it was a continuous type of fever associated only with intermittent burning micturation. She had been treated with Antibioitics for UTI again & again with no results. Seven months latter fever subsided and she developed symmetrical polyarthritis involving both upper limb & lower limb with early morning stiffness more than 2 hours. It was associated with fatigue, swelling of whole body with redness of skin and Reynold's phenomena. In January 2008, she presented to OPD (SCBMCH) advised hospitalisation but patient disappeared. A provisional diagnosis of PSS had been made.

4 months back she developed vitiligo patches over back and upper thorax with thickening of skin throughout the body, difficulty in opening her mouth, ulcers on tips of fingers and toes, difficulty in getting up from a squetting position and rasing her arm and combing her hair.

2 months back she had difficulty in swolling food (both solid & liquid) with drolling of saliva and

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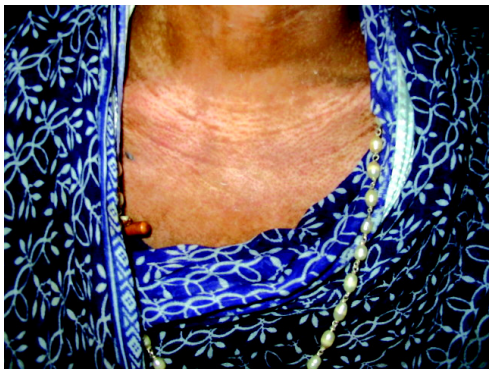
breathlessness on exertion no H/o maler rash, photosensitivity, oral ulcer, genital ulcer or rash or ulcers over body. Previously patient had been treated with high dose Steroids & Endoxen at MKCG Medical College, Berhampur and with Antibioitics & Steriods at Hi-tech Medical College.

General Examination

Patient was conscious, oriented, afebrile, Pulse - 90 bpm, BP - 130/80 mmHg. RR - 26 bpm. sin in thickened through out the body including face, UL/LL, thorax , abdomen and back. Hypopigmented patches over back and thorax, patch of alopecia on



Rt frontal area, Pulp infercts on tips of fingers and toes, Accumulation of saliva in mouth with drooling.

Respiratory system - Normal

CVS - apex not localised

GI system - mouth opening 1½ finger, oral cavity full of saliva, Abdomen skin thickened.

CNS - Only positive finding power grade 4/5 in both UL & LL.

MSK system - Tender B/L small & large joints of both UL & LL with flexer deformity at elbow and knee.

INVESTIGATION revealed – Hb - 10.6 g/dl, ESR - 20, TLC - 20,400, N-90%, L-9%, TPC - 2.6 lakh, urine - album ++ pus cells 20-25, Total urinary protein -159 mg/24 hrs, RPG - 122, Urea - 23, Creatinine - 1.3, LFT - WNL Na+140, K+4.6.

ANA 4+(Homogenous) ds DNA - Negative, C_3 - 137

ENA

SSA - 0.8, SSB - 12.2, SM - 15.6, SM/RNP - 14.1, JO - 1 - 13.13 SCL - 70 (159.3 +ve), LDH - 1143, CPK - 1323.

PFT - Moderate Obs & moderat restriction.

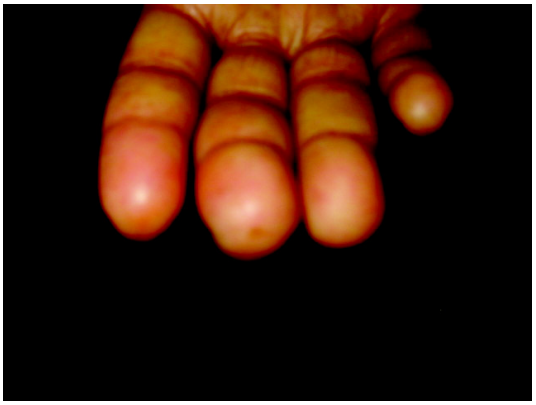
ECG - WNL

2D ECHO - Large perecardial Effusion with early tamponade.

A diagnosis of PSS-dc with polymyosities overlap PSS dc with SLE overlap was made and the patient was put on antibiotics. PPI & Steroids. As the patient was dysphic a pericardiocentesis was done (800 ml fluid removed) on 11.8.2008 aand the fluid was sent for histological & biochemical examination. After pericardiocentesis the condition of the patient improved. The pericardial fluid showed – Clot+, Sugar 96, Protein - 6.2, ADA - 6, Total cell - 600, Lymphocyte 60%, Histocyte & mesothelial cells 40%.

The provisional diagnosis of PSS-dc with polymyocitis overlap was made because of clinical feature of PSS with power grade 4/5 in both upper & lower limbs (proximal myopathy feature) with difficulty in swelling. But lets investigation showed low CPK & LDH levels not fitting into finding of myosites, and the power grade 4/5 may be due to skin thickening.

The second diagnosis of PSS with SLE overlap was done with clinical feature of PSS with patient complaining of alopecia, polyarthrities, pericardial effusion and ANA 4+. But SLE was



excluded as ds DNA was negative, C_3 was normal and not improved in PSS-dc overlap does not occur.

So a final diagnosi of PSS-dc with tubercular pericardial effusion was made with –

1) Clinical features
2) ANA 4+ (homogenous) ??
3) SCL-70 positve (159.3)
4) Perecardial fluid showing high protein content and predominatly lymphocytes.

In view of the above report a final diagnosis of PSS-dc with tubercular peridcardial effusion was made, the patient was put on ATT on 13.8.2008 but suddenly deteriorated and expired on 14.8.2008 at 1 a.m.

Here we are presenting a case PPS-dc with massive pericardial effusion ?? tubercular which was rapidly progressive and proved fatal. The heart is frequently affected in PSS. Cardiac involvement is manifested by myocardial & pericardial disease and conduction ystem abnormalities. Cardiac involvement can also occur secondary to PAH and scleroderma renal crisis. Despite the presence of widespread oblitesetive vasculopathy in SSC, the frequency of clinical or pathological coronary artery disease is not aleviated. Most patients with cardiac involvement remain asymptomatic until heart failure or serious arrhystmics occur.

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WHAT BEHAVES LIKE MENINGITIS MAY ACTUALLY REVEAL PITUITARY APOPLEXY

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ABSTRACT

A 35-year-old female was admitted with fever, headache, vomiting, altered sensorium and neck stiffness. Cerebrospinal fluid examination revealed pleocytosis, an increased protein level and a decreased glucose concentration. On 7th day, patient developed ptosis of left eye. The fever subsided with antibiotics but irrelevant talk persisted. CT scan Brain showed sellar and suprasellar tumor enhancing with contrast. Neurologic deficits gradually improved after removal of the tumor by endoscopic transnasal transphenoidal approach.

Keywords: Meningitis, Pituitary Apoplexy

INTRODUCTION

Pituitary apoplexy may occur spontaneously in a preexisting adenoma; postpartum (Sheehan's syndrome); or in association with diabetes, hypertension, sickle cell anemia, or acute shock. Acute symptoms may include severe headache with signs of meningeal irritation, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness.1 Pituitary apoplexy is a complication in 1% to 2% of all pituitary adenomas.2 Presenting only with meningeal irritation signs, clinically indistinguishable from infectious meningitis are considered rare. We report a 35-year-old female who presented with fever, headache, neck stiffness and no ophthalmoplegia but later was found to have pituitary adenoma with apoplexy.

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CASE REPORT

A 35-yr-old female was admitted following fever, acute headache, vomiting and altered sensorium. Fever had started 5 days prior to presentation; it was high-grade, intermittent not associated with chill and rigor. It was associated with severe headache, vomiting and rapidly declining mental status. There was no remarkable past history of medicosurgical illness. Physical examination revealed temperature of 102 degree Fahrenheit, pulse rate of 114/min, blood pressure of 126/72 mm Hg, respiration rate 22/min and presence of neck stiffness but no limitation of extra ocular movement. The patient was awake and followed simple commands but was not oriented and laughed irrelevantly. Fundoscopy was normal. Laboratory studies showed a TLC of 12,000. Cerebrospinal fluid (CSF) studies revealed protein 300 mg/dl, glucose 12 mg/dl, with 1100 cells/mm3 (polymorphs 97% and lymphocytes 3%) but not erythrocytes. Patient was started on Ceftriaxone and vancomycin for presumed meningitis. After persuasion, as day 4, CT scan of Brain was done revealing a sellar suprasellar tumor enhancing with contrast; with sella erosion. X-ray skull (Translateral view) showed enlarged sella and aerated sphenoid sinus. On 7th day, patients fever had subsided but she had developed ptosis of left eye. Left pupil was dilated, not reacting and left eye remained laterally deviated. Upon MRI of Brain, a pituitary macroadenoma of size 4.0x2.9x2.4 cm. with possible cystic degeneration and intratumoral hemorrhage was identified, but no hydrocephalus or aneurysmal sac was detected. MRA was normal. Serum T3 was 0.608 ng/ml (N: 0.846-2.02 ng/ml), T4 was 2.25 ug/

dl (N: 5.13-14.06), TSH was 0.142 ug/ml (N: 0.270-4.20 uIU/ml). A follow-up CSF study revealed protein 284 mg/dl, sugar 41.4 mg/dl with 70 cells/mm3 (all lymphocytes). CSF culture yielded no growth. The pituitary tumor was removed via endoscopic transnasal transphenoidal approach. The histology revealed pituitary adenoma with extensive areas of necrosis and hemorrhage compatible with pituitary apoplexy.

DISCUSSION:

The signs of meningeal irritation in pituitary apoplexy are caused by subarachnoid hemorrhage that accompany pituitary apoplexy3,4,5 or by sterile chemical meningitis6,7,8. The reported series of chemical meningitis characterized by the state of acute headache, fever, and spinal pleocytosis were clinically indistinguishable from infectious meningitis. Infact, the possibility of infectious or tubercular meningitis in the present patient was not clearly ruled out, nor were her ptosis and ophthalmoplegia present initially. As a result, tumor removal was delayed.

Chronologically, the pathologic profile of apoplexy begins with infarction of the tumor and the surrounding gland, followed by hemorrhage and edema. This sudden increase in intratumoral pressure and volume causes precipitous expansion of the tumor, followed by mechanical compression of the optic apparatus and of structures within the cavernous sinus leading to ptosis, facial pain or diplopia.2

Whereas history accounts of pituitary apoplexy are often associated with a fatal outcome, current management protocols with steroid replacement and urgent decompression have led to good prognoses in most instances. Recovery of vision and oculomotor palsies, although somewhat unpredictable and by no means guaranteed, frequently tend to improve with time.

Pituitary apoplexy may be misdiagnosed as meningitis or subarachnoid hemorrhage. This rare case tells us that pituitary apoplexy must be kept in mind while evaluating a case of meningitis.

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* * *

ATYPICAL PRESENTATION OF TROPICAL PULMONARY EOSINOPHILLIA AS PLEURAL EFFUSION.

S.K. Bhuyan* , D. Padhi*, Seegith M.G *, N. Sahu , P.K. Rout** , S.K Tripathy ***, P.K.Hui*** , P.K. Padhy ******

ABSTRACT

A patient presented with cough worse at night with rt sided pleural effusion ,total peripheral eosinophil count of 3960 cell/microL and serum IgE 10800 .Pleural tap revealed *Wuchereria bancrofti*. The patient was put on diethycarbamazine citrate and recovered in two weeks time.

CASE REPORT

A male patient of 45 years age presented to the OPD of M.K.C.G medical college with complaints of cough worse in the night, pain in the right side of chest..There was no history of wt loss, trauma or passing of worms in stool. He was neither a smoker nor alcoholic. The patient resided in a filarial endemic area.

On examination patient had weight 58kg, icthyosis ,no fever, cyanosis, clubbing ,pulse 78/m, B.P 120/ 80 mm Hg , there was restriction of movements of right hemithorax with shifting of mediastinum to left, on percussion stony dullness was found on right infra axillary and infra scapular area, breath sounds and vocal resonance were reduced in corresponding areas.

Investigation showed

Hb 9.8 gm% , TLC 1100 Cu/mm, N-40,E-36,L-22,B-00,M-02 ESR-60mm(1^{ST} HR)

Total eosiniophil count 3960

Comment on Peripheral Smear- Dimorphic anemia, no parasites.

Serum IgE- 10,800kU/L.

Sputum three samples for AFB were negative for M.Tuberculosis.

Mantoux showed an induration of 3mm at 72 hrs.

X-ray chest PA view showed right sided pleural effusion

Diagnostic pleural tap – Protien-6.4gm/dl, sugar-22mg/dl, pleural fluid ADA-28U/L Cytology showed mesothelial cells , lymphocytes and microfilaria.

Pleural biopsy did not show any ganulomatous lesion.

The patient was advised bed rest and was prescribed diethylcarbamazine citrate 100mg thrice daily for 2 weeks. His symptoms improved after 4 days and repeat x-ray after 2 weeks revealed complete expansion of right lung.

DISCUSSION

Filariasis is a major public health problem in India, *Wuchereria Bancrofti* is the most wide spread filarial organism infecting man. The commonest cause of pleural effusion in india is tuberculosis, however pleural effusion with *Wuchereria Bancrofti* has been reported in 4 cases[1][2]

The case described by us had the peripheral picture as per the current diagnostic criteria of tropical pulmonary eosinophillia .The current reexamined diagnostic criteria for tropical pulmonary eosinophilia include cough worse at night, residence in a filarial endemic area, eosinophil count greater than 3300 cells/µL, IgE levels exceeding 5000 kU/L

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and clinical and hematologic response to diethylcarbamazine [3] however the patient also had right sided pleural effusion from which *Wuchereria Bancrofti* microfilaria was isolated .The probable pathogenesis in clinical manifestations of filariasis are lymphatic obstruction and host immune response to W.bancrofti . Exudative effusion observed in the patient appeareas to be due to lymphangitis and incomplete obstruction of lymphatics ,however the atypical hypersensitivity reaction which is known to occur in patients with lymphatic filarisis may be contributatory.

The patient was put on DEC and recovered completely.

The present case report emphasizes the need to consider filarial etiology in the differential diagnosis in cases of tropical pulmonary eosinophillia with pleural effusion especially in patients from endemic regions.

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AN UNUSUAL CASE OF RHABDOMYOLYSIS

**K. C. Mahanta, R. Pattnaik, G. C. Patri,
S. Mohanty, S. K. Mishra**

INTRODUCTION :

Rhabdomyolysis is the rapid breakdown of skeletal muscle tissue. It occurs in several traumatic situations viz., crush injury, excessive physical exercise, status epilepticus, or non-traumatic conditions like infection (dengue, severe malaria etc), medications (eg statin) or very rarely following insect stings. It may be trivial or at times leads to acute renal failure. Most of these patients recover with conservative management, while some may require intervention and a few succumb due to multi organ failure.1

We encountered an unusual case of rhabdomyolysis recently at Ispat General Hospital (IGH) and present it due to the rarity of the condition.

CASE REPORT

FM, a 70 yrs male was admitted at 8 PM with history of two no of wasp sting over face on 12th September 2008 at noon. He developed vomiting and difficulty in respiration. There was no history of seizure. He was not an alcoholic, hypertensive or diabetic. There was swelling of face and lips, but without edema of the feet. There was no injury on the limbs or body parts. The patient was conscious and afebrile with Pulse 88/minute, BP 140/84 mm Hg. Respiratory system examination revealed occasional rhonchi. Cardiovascular and GI system examination did not show any abnormality. He was treated with Inj Adrenaline, Inj dexamethasone, Inj antihistamines, Inj Rabeprazole, antibiotics and IV Fluids. His urination was about 800 ml/ 24 hrs.

On the next day (13th September) morning he developed difficulty in respiration which got aggravated by 12 noon with extensive bilateral rhonchi. The oxygen saturation was persistently low. He became extremely dyspnoec, anoxic and comatose. Hence, he was intubated and put on ventilator support. However, he did not improve, and ultimately the patient succumbed to ARDS. The total duration of stay was approx 24 hours.

His investigation reports showed- Hb 11.5 gm%, TLC 24200/cmm with 84% polymorphs, RBS 175 mg%, urea 131 mg/dl, serum creatinine 3.5 mg/dl, Na 127 mEq/L, K 5.3 mEq/L, Bilirubin 4.6 mg/dl, SGPT 946 units/dl, CPK 51979/ L. The ECG was normal and did not show any evidence of myocardial injury.

Discussion

Insect stings are known to cause a host of allergic reactions. Stinging insects are mainly of two varieties: vespids (wasps, hornets etc) or apids (honey bees, etc). Most of the bites and stings are self limiting with local allergic reactions viz., redness, swelling, itching and pain at the site of bite. However, multiple stings can lead to hemolysis, shock, encephalitis and acute renal failure.2-6

These are caused by the protein component of wasp venom called "Melittin". Other active components include apamine, phopholipase, histamine and kinins. These have direct or indirect effect on liver, kidney, heart, brain and skeletal muscle.

The major reactions noted often are flushing of skin, swelling of face and legs, cramps in abdomen, painful joints, nausea, vomiting, dysphagia, dyspnoea, faintness and even shock. Systemic symptoms occur when there more than ten stings and when occurs in face region. The worst sufferers are the elderly persons and young children. Anaphylactic shock occurs when the person is allergic to the protein in venom with previous bite.

Physicians encounter cases of bee sting, wasp bites etc in the clinical practice, and most of these

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are associated with minor symptoms and they recover.

Acute renal failure occurs occasionally and few reports are available.7-8 It is usually due to acute tubular necrosis. However, acute tubule-interstitial nephritis has also been reported.8

Rhabdomyolysis is a very rare occurrence in wasp stings. Only a few reports are available by PUBMED search.9,10 The present patient had evidence of hepatic and renal involvement along with rhabdomyolysis. **(Table-1).**

Rhabdomyolysis is also encountered in obstruction of blood supply to muscle (arterial thrombus, or embolism), delirium tremens, tetanus and electrical injury. Certain enzyme problem (eg phosphofructokinase deficiency), heavy metal poisoning, and electrolyte & metabolic disturbances may lead to rhabdomyolysis.

TABLE-1

Comparison of the clinical data of four patients with insect bite

	1	2	3	4
Place of report	Seoul, Korea	Chandigarh, India	Montgomery, USA	Rourkela, Orissa
Year	2003	2006	2007	2008
Reference	Kim et al[10]	Sharma et al[8]	Koya et al[9]	Present report
Insect	Wasp	Hornet	Fire ant	Wasp
Age, sex	63 M	18 M	59 M	70 M
Blood Urea	56*	310	19*	131
Sr Creatinine	3.2	9.2	2.8	3.5
ALT (SGPT)	1494	Normal	167	946
CPK	1,32,000	Normal	6284 1,58,610	51,979
Haemodialysis	No	Given	Given	No
Ventilator	No	No	No	Yes
Hosp Stay	7 days	??	14 days	24 hrs
Recovery time	One month	One month	Four months	Expired
Hb		7.6 gm%	WNL	11.5
TLC		16,200		24,200

*BUN

Though ARF has been encountered frequently with wasp bite, rhabdomyolysis is very rare and no published report is available from India. In addition, the patient had MOF. Due to this rarity we present this case for awareness among physicians.

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* * *

UNUSUAL ECG CHANGES IN A CASE OF ACUTE STEMI

P.C. Bahinipati, P.K. Pradhan

CASE REPORT

BRS, a 53 yrs old male come to hospital with pain chest on examination the patient had pulse 58/ min, BP 170/100 mm Hg. Heart CEO, AB Lt V, ICS, S1-N, S2-N Split, S3-0, S4-0, OS-0 no. lungs clinicaly clear, Abdomen L/S-0 other system NAD. ECG showed sinus Brady cardia, QS in V2; ST-T III, avf. Trop-T was negative, patient was put in NTG drip. Subsequently the pain chest increased with swating. ECG repeated, which showed Acute Ant. wall MI (STEMI). Thrombolysis was done with urokinase 15,00000 unts and Clopidogral, Aspirin, NTG drip was continued post Thrombolysis ECG was taken ST-T uptaking height decreased satisfactorily.

After 1/2 hr again the patient C/O severe pain chest with swating for which ECG was repeated. ECG showed ST-T elevation in I, AV, V2-V5. Similar to Acute STEMI. Another thrombolysis was done with 5,00000 units of Urokinase, LMW 0.6 ml Sc and NTG drip was continued. The patient improved. Subsequent ECG showed decreased ST-T elevation. The hospital stay subsequantly was uneventful and the patient was discharged after 5 days with routine advice.

The patient subsequently attended Apollo Hospital, Hydrabad, where angioplasty was done which showed LAD 99% and RCA 75% stenosis and underwent stenting for LAD and RCA.

DISCUSSION :

The Trop - T Negative at admission could be due to attack within 3 hrs reciprocal changes in Inf leads appearing first. But QS in V2 at that time is difficult to explain. The on going pain chest and subsequent ECG Findings and Trop-T positive indicate acute STEMI. After Thrombolysis the ST-T elevation has decreased > 20% indicating successful Thrombolysis.

The 2nd rise of ST-T in Ant chest leads is probably due to coronary spasm, giving rise to injury pattern of ST-T elevation, which subsided with additional dose of urokinase and NTG drip. The other Possibility could be rebound thrombus formation inspite of LMW heparin dose.

It is interesting in this case that

1. The Q waves appeared prior to 'pardees' sign.

2. Following thrombolysis and decrease of ST-T uptaking there has been a 2nd time ST-T uptaking simulating 'pardees' sign.

3. Subsequently ECG showed QS in V2, indicating muscle with death in antero septal area, while other areas were spared due to thrombolysis.

CONCLUSION :

Atypical ECG pattern could be there in a case of ongoing pain chest and the pt should be on observation and continuous monitoring.

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SARCOIDOSIS : AN UNUSUAL CASE REPORT

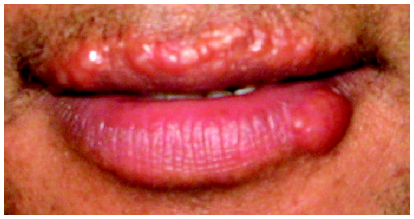
B. Kundu*, J.K. Panda**

INTRODUCTION

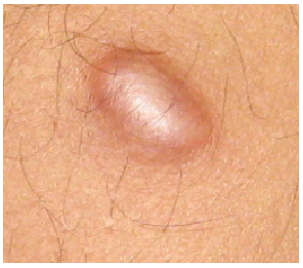
Differential diagnosis of Sarcoidosis is kept in mind in patients presenting with cutaneous features like Erythema Nodosum, parotosis, ankle oedema respiratory symptoms, lymphadenopathy or continued pyrexia. Here is a rare case presenting with papulonodular leisions in lips and skin

Case Report

Mr. SS, a 42 yr male, presented with some skin eruptions which had developed over a few weeks. The lesions are shown below.



Eruptions around the lips-multiple over the upper and single over the lower lips.



Similar lesion over the left knee joint.

The lesions were papulo-nodular, reddish, with yellowish streaking, and soft to firm in touch, without underlying fixation.

The lesions were gradual in onset and progression, without any pain, pruritus, redness or any signs of inflammation. They were soft to firm in touch, and did not bleed on touch.

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There was no h/o of fever/wt loss/loss of appetite /cough /dyspnoea /rash /weakness /dysuria /redness of eyes /arthritis /.

Pt was a teetotaler. He was not a diabetic / hypertensive .He doesn't give any history of tuberculosis or any other chronic illness.

No history of similar lesions in family. There was no history of tuberculosis in the family.

General and systemic examinations were unremarkable and did not reveal any abnormality.

The provisional diagnoses of the lesions were kept by me to be TUBEROUS XANTHOMA.

The routine investigations we are done. before referring him to the dermatologist as he was cosmetically not comfortable with the lesions, especially with those on the face. The investigations are outlined below.

Investigations :-(routine)

Hb - 12.1gm/dl, TLC - 5300/cmm, DC - N60, L36, E4, TPC- 2.4 lacs/cmm, ESR- 32 mm/1st hr.

FBS/PPBS- 77/110, Sr Ca++ -9.6

Lipid profile

TCh - 196, HDL - 40, LDL-130, VLDL - 26

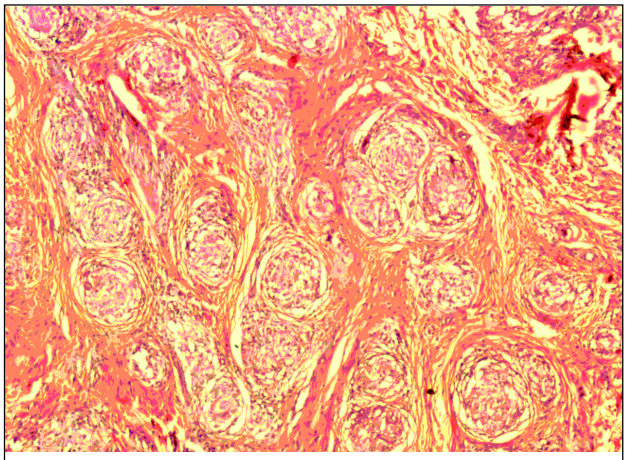
TG - 130, LFT, KFT within normal limits.

Specialized investigations related to the lesions were as follows.

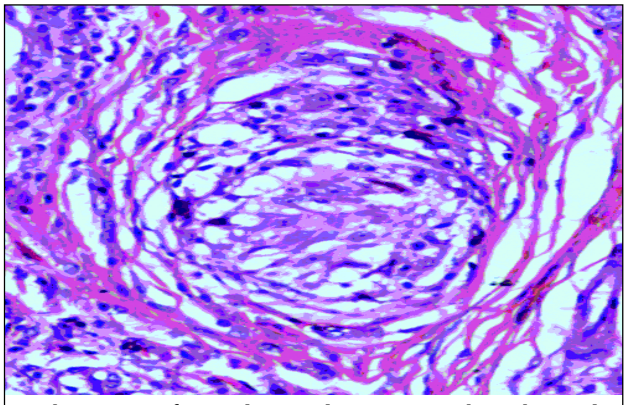
FNAC of lesion- lobules of fat and blood.

Punch biopsy of lesion- unremarkable epidermis. Dermis showed perivascular mononuclear infiltrate only. No features of xanthoma seen in the supplied sample.

As the punch biopsy was not in concordance with the provisional diagnosis, it was decided to do an excisional biopsy of the lesion. The microscopic picture along with the pathological report is shown below.



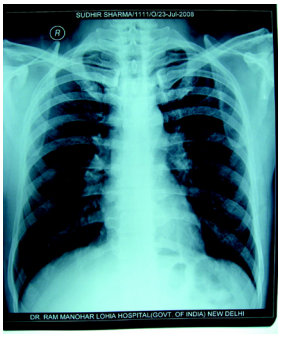
The light microscopic picture of the lesion. Note the many granulomas in the field.



The picture of a single granuloma as seen through an oil immersion microscope. Note the absence of caseation.

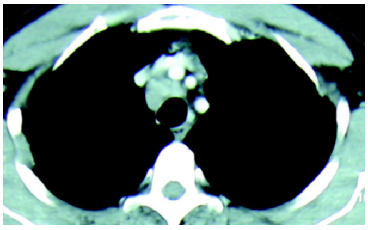
"Fibroconnective tissue revealing well circumscribed granulomas composed of mainly epitheloid cells, few giant cells and lymphocytes. Stains for AFB are negative."

The presence of noncaseating granulomas in a young male pointed the diagnosis to '**sarcoidosis**', and prompted the search for other features. They are shown below.

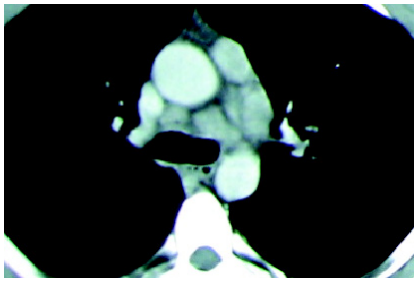


CXRay of the patient was normal.
USG abdomen –normal
Sr cortisol level (morning)-7.37(N)
Se ACTH levels—21.5(N)
Sr ACE levels-117 units (n=8-65) [increased levels can be found in histoplasmosis, alcoholic liver disease, idiopathic pulmonary fibrosis, dm, crf, tb, amyloid, Hansens, Hodgkin's, gauchers]. The patient did not have clinical features of any of the other diseases mentioned.

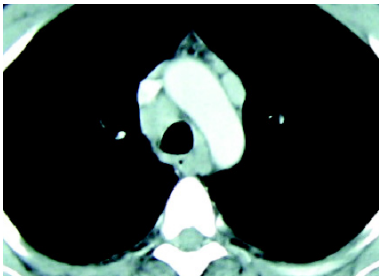
Although the chest radiograph did not suggest any lymphadenopathy, we still got a CECT chest done. The salient findings are shown below.



CECT chest showing the enlarged pre-tracheal group of lymph nodes (arrow).



CECT chest showing the pre and post aortic nodes (thick and thin arrows respectively)



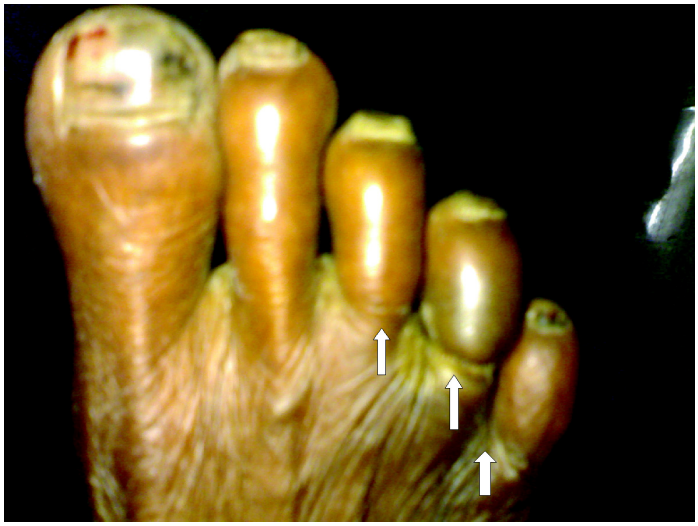
CECT chest showing the enlarged pre-carinal group of nodes. (White arrow)

Conclusion :

Sarcoidosis may be deceptive to present with skin leasions like xanthoma

AINHUM

A. Choudhury*, J.K. Panda, P.K. Padhy****, R. Mohanty***, S.C. Singh**, S.S. Panda***



This patient a 50 year lady from coastal Orissa admitted to medicine ward as a case of UTI with reactive arthritis but incidentally we found that she had constrictions at the base of the 3rd,4th & 5th toe without gangrene or ulcer but patient was asymptomatic and unaware of this. The lady used to walk barefoot from childhood.

Ainhum is the auto amputation of a digit, usually of the fifth great toe which may be bilateral as a result of constricting scar in the form of a band or groove. It is the dactilolysis of a toe most likely triggered by trauma usually related to walking bare foot, however exact cause is not known. A constricting groove develops from plantar aspect and progressively constricts the circumference of the toe until spontaneous auto amputation occurs.

It is rare outside Africa. Common among black Africans (incidence 0.2-2%).

Initially asymptomatic, later stage presents with pain which may be intense as constriction groove deepens finally causing bloodless auto amputation. It should be differentiated from **Pseudoainhum** which may be Congenital or Acquired (leprosy, Discoid Lupus Erythematosus, Syphilis, Yaws, Porokeratosis, and Ptyriasis Rubra Pilaris)

No definitive treatment available and depend upon the stage of presentation. Early cases are treated with division of fibrotic band or Z-plasty, intralesional triamcinolone injection.

Good foot care is critical. Secondary infection is major complication which should be looked for.

* * *

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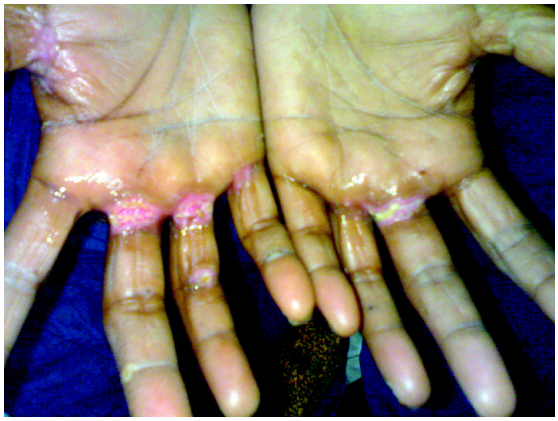
EYTHROMELALGIA

A. Choudhury*, R. Mohanty*, J.K. Panda**, P.K. Padhy****, S.C. Singh**, S.K. Jena***



This patient a 28year married Hindu female from coastal Orissa presented with H/O severe burning pain of both the hands and feet but more in the hands for 2months which characteristerically relieved by putting the hands in ice cold water to reappear again .Symptoms were not related to activity. Thorough clinical examination and routine evaluation revealed no abnormality except warm moist hand and presence of ulcers in the finger creases as shown. The patient was put on trial with aspirin 300mg BID,gabapentine 75mg BID,methylcobalamine and topical antibiotic. On follow up after one month patient was doing well but lost to subsequent follow up.

It is a rare disorder characterized by burning pain, warmth & redness of the extremities. The early onset or primary has female preponderance (M: F 1:2.5) while the secondary form due to myeloproliferative disorder has a male dominance (M: F 3:2).it affects over wide age group primary (7-76years), secondary (18-81years). The presentation is episodic to start with itching and progresses to severe burning pain .lower limb affected commonly than upper extremity. Pain exacerbated by warming or dependent position of the extremity and relieved by cooling or elevating the arm. During the episode the extremities appear warm, tender & appear dusky red sometimes mottled.Acrocyanosis may be observed and progression to necrosis of digital end and ischemic ulcer.

Causes are primary (idiopathic), myeloproliferative diseases(mostly polycythemia vera,essential thrombocytosis), drugs(pergolide, bromocriptine, nifedipine), infection by pox virus(caused epidemic in China),genetic predisposition &mushroom poisoning(*Clitocybe* species).Treatment in general includes cooling &elevation of the extremities. For secondary causes Aspirin is the best choice at a dose of 500mg PO once daily which can be titrated to max. 4gm/d(650mg q4hr) anagrelide is alternative .But for primary cause treatment is dismal,propanolol,epinephrine sodium nitropruside,gabapentine,TCA,high dose magnesium,prostacycline,lidocaine or mexiletine often tried.

The prognosis depend upon the etiology but aspirin responsive have a better outcome some case also remit spontaneously.

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- Hon Editor.