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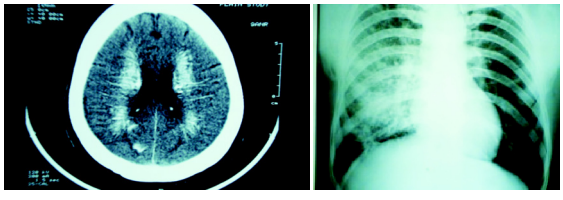

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Editorial

PREDIABETES : AN EMERGING CARDIO VASCULAR RISK

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

Diabetes, a global problem is posing a biggest threat ever witnessed to World's population. It is estimated that by 2025, 380 million persons worldwide will have diabetes[1]. Increase in the incidence of diabetes, association of cardiovascular disease and the accompaning high mortality & morbidity make glucose perturbations a serious public health problem.

Before developing frank diabetes all patients pass through a phase of metabolic abnormalities which is called as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) and frequently they remain undiagnosed for many years because hyperglycemia develops gradually and at earlier stages patient does not notice any of the classic symptoms of diabetes. Such patients though not symptomatic are at increased risk of developing macro or micro vascular complications, which may at times be the presenting feature at the time of diagnosis of diabetes.

The term "prediabetes" which embraces IGT and IFG is a relatively new clinical entity introduced in 2002 by Department of Health and Human Services (DHHS) and ADA with the aim to highlight the seriousness of the condition and to motivate people to get appropriate treatment. "Prediabetes" a condition that raises a person's risk of developing type 2 diabetes, heart disease & stroke without intervention and appropriate treatment. People with prediabetes are at risk for developing type 2 diabetes within 10yrs[2].

Criteria for the diagnosis of "Prediabetes" are given by American Diabetes Association[3].

1. FPG < 100 mg/dl : Normal
2. FPG : 100-125mg/dl Impaired fasting glucose.
3. 2hr PG : 140-199 mg/dl Impaired glucose tolerance. (After 75gm of oral glucose drink)

People with diagnosed prediabetes should have regular testing every year to monitor for developing type2 diabetes.

Prediabetes have an increased risk of developing CVD and all cause mortality[4]. The data demonstrated by Diamantopoulos et al. showed that metabolic syndrome and prediabetes have an overlapping pattern. Metabolic syndrome appears to have a more pronounced effect in early renal dysfunction and increased inflammatory activation while prediabetes tends to be associated with early carotid structural changes[5].

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Several reviews have found that lifestyle changes like diet, moderate intensity physical activity (such as walking for 2 ½ hr each week) and weight reduction of approximately 8-10% of initial body weight reduces the development of diabetes around 58% over 3yrs. In the "diabetes prevention program" people treated with metformin reduced their risk of developing diabetes by 31% over 3yrs[6]. Other pharmacological treatment like acarbose also reduced the risk by 25% over 3yrs. The demonstration by recent randomized controlled trials that type2 diabetes mellitus is preventable has raised the hope of reducing cardiovascular mortality & morbidity by early diagnosis of prediabetes and interventions like lifestyle modification & pharmacological therapy when necessary.

The study conducted by Jena S.K. et al in our institute shows that the mean carotid IMT in controls was 0.602±0.116mm and in prediabetics was 0.692±0.086mm. The mean femoral IMT in control was 0.528±0.091mm and 0.574±0.099mm in prediabetics. This shows that IMT was higher in prediabetics in comparison to controls (both in carotid and femoral arteries) which was statistically significant. They showed that prediabetics are associated with increased incidence of cardiovascular risk factors like dyslipidemia, obesity & hypertension. However further studies are required only in prediabetics not associated with cardiovascular risk factors to show whether it is an independent risk factor for increase in IMT.

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Original Article

CLINICO-ETIOLOGICAL PROFILE OF ATRIAL FIBRILLATION : AN OBSERVATIONAL STUDY IN A REFERRAL HOSPITAL IN ORISSA

R. Mohanty*, U.K. Patnaik**
C.B.K. Mohanty*, S.K. Sahoo******

ABSTRACT

Atrial fibrillation (AF) is a common supraventricular arrhythmia that has assumed increasing importance as global demographic tide results in a growing elderly population. The impact of AF on morbidity and mortality are substantial. Few studies have been conducted on this topic utilizing modern sophisticated investigations like Trans.esophageal Echocardiography (TEE) in tertiary care hospital. The present study was undertakenwith the aim of determining Clinico-aetiological profile of AF in hospitalized patient~using conventional transthoracic as well as TEE. Out of 202 hospitalized AF patients, diagnosed by defined clinical and ECG criteria, Transthoracic echocardiography (TTE) was done in 145 cases and TEE in 30 cases who also had TTE. 56.44% patients were males and 43.56% females with maximum patients in age group 30 to 60 years. Dyspnoea was the most common clinical presentation (68.32%). Rheumatic heart disease (RHD) accounted for 64.82% cases followed by dilated cardiomyopathy (17.24%) thus explaining the predominant population with AF in younger age group. TEE, being a sensitive tool, showed superiority to TTE in evaluating left atrial dimension and in detecting LA clot (P=O.01) and spontaneous echo contrast (SEC) in left atrium (P=0.01). Prediction of thromboembolism in AF was significantly higher in presence of clot in LA or left atrial appendage (P=O.001). Therefore, presence of clot in LA or its appendage puts the patient in moderate to high risk of thromboembolism and necessitates preventive measures. ***Keywords*** *: Atrial Fibrillation, supraventricular arrhythmia.*

INTRODUCTION:

The earliest record of AF seems to be in the yellow Emperor's Classics of Internal Medicine in the seventeen century1. William Harvey however is credited with the first description of "auricular fibrillation" in animals in 1628. After Harvey's description, the misunderstanding that the pulse was independent of heart beat, continued to prevail, likely because of the dissociation that frequently coexists between the irregular heart contractions and the palpable radial pulse in AF. This is now well recognized as the pulse deficit, which can be a valuable clue to the bedside diagnosis of AF. In 1863 'Chauveau and Marey'[2] conducted various studies on cardiac physiology utilizing the sphygmograph an instrument that used to record the pulse graphically, and thereby described a pulse tracing from a patient with AF. Various description of irregular pulse as "intermission of pulsation of heart" (Laennec), "ataxia of pulse" (Bouilland), "delirium of cordis" (Nothangel), and finally "pulsus irregularis perpetus" (Herring) latter ensued[3]. In 1907, Arthur Cushney at University College of London Published the first case report of AF in his patient after an operation for ovarian fibroid recorded with a "Jacques sphymochronograph"4. This was the first correlative clinical report on the electrical record and palpated irregularity of the pulse in AF. In 1909, Thomas Lewis described classic absence of 'Pwaves' and 'irregularity of 'f waves' that define atrial fibrillations.

Various studies since the discovery of AF have led to elucidation of different mechanisms producing it. The understanding of mechanism underlying the initiation

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and maintenance of AF has evolved over the past decades. The earliest concept of reentry proposed by Winterberg in 1906[6] and by Lewis and Schleiter in 1912[7] advocated that rapid focal activity from one or more centers accounted for AF. In 1913, Mines[8] showed that the mechanism of re-entry was an impulse circling a large anatomic obstacle. In 1947 Scherf9 revived the theory of focal trigger in AF. In the 1960s, More and colleagues[10] supported the theory of randomly propagating multiple wavelets as the mechanism underlying AF. Atrial cycle length has been studied as a predictor of paroxysmal AF. In the 1970s Alliessie and colleagues[11] introduced the concept of "leading circle re-entry". All these theories of random re-entry explained the sustenance of AF but how it was initiated was also warranted. Alliessie and colleagues[12] offered several explanations: a "stable background circuit" capable of initiating new AF when the earlier episode dies out, abnormal focal trigger sites in atria, and the possibilities of echo beat from AV node or from accessory pathway.

The present understanding is that AF requires a "critical mass" needed to maintain the arrhythmia and there is a critical rate greater than which organized atrial activity cannot be continued. Thus, at a certain rate, organized atrial activity can disintegrate into AF provided that the critical tissue mass is available to sustain it. Recent studies in isolated human atrial preparation showed that a single meandering functional re-entrant wavefront produced AF[13]. Recent work by Jalife and colleagues[14] questions the randomness of atrial activity in AF. Their study suggests the presence of a possible "mother circuit" that serves as a periodic background focus; the presence of anatomic obstacles (e.g. scar, orifices) serves to break up the wave front from the mother circuit into multiple wavelets that spread in various directions. Wu and colleagues[15] have proposed the role of pectinate muscles as obstacles that break the activation wave, thus promoting re-entry. The likelihood that focal activation plays some role in AF is well accepted. In 1966, in an anatomic study of left atrium pulmonary vein (PV) junction in human hearts, Nathan and Eliakim[16] reported that the proximal portion of PV has a sleeve of myocardium that is direct extension from adjacent atrial tissue and is electrically coupled to the atrium. Haissaguerre and colleague[17] reported arrhythmogenicity of the PVs as possible focal trigger of AF. The myocardial sleeves that extend from the left atrium onto PVs seem to be the pathologic correlate of arrhythmogenic focus. Since then, multiple other foci of AF have been discovered "in the thoracic venacava, coronary sinus[18], and vein of Marshall[19]. The autonomic basis of AF was explored by Columel,20 who classified AF as adrenergic or vagally mediated. There has also been research implicating genes that predisposes to AF.

Classification

The American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) recommended in their guidelines the following classification system based on simplicity and clinical relevance.[21]

Category of AF	Defining Characteristics
First detected	Only one diagnosed episode.
Paroxysmal	recurrent episodes that self-terminate in less than 7 days
Persistent	recurrent episodes that last more than 7 days.
Permanent	an ongoing long-term episode

All cases of atrial fibrillation patients are initially placed in the category called "first detected AF". These patients may or may not have had previous undetected episodes. If a first detected episode self-terminates in less than 7 days and then another episode begins later on, the case has moved into the category of "paroxysmal AF". Although patients in this category have episodes lasting up to 7 days, in most cases of paroxymal AF the episodes will self-terminate in less than 24 hours. If instead of the episode lasts for more than 7 days, it is unlikely to selfterminate and it is called "persistent AF". In this case, the episode may be terminated by cardioversion. If cardioversion is unsuccessful or it is not attempted, and the episode is

ongoing for a long time (e.g. a year or more), the patient's AF is called "permanent AF".

Episodes that last less than 30 seconds are not considered in this classification system. Also, this system does not apply to cases where the AF is a secondary condition that occurs in the setting of a primary condition that may be the cause of the AF.

Atrial fibrillation produces several hemodynamic effects, including loss of atrial contraction, and an irregular ventricular rhythm. The loss of mechanical AV synchrony may have a dramatic effect on ventricular filling and cardiac output when there is reduced ventricular compliance, as with left ventricular hypertrophy with hypertension, restrictive cardiomyopathy, hypertrophic cardiomyopathy, or the increased ventricular stiffness associated with aging. In addition, patients with mitral stenosis, constrictive pericarditis, or right ventricular infarction typically experience marked hemodynamic deterioration at the onset of AF. The loss of AV synchrony results in a decrease in LV end-diastolic pressure (LVEDP) as the loading effect of atrial contraction is lost, there by reducing stroke volume and AV contractility by Frank-Starling mechanism. Although there is a reduction in the LVEDP, there is an increase in the left atrial mean diastolic pressure. Patients with significant restrictive physiology may experience pulmonary edema and/or hypotension with the onset of AF. In contrast patients with dilated cardiomyopathy and high LV filling pressures may experience minimal hemodynamic compromise with atrial fibrillation, if their LV compliance is not significantly impaired. The inappropriately rapid ventricular rate during AF also limits the duration of diastole and reduces the ventricular filling. In occasional patients the first manifestation of atrial fibrillation may be CHF related to tachycardia induced cardiomyopathy[22]. This clinical syndrome is generally limited to patients who experience minimal or no palpitation during atrial fibrillation with a sustained ventricular rate > 120 beats/min. for sustained periods. Because the patients don't experience symptoms, they don't seek medical care, thus often come to medical attention with signs and symptoms of heart failure. In these patients control of ventricular rate by cardioversion, AV nodal medication, or catheter ablation typically reverses the impaired LV function within weeks. The irregular ventricular rate has adverse hemodynamic effects that are independent of ventricular rate. Irregularity significantly reduces cardiac output[23] and coronary blood flow[24] compared with a regular ventricular rhythm at the same average heart rate. The effect of ventricular irregularity on coronary blood flow may explain in part why some patients with AF experience precordial pain in the presence of normal coronary arteriography.

Patients with heart failure often do worse when in atrial fibrillation, and it is difficult to know whether this is caused by loss of atrial contraction, too fast a ventricular rate, irregularity of rhythm, or a combination of factors. Recent ablation data suggests that successful maintenance of sinus rhythm in patients with previous persistent atrial fibrillation with a good rate control can substantially improve LV function[25].

Thromboembolism

Stroke is the most feared complication of AF, prevention is a major focus of and its management of patients with this condition. The risk factors for stroke in AF are prior history of stroke or TIA, age > 75 years, history of hypertension, diabetes mellitus, and congestive cardiac failure, mitral stenosis, left ventricular dysfunction, marked left atrial enlargement (>5 cm), and spontaneous echo contrast on echocardiography[26]. Most thrombi associated with AF arise within left atrial appendage. Flow velocity within left atrial appendage is reduced during AF because of the loss of organized atrial contraction. Several factors contribute to the enhanced thrombogenicity of AF. Nitric oxide (NO) production in the left atrial endocardium is reduced in experimental AF, with an increase in levels of prothrombotic protein plasminogen activator inhibitor-1 (PAI-1). The lowest levels of NO and highest levels of PAI-1 were recorded in the left atrial appendage during AF. Patients with AF have elevated level of beta thromboglobulin and platelet factor-4[27]; elevated plasma

level of von Willebrand Factor (vWF), soluble thrombomodulin and fibrinogen have been reported in patients with permanent AF with no evidence of diurnal variation in thrombogenicity.

Atrial fibrillation is an independent risk factor for stroke; it is associated with a four-to-five fold higher risk than in the unaffected population[28,29]. Overall, this rhythm disorder is implicated in approximately 75,000 strokes per year and is probably the major cause of embolic stroke[30]. Patients with paroxysmal or intermittent atrial fibrillation have annualized stroke rate (3.2%) similar to that in patients with chronic or sustained atrial fibrillation (3.3%)31. The coexistence of other factors in patients with atrial fibrillation may compound the risk of stroke. The older patients are not only more prone to atrial fibrillation but their risk of stroke is considerably increased compared with younger patients with atrial fibrillation. The propensity of the elderly for stroke may be related to a higher prevalence of co-morbid conditions and to the dual factors of age and chronicity. Both increasing age and chronicity of atrial fibrillation co-relate strongly with increased left atrial size[32].

METHODS :

This study was conducted between January 2008 and September 2009 in the Department of Medicine and Department of Cardiology, S.C.B. Medical College and Hospital, Cuttack. In this study, all patients with electrocardiographically diagnosed atrial fibrillation admitted to the medicine ward / Cardiology ward of S.C.B. Medical College, Cuttack were taken as subjects.

Patients admitted to the Department of Medicine and Department of Cardiology were first clinically examined for presence of atrial fibrillation with following clinical criteria.

Clinical Criteria :

· Irregularly irregular pulse, pulse deficit> 10, absence of 'a' wave in JVP, variable 1st heart sound.

Then 12 lead electrocardiography (ECG) was done in all the clinically suspected patients for confirming the presence of atrial fibrillation with the following electrocardiographic criteria.

E.C.G. Criteria :

Irregular wavy base line produced by 'f wave at the rate of 350-600 beats / min., absence of 'p' wave, a ventricular rate (QRS) that is quite irregular.

All the patients with following criteria were taken as subjects.

Features of AF in ECG, paroxysmal AF with ECG documentation, developing AF during hospitalization.

After confirmation of atrial fibrillation by ECG, they were subjected to transthoracic echocardiography for finding out the cause and to see for any clot or spontaneous echo contrast. All suitable cases were then subjected to transesophageal echocardiography except the cases in which clot was found in TTE.

Clinical features of patients, age corelation for development of atrial fibrillation, aetiology and complications in the presence of AF were tabulated.

STATISTICAL ANALYSIS:

SPSS software was used for all statistical analysis. Patient characteristics and outcome of interest was calculated with 95% confidence interval. The probability <0.05 was considered to be significant.

RESULTS :

Out of a total number of 34,452 cases admitted to medical wards during this period, 202 cases had atrial fibrillation giving a prevalence rate of 0.586%. Transthoracic echocardiography was done in 145 cases and transoesophageal echo in 30 cases. Out of the 202 cases a total of 114 (56.44%) were male and 88 (43.56%) were female(Fig.1).

Distribution of atrial fibrillation by age group and gender was done, which showed a maximum distribution of cases in the middle age group (30-60 years) with an average age of between 47 and 50 years (Fig.2,Table 1).

The clinical profile of patients presenting with atrial fibrillation showed a high incidence of features of neurological deficit on account of systemic embolization (26.73%) (Fig.3,Table 2). Aetiologically rheumatic heart disease accounted for the majority of cases of AF (64.82%) (Table 3).

Table - 1

DISTRIBUTION OF ATRIAL FIBRILLATION BY AGE GROUP AND GENDER

Age group(Yrs)	Male	%	Female	%	Total	%
<20	3	1.48	5	2.47	8	3.96
21-30	10	4.95	11	5.44	21	10.40
31-40	22	10.89	15	7.42	37	18.31
41-50	25	12.37	22	10.89	47	23.26
51-60	25	12.37	19	9.40	44	21.78
61-70	18	8.90	11	5.44	29	14.35
71-80	9	4.45	5	2.47	14	6.93
>80	2	0.99	0	0	2	0.99
Mean ± SD	50.03 ± 15.24		47.07 ± 15.5		48.98 ± 15.3	

Table - 2

CLINICAL PROFILE OF PATIENTS WITH ATRIAL FIBRILLATION

Clinical Profile	No of Cases	%
S.O.B.	138	68.32
Embolism	54	26.73
Chest pain	22	10.89
Palpitation	37	18.31
Fatigue	10	4.95
Dizziness	13	6.43
C.H.F.	80	39.6

Transoesophageal echocardiography was far superior to transthoracic echocardiography in the detection of clot in the left atrium(FigA). It was further observed that the presence of clot in the left atrium correlated strongly for the presence of embolism (Table 4).

Furthermore an increase of LA size to above 5cm predisposed to the development of clot(Table 5,Fig.5).

Table - 3
Aetiological Profile of Atrial Fibrillation in Hospitalised Patients

Aetiology	No. of Cases	%
RHD	94	64.82
DCM	25	17.24
Thyrotoxicosis	7	4.82
CAD	5	3.44
ASD	4	2.75
Hypertension	4	2.75
Lone	3	2.06
Cor Pulmonale	2	1.37
RCM	1	0.68
Total	**145**	

DISCUSSION :

Atrial fibrillation is the most common sustained disturbance of cardiac rhythm and its prevalence appears to be increasing as the population ages[33,34]. Echocardiography plays an important role in the evaluation of patients with atrial fibrillation, and it has been very useful in elucidating the mechanisms of stroke in atrial fibrillation. Transthoracic echocardiography is performed commonly for intial evaluation of atrial

Table - 4
Comparision of Association of Clot with Embolism in Atrial Fibrillation Patients

	Total	Clot	%	No. Clot	%
Embolism	51	16	31.37	35	68.62
No. Embolism	94	8	8.51	86	91.48
		P Value = 0.001			

Table - 5
Comparision Between Left Atrial Size and Presence of Thrombus

LA Size	Total	Clot	%	No. Clot	%
>5 cm	91	20	21.97	71	78.02
<5 cm	54	6	11.11	48	88.88

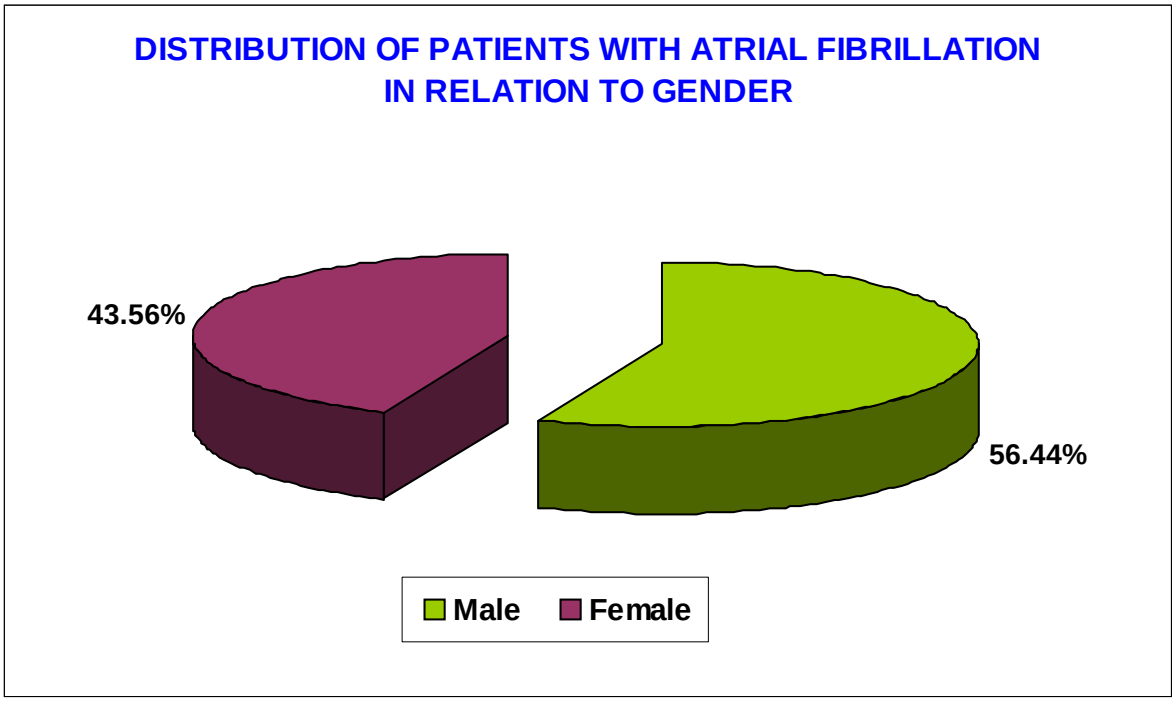
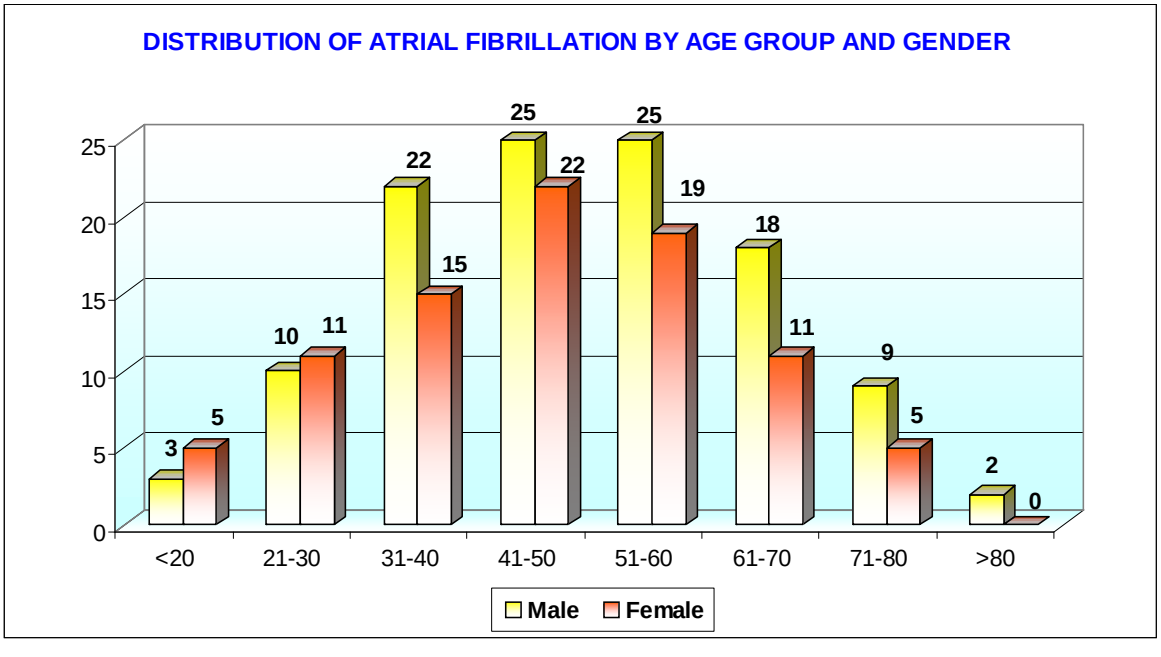

DISTRIBUTION OF PATIENTS WITH ATRIAL FIBRILLATION
IN RELATION TO GENDER
43.56%
56.44%
Male
Female

Fig. 1


DISTRIBUTION OF ATRIAL FIBRILLATION BY AGE GROUP AND GENDER
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31-40
41-50
51-60
61-70
71-80
>80
Male
Female

Fig. 2

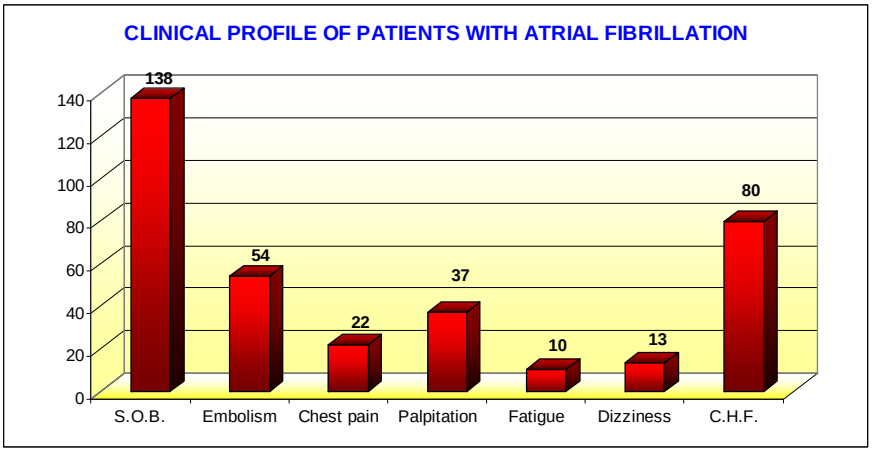


Fig. 3

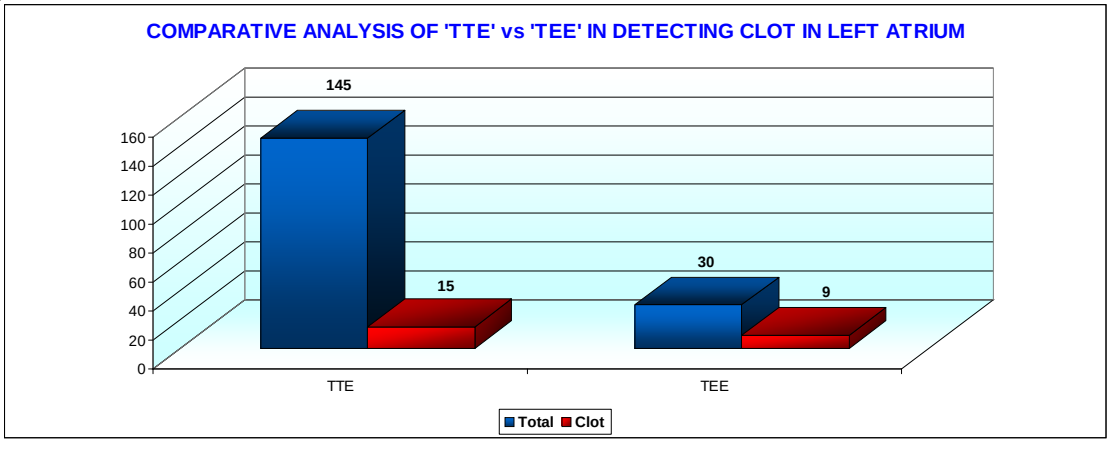
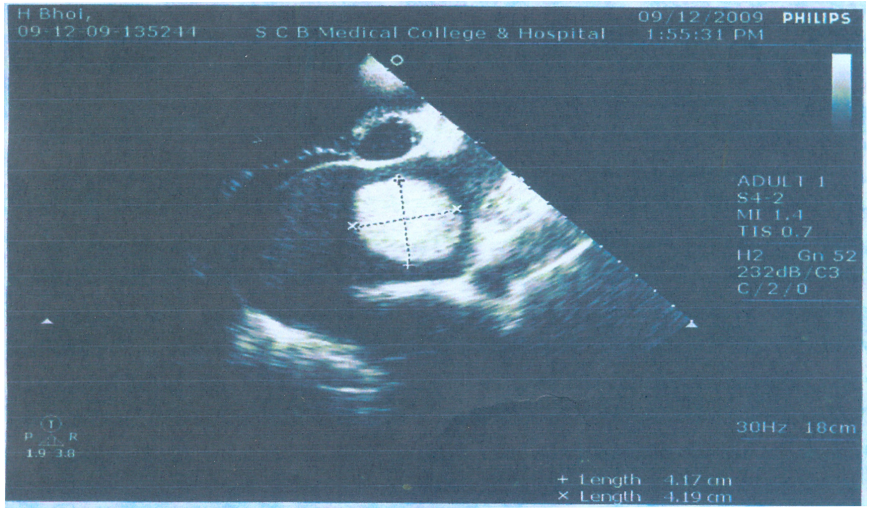


Fig. 4



Transthoracic echocardiography: short axis view showing clot (4.17x4.19 cm) & SEC in LA

fibrillation, when it enables clinicians to screen for occult pericardial, myocardial and valvular heart diseases.

Systemic thromboembolism remains a frequent and potentially catastrophic complication of atrial fibrillation and therefore numerous investigators have sought methods of risk stratifying patients to determine the role of anticoagulation[35]. Transthoracic echocardiography (TTE) is limited, however, by inadequate visualization of left atrial appendage from where cardioembolic events are believed to originate.

Transesophageal echocardiography is superior to transthoracic echocardiography in visualizing LA appendage and identifying LA thrombous[36] with a sensitivity that approaches 100%[37].

Atrial fibrillation is a common supraventricular arrhythmia that has assumed increasing importance as global demographic tide results in a growing elderly population. The impact of atrial fibrillation on mortality and morbidity are substantial. Though several studies on this common rhythm disorder are available in literature, very few have conducted utilizing modern sophisticated investigations like TEE in a tertiary care hospital. Furthermore few studies have been conducted in India on atrial fibrillation especially on the role of TEE in atrial fibrillation.

The present study was undertaken with the aim of determining clinico-aetiological profile of atrial fibrillation in hospitalized patients using conventional transthoracic as well as transesophageal echocardiography.

This study was conducted between January 2008 and September 2009 in the Department of Medicine and Department of Cardiology, S.C.B. Medical College and Hospital, Cuttack. In this study, all patients with electrocardiographically diagnosed atrial fibrillation, admitted to the Medicine ward / Cardiology ward of S.C.B. Medical College, Cuttack were taken as subjects.

A total of 202 cases were admitted during the study period out of which, echocardiography could not be done in 57 cases because of poor general condition of patients, death, non cooperation, and patients who left against medical advice. Transthoracic echocardiography was done in rest 145 cases out of which transesophageal echocardiography was done in 30 cases.

A total of 34,452 patients were admitted during the study period out of which 202 were electrocardiographically diagnosed cases of atrial fibrillation. The prevalence comes out to be 0.586%.

Past et a1[38,39] have shown the prevalence rate to be 0.55 to 1%, where as in the study by Domanski MJ, the prevalence rate was 0.4%[34]. Though the prevalence of atrial fibrillation in the present study is similar to the other studies, those were community based epidemiological studies and none were done in hospitalized patients.

Out of the 202 patients admitted, 114 were male (56.44%) and 88 were female patients (43.56%). The incidence of hospitalization in male patients was more than females. Studies have shown that men are at moderately higher risk of atrial fibrillation than women[40].

There was no significant difference between male and female patients in relation to mean age (50.03 ± 15.24 in male vs 47.07 ± 15.5 in female) and age groups ($P = 0.175$). In both sexes nearly 2/3rd of patients were in the age between 31 to 60 years. This hospital distribution of atrial fibrillation cases were in contradiction to the community distribution[39] which shows more cases to be in the older age group. This is probably because of increased incidence of rheumatic fever in developing countries like India, causing early complications as atrial fibrillation secondary to valvular heart ‘disease. Rheumatic atrial fibrillation occurs approximately 15 years earlier than atrial fibrillation due to hypertension or coronary artery disease as observed by Kunishige et a1.[41]. Studies have shown later onset of atrial fibrillation in women[42,43] probably due to the fact that women are older at the time of first presentation of ischemic heart disease. However in the present study women were found to have atrial

fibrillation at earlier age, again because increased number of caese were due to Rheumatic heart disease.

In our study patients presented with variety of symptoms to the hospital, out of which shortness of breath was the most common symptom to be presented with, which was 68.32% of the total cases. Thromboembolism was another common cause of hospitalization which constituted 26.73% cases. Other symptoms included are chest pain, palpitation, fatigue, and dizziness. Fatigue was the least common symptom of presentation (4.95%). Congestive heart failure (CHF) was common presentation accounting for 39.6% of cases. CHF was a powerful independent predictor of occurrence of atrial fibrillation in the Framingham study, in both symptomatic and asymptomatic LV dysfunction[44]. According to several studies atrial fibrillation is diagnosed in 10 to 35% of patients with CHF during the course of the disease and is related to clinical severity of its symptoms[45,3,46-49]. These datas correlate with that of our observations.

Table-5 delineates the various aetiologies of atrial fibrillation, among which Rheumatic heart disease was the most common cause for atrial fibrillation being responsible for 64.82% of the total cases. This is similar to the study conducted by **Maru M** etal.[50] which showed 66% of atrial fibrillation patients having Rheumatic Heart Disease.

Dilated Cardiomyopathy (DCM) was the second most common reason for hospitalization, constituting 17.24% of total patients. Other causes for hospitalization were thyrotoxicosis (4.82%), coronary artery disease (3.44%), atrial septal defect (2.75%), hypertension (2.75%), cor pulmonale (1.37%), lone AF (2.06%), and restrictive cardiomyopathy (0.68%). In the developed countries the spectrum of structural heart disease in· atrial fibrillation patients have changed significantly over the last century[51]. In general, the prevalence of RHD decreased significantly (5%-15%) where as hypertension and coronary artery disease became more common. These datas are in contrast to our observations where RHD is still the number one cause of atrial fibrillation. Interestingly OCM was the second common cause of atrial fibrillation, presumably because of the associated CHF as atrial fibrillation co-exists with LV dysfunction in a significant proportion of population with CHF. However, the incidence atrial fibrillation due to coronary artery disease and hypertension were less compared to other studies.[52]

The above study showed that transesophageal echocardiography is more sensitive in finding out clot in left atrium or LA appendage than transthoracic echocardiography (P=0.01). This is similar to the result shown by Klein AL et al. Comparing the finding of spontaneous echocontrast (SEC) in the left atrium or left atrial appendage in our study by transthoracic echocardiography and transesophageal echocardiography, it was seen that the detection of spontaneous echocontrast by transesophageal echocardiography was significantly higher (P=O.001) than by transthoracic echocardiography. So transesophageal echocardiography is very sensitive in finding out spontaneous echocontrast than transthoracic echocardiography. This is in par with the study by Kasliwal RR et a1[53].

The incidence of thromboembolism in atrial fibrillation was significantly higher in patients who had clot in LA or LA appendage compared to patients without clot in LA or LA appendage (P=0.001).

The prediction of thromboembolism in patients with atrial fibrillation by K. Madhaban Krishnamurty et al shows there is increased chance of embolisation in patients with LA or LA appendage c1ot[54]. Contrary to the finding by Kasliwal et al which shows that there is increased likelihood of thromboembolism in patients with spontaneous echocontrast, our study derived no significant difference in embolism between atrial fibrillation patients with SEC and atrial fibrillation patients without SEC. (P = 0.697).

Though the probability of detection of clot was more in patients with LA size > 5cm than the patients with the LA size <5 cm, the difference was not significant (P =0.15). The above study showed that

spontaneous echocontrast was more often present in patients with enlarged left atrium than those who didn't have and the difference was significant (P = 0.014).

The prevalence of atrial fibrillation in hospitalized patients is comparable to that in community based studies. The increased incidence of RHD in our setting accounted for the majority of cases of atrial fibrillation. Among them, majority were mitral valve disease with mitral stenosis being present in 93.6% cases both alone and in combination. This was also responsible for earlier presentation of cases. However, unlike other studies, the proportion of cases due to CAD and hypertension were less. This may be attributed to paroxysmal forms of atrial fibrillation, which are more common in nonvalvular type of the disease[55]. Though hypertension is a common underlying aetiology for atrial fibrillation[56], our studies didn't reveal this, may be because of paroxysmal or asymptomatic atrial fibrillation which didn't warrant hospitalization.

Transesophageal echocardiography provides a superior assessment of LA appendage in most patients compared to transthoracic echocardiography. The incidence of clot observed by transesophageal echocardiography in patients with atrial fibrillation varies widely, depending on the population studied. Despite thrombus detection in upto 10 to 15% of patients with atrial fibrillation, even while anticoagulated, the rate of risk of stroke following cardioversion is a fraction of this number. This discrepancy is likely multifactorial but may be accounted for by over diagnosis of thrombus or clinically silent events[38]. It is also likely that not all thrombi are prone to embolization. This explains our observation that more number of patients with LA clot had embolization compared to patients without clot in LA, but not all patients with LA clot have embolic phenomena.

Spontaneous echocontrast (SEC) is identified commonly among patients with atrial fibrillation. The wispy, smoke-like echo reflections observed are thought to be produced by backscatter from red cell aggregates at low flow rates, and they are a marker of haematologic stasis and prothrombotic environment[57,58]. Many clinical studies have attempted to further characterize the relationship between spontaneous echocontrast and thromboembolic risk. In the Stroke Prevention in Atrial Fibrillation Study(SPAF) III, Zabalgoitia evaluated 786 participants and categorized them as low, moderate and high risk. LA appendage thrombus was found in 3%, 8%, and 15% patients respectively. Dense spontaneous echocontrast was associated independently with increased thromboembolic risk with a relative risk of 3.7[59] .

In another study by Leung, spontaneous echocontrast was visualized in 59% of cases[60]. However, two prospective studies have failed to show a relationship between spontaneous echocontrast and thromboembolism, though both may have been under powered to do S061. In our study too, the incidence of thromboembolism didn't show significant difference in those who had spontaneous echocontrast than those who didn't.

Because of frequent association between spontaneous echocontrast and cardio-embolic events, a through investigation of LA appendage is warranted. whenever dense spontaneous echocontrast is identified. Even if thrombus is not found, these patients should be considered at high risk for embolic events.

Despite the added prognostic information that can be acquired by transesophageal echocardiography, controversy exists as to the value of routine screening of all patients with atrial fibrillation, particularly those defined as low risk[62]. Individuals at moderate to high risk for thromboembolism, however, may derive benefit from further risk stratification by doing transesophageal echocardiography.

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Original Article

EPIDEMIOLOGY AND CLINICAL ASPECTS OF SICKLE CELL DISEASE IN INDIA

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ABSTRACT

Sickle cell disease an autosomal recessive disease characterized by point mutation in beta globin gene (A→ T) at sixth amino acid codon resulting in HbS (sickle hemoglobin), but behaves clinically as a multigenic trait with exceptional phenotypic variability. Various genetic factors like HbF concentration, the beta globin gene cluster haplotype, alpha thalassemia, XmnI polymorphism and environmental factors have been proposed as the modulators of clinical severity. Our study reveals that western Orissa has high prevalence of the sickle cell gene and it is prevalent in both tribal and non tribal population. The commonest morbidity is painful crisis. Higher HbF reduces the frequency of painful crisis. Malaria is the commonest infection, a precipitating factor for painful crisis & responsible for all deaths in these sickle cell disease cases. Persistent splenic enlargement is common. AVN is associated with tuberculosis. CRF is prevalent, while leg ulcer, priapism & stroke are uncommon. In spite of Asian haplotype & high HbF level the disease is not benign. Malaria & Tuberculosis are important cause of high morbidity & mortality. ***Keywords :*** *Sickle Cell Disease, Epidemiology, Clinical Features.*

INTRODUCTION:

Sickle cell disease is an autosomal recessive disease characterized by point mutation in beta globin gene (AàT) at sixth amino acid codon resulting in HbS (sickle hemoglobin), which polymerizes on deoxygenation leading to sickle shaped red blood cells.

Patients of sickle cell disease may present with chronic organ dysfunction like hepatic failure, renal failure, chronic anaemia, various infections like hepatitis B and C virus infection, malaria, osteomyelitis and septicemia. They may also present with acute life threatening complication like painful crisis, hemolytic crisis, aplastic crisis and megaloblastic crisis. Pregnant mother with sickle cell disease suffer from serious problem of repeated crisis increased incidence of infection or even sudden death. The foetus also has increased morbidity in form of intrauterine growth retardation, premature labour and abortion.

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Sickle Cell Disease (SCD) is a monogenic disorder but behaves clinically as a multigenic trait with exceptional phenotypic variability. Although the explanation for this phenotypic heterogeneity remains incomplete the various genetic factors which have been identified as the modulators of clinical severity are HbF concentration, the beta globin gene cluster haplotype, alpha thalassemia, XmnI polymorphism and X-linked factors. HbF is the most commonly studied and the only known cis-acting genetic modulator of SCD (Steinberg *et. al.*, 2004). Environmental factors like *Plasmodium falciparum* malaria also plays an important role in the morbidity of sickle cell disease.

There are five beta globin gene cluster haplotypes namely Benin, Senegal, Bantu (CAR), Cameroon and Asian haplotype which is otherwise also called Arab-Indian haplotype probably represent an independent HbS mutation and is found in eastern Saudi Arabia and India (Nagel *et. al.*, 2001). Sickle Cell Disease patients with Benin, Bantu, and Cameroon haplotypes generally have low levels of HbF and have a severe phenotype, while Senegal and Asian- Indian haplotypes are associated with higher levels of HbF and have a relatively milder course. The strong association of Xmn-I site with the

Arab Indian haplotype of Sickle Cell disease is thought to be associated with high fetal hemoglobin concentration and confer a benign course of the disease.

MATERIAL AND METHODS:

- Place of Study: The study was undertaken on 1120 sickle cell disease (HbSS) patients enrolled in the Sickle Cell Clinic and Molecular Biology Laboratory of V.S.S. Medical College Hospital, Burla, in the state of Orissa, India. It is a tertiary care, 710 bed multi-specialty hospital. It is a referral hospital for 12 million people residing in western part of Orissa State and eastern part of Chhatisgarh State. Majority of the inhabitants of these areas are tribals (aboriginals).
- Duration: May 1998 to April 2009.
- Catchment area : The state of Orissa and Chhatisgarh (with population of 40 million).
- Enrollment criteria: Cases attending directly in the clinic with symptoms of SCD, referred from other hospitals, family members of SCD patients found positive after routine screening, and those found positive during cross sectional prevalence studies.
- Sickling slide test was done as the initial screening procedure & those found positive were subjected for alkaline agarose gel Hb electrophoresis (pH 8.6). Quantization of HbF was done by HPLC (Biorad, USA). Confirmation of sickle mutation Cd6 (GAG-> GTG) was done by ARMS-PCR.
- On inclusion, patients were registered, detailed history and clinical examination was conducted and recorded in a designed format. The patients were followed up at the Sickle Cell Clinic at 3 months interval, or earlier if they develop any health problem warranting medical attention. At entry detailed baseline studies were done on all the patients including CBC, renal function test, liver function test, radiological examination of shoulder and Hip, USG of abdomen. Specific investigations were done as and when required.

Enrollment of cases in the present study

	No cases
Total cases enrolled	1610
Total Sickle Cell Disease cases	1495
Sickle Cell Disease cases lost to follow up/ inadequate follow up: **Excluded**	375
Total Sickle Cell Disease cases taken in this study	1120

Epidemiology of Sickle Cell Disease in India:

It has been estimated that approximately 7% of the world population are carriers of inherited hemoglobin disorders and that 300 000–400 000 babies with severe forms of these diseases are born each year. The sickle-cell gene is distributed widely throughout sub-Saharan Africa, the Middle East and parts of the Indian sub-continent. In India carrier frequencies range from 5% to 40% or more of the population.

India is a vast country with more than 1 billion population. As per the 2001 census, there are about 635 biological isolates (tribes and sub tribes) that constituted 10% (about 110 million) of the total population of India. Tribal communities in India constitute the largest tribal population in the world. Most of them have been practicing endogamy for a long period of time, for which tribal communities are highly vulnerable to various hereditary diseases.

Lehman & Cutbush reported the first case of sickle cell gene from India in the tribal populations of Nilgiri Hills, India. In the Indian sub-continent, carrier frequencies of sickle cell gene range from 5% to 40% or more of the population. India can be divided into 3 zones according to the prevalence of sickle cell gene i.e., highly prevalent(21-40%), Moderately prevalent (5-20%) and low prevalence(<5%). Estimated number of sickle cell homozygotes are 1,31,375 and heterozygotes are 24,34,170 in our country.

Seven states located in central India namely Gujarat, Madhya Pradesh, Chhatisgarh, Orissa, Maharastra, Chhatisgarh and Andhra Pradesh have the maximum number of cases.

Orissa, the most picturesque state in eastern India, occupies a unique place in the tribal map of the country having largest number of tribal communities (62 tribes including 13 primitive tribes) with a population of 8.15 million constituting 22.3% of state's population. In 17 out of the 30 districts sickle cell gene is highly prevalent. Unlike other parts of the world sickle cell gene is widely prevalent both in tribal and non tribal population.

In certain non tribal caste Hindus like Chasa , Kuilta and Agharia the prevalence is as high as 40%. The first case of sickle cell from the state of Orissa in 1967 was from Agharia caste. Incidentally I belong to

Agharia caste and my family is a classical example of magnitude of the problem in our community state and country. In a cross-sectional study conducted by us in 860 volunteers from 3 villages in this area in the year 2007, the prevalence of various hemoglobin disorders observed were, sickle cell hemoglobinopathy 21%, alpha thalassemia 25%, beta thalassemia 5.0%, and HbE and HbD <1% each (Unpublished observations).

In our Hospital, 2000 cases attend to the Sickle cell clinic and 500 cases are admitted annually. For this reason we have a sickle cell clinic started in 1998 and Molecular Biology Laboratory established in 2005 under the Sickle Cell Project financed by the Government of India for complete diagnosis of various hemoglobinopathies, outdoor consultation, registration, counseling, research and followup of sickle cell patients.

Various sickle cell hemoglobin disorders enrolled under sickle cell research project, V.S.S.Medical College, Burla :

Hb Pathy	No cases
SS	1495
S-beta thalassemia	85
SD	10
SC	2
S-HPFH	2
SE	2
Total	1596

Ethnicity & Caste

Caste	No.	%age	Total	Total%
Non Tribal (Caste Hindu)				
Kuilta	221	19.7		
Agharia	154	13.7		
Gouda	151	13.5		
Chasa, Teli, Dumal, others	252	22.5	**778**	**69.5**
Schedule Caste				
Gonda, Harijan, SC, Other	285	25.4	**285**	**25.4**
Schedule tribe				
Kandara, Bhuyan, Kandha, Kudia , others	34	3	**34**	**3**
Muslim	5	0.4	**5**	**0.4**
Christian	18	1.6	**18**	**1.6**
	1120	100	**1120**	**100**

The findings show that Sickle gene is widely prevalent in Non tribal & tribal populations being more frequent in some caste Hindus.

Age and sex distribution of Sickle Cell Disease cases:

AGE	Male No. (%)	Female No. (%)	Total No. (%)
<=10	112(10)	70(6.3)	182(16.3)
11 - 20	215(19.2)	139(12.4)	354(31.6)
21 - 30	240(21.4)	112(10)	352(31.4)
31 - 40	111(9.9)	50(4.5)	161(14.4)
41 - 50	35(3.1)	16(1.4)	51(4.6)
51 - 60	12(1.1)	5(0.4)	17(1.5)
61 - 70	2(0.2)	1(0.1)	3(0.3)
Grand Total	**727(64.9)**	**393(35.1)**	**1120(100)**

Majority of patients in the study were 11-30 year range. A small but significant number of patient (7%) have survived beyond 40 years.

Clinical Feature:

Vasocclusive (Painful) crisis:

Painful crisis is the commonest cause of presentation found in 86.6%) cases suffered one or more episodes of painful crises. Although average rate of painful crises was 1.3 episodes / year, the frequency is highly variable. More than 3 episodes a year was observed in 122(11.0%) cases, which accounted for 40.1% of the episodes.

Distribution of rate of vasocclusive crisis

	Male	**Female**	**Total**
No VOC	86(11.9)	63(16.2)	149(13.4)
<1	312(43.3)	157(40.5)	469(42.3)
1 - 2	166(23.1)	91(23.5)	257(23.2)
2 - 3	78(10.8)	33(8.5)	111(10.0)
3 - 4	41(5.7)	20(5.2)	61(5.5)
4 - 5	16(2.2)	6(1.5)	22(2.0)
5 - 6	6(0.8)	6(1.5)	12(1.1)
6 - 7	6(0.8)	0(0.0)	6(0.5)
7 - 8	2(0.3)	2(0.5)	4(0.4)
8 - 9	2(0.3)	4(1.0)	6(0.5)
9 - 10	3(0.4)	1(0.3)	4(0.4)
10 - 11	0(0.0)	3(0.8)	3(0.3)
11 - 12	0(0.0)	1(0.3)	1(0.1)
12 - 13	1(0.1)	0(0.0)	1(0.1)
14 - 15	0(0.0)	1(0.3)	1(0.1)
17 - 18	1(0.1)	0(0.0)	1(0.1)
Total	**720(65.0)**	**388(35.0)**	**1108(100.0)**

Severity and Nature of anemia:

The severity and cause of anemia was evaluated in all the patients. Majority of the patients i.e., 48.3% had moderate anemia. 15.9% were severely anemic. The anemia was normocytic & normochromic in 51.4% cases, whereas macrocytosis was found in 1.7% cases.

Evaluation of microcytosis in sickle cell disease

In the present series 46.9% of cases had microcytosis (MCV<80). The cause of microcytosis was evaluated in 92 cases of Sickle Cell Disease . Serum ferritin was measured by ELISA, Bone marrow iron staining was done by Perls stain, Alpha Thalassemia was evaluated by Multiplex PCR. 42 % of Sickle Cell Disease patients with microcytosis had evidence of Iron deficiency, 38 % had alpha thalassemia both homo- and heterozygote, whereas in the rest the cause could not be ascertained.

Liver & Gall bladder:

82% of patients had hemolytic jaundice. However, serum bilirubin >6mg% in absence of crisis was documented in 66 out of 485 cases (13.6%). Conjugated & unconjugated hyperbilirubinemia was found in 34 (7%) and 32 (6.6%) cases respectively. The cause of unconjugated hyperbilirubinemia was Falciparum malaria in 18 cases & hyperhemolysis in 14 cases. Abdominal ultrasound was done in 423 cases 23.4% of cases had gall stone,. Ten cases had undergone surgical cholecystectomy.

Spleen

Splenomegaly was found in 50.8% cases , 2.2% cases had undergone surgerical splenectomy, persistent splenomegaly and gross splenic enlargement are peculiarities of Sickle Cell Disease in India. Recurrent malaria was cause of persistent splenomegaly in 34% cases. Splenic atrophy and autosplenectomy was found in 11.4% cases.

Skeleto-Muscular changes

Radiological examination of hip joint was done in 475 cases. Osteomyelitis, acute & chronic was found in 11 (1%) cases. Generalized osteoporesis was found in 26(2%) cases. However one of the most debilitating complications of avascular necrosis (AVN) of hip was found in 87(18.3%) of cases. 20(4.2%) had bilateral hip necrosis, while none of the cases had AVN of shoulder.

Infections:

436 cases (39%) had various forms of infections. Malaria (falciparum and Vivax) was the commonest infection & was found in 23.6% cases. Tuberculosis involving lungs, bone, meninges, pleura was the second commonest cause of infection found in 5.7% cases. upper respiratory tract infection, pneumonia and urinary tract infection were found in 5.7%, 2% & 2% cases respectively.

128 consecutive cases of Sickle Cell Disease were screened for markers of Hepatitis B & C infection and compared with 100 healthy controls HbsAg was measured by Sandwich ELISA technique, Anti-HBc IgM was determined by antibody capture ELISA technique and anti-HCV was done by ELISA. 22 cases (17.2 %) were positive for markers of Hepatitis B infection whereas 12 (9.4%) cases were positive for hepatitis C infection. In a control group 4% were positive for HBV infection & 2% were positive for HCV infection. Six cases (4.7%) were positive for both HBV and HCV infections.

Renal Failure:

Urine analysis, estimation of serum urea and creatinine and ultrasonography of abdomen was conducted in 505 cases. Creatinine >1.4mg & GFR <90ml indicative of renal failure was found in 17% cases. 5% of cases had normal GFR with non-nephrotic proteinuria <3g in 24hrs. Urinary tract infection was the presenting complaint in 6% of cases. Histopathological study of sickle cell nephropathy in 14 cases revealed enlarged & congested glomeruli in 21% cases, focal glomerulo sclerosis in 28% cases & membranoproliferative changes in 21% cases.

Leg Ulcer was found in 23(2%) of our cases.

Priapism was found in 3 cases in our series.

Is Indian Sickle Cell Disease benign in comparison to other populations?

Although the âs gene in Indian Sickle Cell Disease patients is linked to Asian Indian haplotype the clinical feature was not benign as reported earlier, as depicted in the table below.

	India	CSSCD/ Jamaica
No painful crisis	13.4%	39%
Pain rate	1.3	0.8
AVN	18.3%	4-19%
Cholelithiasis	27%	31%
Hb	8.2g%	8g%
Mortality	4.7%(2.4 /100 pt year)	2.6%(0.5 / 100 pt year)
Leg Ulcer	1.9%	10-75%
Priapism	0.3%	2-6%
HbF	22.3± 6.9% (3.9 – 46.5%)	6.11 ± 4.21 % (0.4- 33.2)

Cause of Death

Cause	No.	%
VOC ACS-24 MOD-10 Other-10	23	44
Falciparum Malaria	14	26
RF	7	14
CVA	3	6
Others	5	10
	53	100

Fifty three of 1120 cases had in hospital death (4.7%). Of these 33 were male and 20 were female. Average age of death was 26.9 years. The commonest cause of death was vasocclusive crisis (44%). In this group acute chest syndrome was the cause in 24% &10% had multiorgan dysfunction(MOD). Falciparum malaria leading to various complications was cause of death in 26% cases. Third leading cause of death was renal failure in 14% cases & 6% died due to intracranial hemorrhage.

CONCLUSION:

Prevalence of sickle cell gene is high in India & both tribal and non-tribal populations are affected. 6.7 % patients are asymptomatic. The commonest symptom is painful crisis (86.6%). Higher HbF has been found to reduce the frequency of painful crisis. Malaria is the commonest infection, is a precipitating factor for painful crisis & responsible for 26% of all deaths. Persistent splenic enlargement is common & related to high HbF & malaria. AVN is found in 19.3%. In 12.6% cases AVN was associated with tuberculosis. CRF is prevalent in 17% cases & increased progressively with age. Leg ulcer, Priaprism & Stroke are uncommon. Mortality was 2.6 per 100 pt year. The commonest cause was painful crisis (44%) followed by malaria (26%). In spite of Asian haplotype & high HbF level the disease is not benign. Endemic malaria & Tuberculosis are important cause of high morbidity & mortality.

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Original Article

A STUDY OF CARDIOVASCULAR RISK FACTORS IN PATIENTS OF PRE-DIABETES (IFG & IGT) WITH SPECIAL REFERENCE TO CAROTID AND FEMORAL INTIMA MEDIA THICKNESS

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ABSTRACT

35 patients of pre-diabetes and 35 age- and sex-matched normoglycemic controls were taken for study. They were subjected to history, clinical examination, routine blood chemistry, FBS, 2hr PGBS, lipid profile, ECG, echocardiography, carotid and femoral Doppler study. Mean age in controls was 49.857 ± 12.086 years, whereas in cases it was 52.08 ± 11.749 years. Carotid and femoral IMT were different in the two groups to a degree of statistical significance; these were more in smokers and hypertensives compared to non-smokers and non-hypertensives. The mean IMT correlated well with both increasing age in both control group and pre-diabetics. Total cholesterol, triglyceride and LDL-cholesterol differed between the groups to a degree of statistical significance. Our data shows that IGT and to a lesser extent IFG are associated with impaired cardiovascular conditions (whether risk factors or IMT) . These findings provide further evidence for increased cardiovascular risk associated with pre-diabetes and further stresses the need for early screening and management of pre-diabetes. ***Keywords :*** *Pre-diabetes, Cardiovascular risk factors, carotid & femoral intima media thickness.*

INTRODUCTION

Worldwide, the number of persons with diabetes mellitus(DM) is expected to double in the next 25 years and to affect more than 350 million individuals by 2030. Recent estimates have ranked India number one in the world in the number of diabetic patients in any given country. Pre-diabetes, a relatively new term coined by the American Diabetic Association, includes both impaired fasting glucose(IFG) and impaired glucose tolerance(IGT), which have been demonstrated to be risk factors for the subsequent development of both DM and CVD. Carotidsonography is now playing a major role in assessing the vascular pathology, by measurement of intima-medial thickness(IMT) which is taken as a reliable surrogate measurement of intimal thickening. Recent studies shows that metabolic syndrome components impacted selectively on IMT at femoral site. The primary objective of this study was to compare the association between pre-diabetes and both IMT (carotid and femoral) and major CVD risk factors (blood pressure, smoking , lipid profile, waist circumference, BMI).

AIM AND OBJECTIVES OF THE STUDY

To study the Intima media thickness (carotid and femoral) in pre-diabetic patients. To assess the cardiovascular risk factors (blood pressure, smoking, lipid profile, waist circumference, BMI) and compare between them with respect to Intima media thickness.

MATERIALS AND METHODS

35 patients of pre-diabetes (Diagnosis of pre-diabetes as per American Diabetes Association guidelines, 2007) & 35 numbers of age and sex matched

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controls (normoglycemic) were taken for comparison purpose. Examination during OPD/Admission included Medical History, Clinical Examination, Routine Blood Chemistry, FBS, 2hr PGBS, Lipid Profile, ECG, Echocardiography, Carotid and Femoral Doppler study. Results were analyzed with Graph Pad Instat 3. All descriptive data were expressed as means ± SD, and these values were used as descriptive measures of normally distributed variables. Statistical significance of parameters between groups was evaluated using Student's t test, and 95% CIs for differences between groups were also calculated. Analysis of covariance (ANOVA) was used to compare the mean IMT between cases and controls and between cases belonging to different subtypes. Statistical significance was inferred at $P<0.05$. The strength of correlation between the various lipid fractions, age, waist circumference, BMI and the IMT were separately calculated using the Pearson correlation analysis.

RESULTS

TABLE 1: DISTRIBUTION OF SELECTED CLINICAL AND METABOLIC RISK FACTORS IN STUDY GROUPS.

RISK FACTORS	CONTROL(n=35)	CASES(n=35)	Unpaired 't' test (p value)
AGE (in yrs.)	49.857± 12.086	52.08±11.749	0.448
MALE:FEMALE	27:8	29:6	---
SMOKING	18(51.42%)	13(37.14%)	0.335
ALCOHOL	11(31.42%)	8(22.85%)	0.596
HYPERTENSION	12(34.28%)	12(34.28%)	1.190
WAIST CIRCUMFERENCE (in cm)	84.45±9.841	86.457±9.124	0.381
BMI(kg/m2)	22.18±5.52	23.11±4.29	0.434
FBS(mg/dl)	86.28±8.59	104.11±11.93	0.000
2hrPG(mg/dl)	118.48±14.89	160.14±24.32	0.000
TOTAL CHOLESTEROL(mg/dl)	185.42±44.21	182.37±45.29	0.077
TRIGLYCERIDES(mg/dl)	173.62±53.43	166.51±33.58	0.507
LDL-C(mg/dl)	108.17±38.05	107.63±38.90	0.953
HDL-C(mg/dl)	43.17±54.85	41.34±6.65	0.520
VLDL-C(mg/dl)	34.57±10.78	33.17±6.94	0.214

The mean age in the controls was 49.857±12.086 years, whereas the mean age in cases was 52.08±11.749 years. The male:female ratio in controls was 3.3:1 and in cases was 4.8:1. The mean waist circumference in controls was 84.45±9.841 cm, whereas in cases was 86.457±9.124cm. The mean BMI in controls was 22.18±5.52kg/m^2 and in cases was 23.11±4.29kg/m^2. The mean FBS in controls was 86.28±8.59 mg/dl and in cases was 104.11±11.93 mg/dl. The mean 2hr PG in controls was 118.48±14.89 mg/dl and in cases was 160.14±24.32 mg/dl. The lipid parameters were more in controls than cases, however it was not statistically significant.

TABLE 2: COMPARISON OF MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS.

IMT(in mm)	CONTROL(n=35)	CASES(n=35)	Unpaired 't' test (p value)
CAROTID	0.602±0.116	0.692±0.086	0.000
FEMORAL	0.528±0.091	0.574±0.099	0.04

The mean carotid IMT in controls was 0.602±0.116mm and in cases was 0.692±0.086mm. The mean Femoral IMT in controls was 0.528±0.091 mm and 0.574±0.099mm in cases. The IMT was higher in prediabetics in comparison to controls and was statistically significant.

TABLE 3:

COMPARISON OF MEAN CAROTID AND FEMORAL IMT IN MALES AND FEMALES

IMT(in mm)	CONTROL(n=35)			CASES(n=35)		
	MALE	FEMALE	Unpaired 't' test (p value)	MALE	FEMALE	Unpaired 't' test (p value)
CAROTID	0.620±0.11	0.541±0.09	0.09	0.698±0.08	0.659±0.094	0.31
FEMORAL	0.538±0.08	0.494±0.09	0.23	0.581±0.10	0.542±0.54	0.35

The mean carotid IMT in control groups in males and females were 0.620±0.118mm and 0.541±0.092mm respectively, whereas the mean Femoral IMT was 0.538±0.089mm and 0.494±0.095mm respectively. The mean carotid IMT among cases in males and females were 0.698±0.085mm and 0.659±0.094mm respectively, whereas the mean femoral IMT were 0.581±0.106mm and 0.542±0.054mm respectively. The mean IMT was higher in males in comparison to females and was statistically significant in controls.

TABLE 4:

CORRELATION BETWEEN MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

GROUP	CAROTID IMT (in mm)	FEMORAL IMT (in mm)	Correlation coefficient (r)	p value
CONTROL(n=35)	0.602±0.116	0.528±0.091	0.893	<0.00
CASES(n=35)	0.692±0.086	0.574±0.099	0.848	<0.00

There was a positive correlation between the mean carotid and femoral IMT in the study groups and was statistically significant.

TABLE 5: RELATIONSHIP BETWEEN AGE AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

AGE DISTRIBUTION	CONTROL (n=35)		CASES (n=35)	
	CAROTID IMT(in mm)	FEMORAL IMT(in mm)	CAROTID IMT(in mm)	FEMORAL IMT(in mm)
25-34	0.458±0.069	0.425±0.070	0.625±0.040	0.526±0.040
35-44	0.526±0.044	0.471±0.015	0.600±0.034	0.495±0.020
45-54	0.607±0.097	0.528±0.066	0.682±0.069	0.554±0.040
55-64	0.654±0.105	0.573±0.100	0.734±0.091	0.622±0.147
65-74	0.725±0.176	0.585±0.007	0.737±0.080	0.603±0.038

The IMT values were higher among the prediabetic subjects at all age points compared with the control subjects. The mean IMT gradually increased across all the age groups in controls.

TABLE 6: RELATION BETWEEN SMOKING AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

IMT(in mm)	CONTROL(n=35)			CASES(n=35)		
	SMOKERS	NON SMOKERS	Unpaired 't' test (p value)	SMOKERS	NON SMOKERS	Unpaired 't' test (p value)
CAROTID	0.660±0.107	0.540±0.092	0.001	0.700±0.098	0.687±0.081	0.681
FEMORAL	0.568±0.082	0.486±0.082	0.006	0.609±0.144	0.554±0.054	0.112

The mean carotid IMT values in smokers and non smokers in control groups were 0.660±0.107mm and 0.540±0.092mm respectively and the mean femoral IMT in controls were 0.568±0.082mm and 0.486±0.082mm respectively. In cases the mean carotid IMT in smokers and non smokers were 0.700±0.098mm and 0.687±0.081mm respectively and the mean femoral IMT were 0.609±0.144mm and 0.554±0.054mm respectively.

The mean IMT values were higher in smokers than in non smokers and were statistically significant in control groups.

TABLE 7: RELATION BETWEEN HYPERTENSION AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

IMT(in mm)	CONTROL (n=35)			CASES (n=35)		
	HTN	NON HTN	Unpaired 't' test (p value)	HTN	NON HTN	Unpaired 't' test (p value)
CAROTID	0.693±0.090	0.554±0.090	0.000	0.719±0.103	0.677±0.074	0.117
FEMORAL	0.607±0.075	0.486±0.068	0.000	0.617±0.144	0.552±0.057	0.063

The mean carotid IMT values in hypertensive and normotensive subjects in control groups were 0.693±0.09mm and 0.554±0.09mm respectively and the mean femoral IMT in controls were 0.607±0.075 and 0.486±0.068mm respectively. In cases the mean carotid IMT in hypertensive and normotensive subjects were 0.719±0.103mm and 0.677±0.074mm respectively and the mean femoral IMT were 0.617±0.144mm and 0.552±0.057mm respectively.

The mean IMT values were higher in hypertensive subjects in comparison to normotensive subjects in both cases and controls and was found to be statistically significant among control group.

TABLE 8: RELATION BETWEEN ALCOHOL AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

IMT (in mm)	CONTROL (n=35)			CASES (n=35)		
	ALCOHOLICS	NON ALCOHOLICS	Unpaired 't' test (p value)	ALCOHOLICS	NON ALCOHOLICS	Unpaired 't' test (p value)
CAROTID	0.643±0.106	0.583±0.117	0.162	0.633±0.058	0.709±0.086	NS
FEMORAL	0.572±0.090	0.508±0.086	0.052	0.528±0.052	0.588±0.107	NS

The carotid and femoral IMT did not vary much with respect to alcohol intake and no relationship was found in prediabetics or control group.

TABLE 9: CORRELATION OF MEAN CAROTID IMT WITH VARIABLES IN STUDY GROUPS.

VARIABLES	CONTROL (n=35)		CASES (n=35)	
	Correlation coefficient (r)	p value	Correlation coefficient (r)	p value
AGE (in yrs.)	0.687	0.000	0.557	0.000
WAIST CIRCUMFERENCE (in cm)	0.317	0.063	-0.154	0.376
BMI(kg/m2)	0.015	0.937	-0.219	0.205
TOTAL CHOLESTEROL(mg/dl)	0.038	0.826	0.079	0.650
TRIGLYCERIDES(mg/dl)	0.056	0.748	-0.086	0.621
LDL-C(mg/dl)	-0.003	0.984	0.080	0.646

TABLE 10: CORRELATION OF MEAN FEMORAL IMT WITH VARIABLES IN STUDY GROUPS

VARIABLES	CONTROL (n=35)		CASES (n=35)	
	Correlation coefficient (r)	p value	Correlation coefficient (r)	p value
AGE (in yrs.)	0.611	0.000	0.425	0.010
WAIST CIRCUMFERENCE (in cm)	0.273	0.112	0.018	0.917
BMI(kg/m2)	0.017	0.918	-0.071	0.683
TOTAL CHOLESTEROL(mg/dl)	0.095	0.584	0.262	0.127
TRIGLYCERIDES(mg/dl)	0.014	0.935	0.002	0.988
LDL-C(mg/dl)	0.049	0.778	0.259	0.133

The mean IMT correlated well with increasing age in both control group and prediabetics. Other variables did not correlate significantly.

TABLE 11: RELATION BETWEEN BMI AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

STUDY GROUPS	BMI	CAROTID IMT MEAN±SD	Unpaired 't' test (p value)	FEMORAL IMT MEAN±SD	Unpaired 't' test (p value)
CONTROL (n=35)	≤23	0.589±0.120	0.407	0.523±0.104	0.692
	>23	0.623±0.110		0.536±0.066	
CASES (n=26)	≤23	0.698±0.070	0.678	0.560±0.058	0.738
	>23	0.686±0.090		0.580±0.126	

The mean IMT were also higher in control group in subjects with BMI > 23kg/m^2 in comparison to subjects with BMI < 23kg/m^2, though it did not achieve statistical significance.

TABLE 12: RELATION BETWEEN WAIST CIRCUMFERENCE AND MEAN CAROTID AND FEMORAL IMT IN STUDY GROUPS

STUDY GROUPS	WAIST CIRCUMFERENCE	CAROTID	Unpaired 't' test (p value)	FEMORAL	Unpaired 't' test (p value)
CONTROL (n=35)	MEN < 85 & WOMEN < 80	0.587±0.123	0.477	0.521±0.192	0.667
	MEN > 85 & WOMEN > 80	0.616±0.111		0.535±0.082	
CASES (n=26)	MEN < 85 & WOMEN < 80	0.715±0.076	0.532	0.581±0.059	0.729
	MEN > 85 & WOMEN > 80	0.671±0.091		0.569±0.125	

The mean IMT were also higher in control group in subjects with greater waist circumference (men>85cm and women>80cm) in comparison to subjects with lesser waist circumference (men<85cm and women<80cm).

TABLE 13: COMPARISON OF CLINICAL AND METABOLIC FACTORS ACROSS CATEGORIES OF IMPAIRED GLUCOSE REGULATION

VARIABLES	IFG/NGT (n=12)	NFG/IGT (n=13)	IFG/IGT (n=10)	p value
AGE (in yrs.)	54.30± 11.50	49.20±13.10	53±10.00	0.553
MALE:FEMALE	9/3	11/2	9/1	--
SMOKING	5/12	5/13	3/10	--
ALCOHOL	4/12	2/13	2/10	--
HYPERTENSION	5/12	3/13	4/10	--
WAISTCIRCUMFERENCE (in cm)	87.5±6.36	84.23±7.79	88.10±13.10	0.547
BMI(kg/m^2)	22.98±3.54	22.48±3.14	24.10±6.27	0.682
FBS(mg/dl)	111.83±7.73	91.07±6.57	111.80±4.18	0.000
2hrPGBS(mg/dl)	132.91±4.23	167.69±17.97	183.00±11.48	0.000
TOTAL CHOLESTEROL(mg/dl)	208.08±18.46	174.76±52.37	161.40±47.16	0.036
TRIGLYCERIDES(mg/dl)	185.83±17.30	168.53±22.30	140.70±44.59	0.004
LDL-C(mg/dl)	129.92±17.85	98.30±46.19	93.00±38.20	0.042
MEAN CAROTID IMT (in mm)	0.645±0.046	0.707±0.072	0.727±0.118	0.570
MEAN FEMORAL IMT (in mm)	0.543±0.056	0.568±0.052	0.621±0.162	0.185

The mean carotid IMT increased most notably at the level of subjects with both IFG and IGT (0.645mm, 0.707mm and 0.727mm for subjects with IFG, IGT and IFG+IGT respectively).

The mean femoral IMT also increased most notably at the level of subjects with both IFG and IGT (0.543mm, 0.568mm and 0.621mm for subjects with IFG, IGT and IFG+IGT respectively).

SUMMARY AND CONCLUSION

After exclusion, 35 cases of prediabetes (Diagnosis of prediabetes as per ADA guidelines 2007) were included in the study.

The control group consisted of 35 normoglycemic persons matched by age, gender and risk factors.

Raised Total cholesterol was found in 12(34.28%) subjects of both control and prediabetic group. Raised Triglycerides was found in 24(68.57%) of controls and 26(74.28%) of cases. Raised LDL-C was found in 19(54.28%) of controls and 20(57.14%) of cases. Overall, Dyslipidemia was more prevalent in prediabetics in comparison to the control group, however it was not statistically significant. There was considerable overlapping and quite a few patients had more than one lipid abnormality in various combinations.

The mean waist circumference was more in cases in comparison to controls. The mean BMI was more in cases in comparison to controls.

The mean carotid IMT in controls was 0.602±0.116mm and in cases was 0.692±0.086mm. The mean Femoral IMT in controls was 0.528±0.091 mm and 0.574±0.099mm in cases. The IMT was higher in prediabetics in comparison to controls and was statistically significant.

The mean IMT was higher in males in comparison to females and was statistically significant in controls.

There was a positive correlation between the mean carotid and femoral IMT in the study groups and was statistically significant.

The mean IMT correlated well with increasing age in both control group and prediabetics.

The IMT values were higher among the prediabetic subjects at all age points compared with the control subjects.

The mean IMT values were higher in smokers than in non smokers in both cases and controls and were statistically significant in control groups.

The mean IMT values were higher in hypertensive subjects in comparison to normotensive subjects in both cases and controls and was found to be statistically significant among control group.

The carotid and femoral IMT did not vary much with respect to alcohol intake and no relationship was found in prediabetics or control group.

The mean IMT were also higher in control group in subjects with BMI > 23kg/m^2 in comparison to subjects with BMI < 23kg/m^2, though it did not achieve statistical significance.

The mean IMT were also higher in control group in subjects with greater waist circumference (men>85cm and women>80cm) in comparison to subjects with lesser waist circumference (men < 85cm and women < 80cm).

The mean carotid IMT increased most notably at the level of subjects with both IFG and IGT (0.645mm, 0.707mm and 0.727mm for subjects with IFG, IGT and IFG+IGT respectively).

The mean femoral IMT also increased most notably at the level of subjects with both IFG and IGT (0.543mm, 0.568mm and 0.621mm for subjects with IFG, IGT and IFG+IGT respectively).

Our data show that IGT and to a lesser extent IFG are associated with impaired cardiovascular conditions (whether risk factors or IMT). These findings provide further evidence for increased cardiovascular risk associated with pre-diabetes (the increased cardiovascular risk associated with DM is well established) and further stress the need for early screening and management of pre-diabetes.

Overall, Doppler Ultrasonography appears to be a useful diagnostic tool for assessing the Intima Media Thickness.

The IMT may be regarded as the closest investigation to an arterial biopsy. Therefore, the morphological and dimensional information obtained from duplex scans may be used in addition to classical risk factors for risk assessment. Indeed, new guidelines (ATPIII) from the United States actually state that additional predictors of risk (e.g. imaging) could influence a clinician's decision to intervene with medication. B-mode scanning could become an important non-invasive, accurate and reproducible method to assess cardiovascular risk in the future.

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"We congratulate **Prof. Dr. Sidhartha Das** on the occasion of being conferred with prestigious FRCP for his life time academic achievements, administrative excellence, clinical skills and an exemplary personality".

Editor, OPJ

Original Article

CARDIAC BIOMARKERS IN PROGNOSIS OF ACUTE CORONARY SYNDROME

K. Sen,* S.K. Mahapatra, P.C. Dash,*** S. Behera,*** A. Acharya,******

ABSTRACT

Acute coronary syndrome (ACS) is an unifying term representing a common end result, acute myocardial ischemia which encompases three distinct entities STEMI, NON- STEMI, Unstable Angina several cardiac biomarkers like myoglobin, CK-MB, TROP-T, Hs-CRP) have diagnostic value in ACS. Out of 68 patients admitted to S.C.B. Medical College with ACS 44 patients were subjected to Hs-CRP, CK-MB, Myoglobin and ECG, 2D echocardiogram test. 23 cases are found to be STEMI and 21 cases are non-STEMI. Complications like arrhythmia, AV Block, LVF, cardiogenic shock are seen in 25 cases. Mean CK-MB was 17.155, Trop-T was 0.39, CRP was 4.127 and myoglobin was 180.300. Six patients died in the hospital. High level of myoglobin, CK-MB & TROP-T, are correlated in the prognosis of ACS in relation to its complication and mortality.
***Keywords** : Acute Coronary Syndrome, Cardiac Biomarkers.*

INTRODUCTION:

Acute Coronary Syndromes (ACS) comprises the spectrum of unstable cardiac ischaemia from unstable angina to acute myocardial infarction (STEMI & NON-STEMI).

Serum cardiac biomarkers like myoglobin, CK-MB and TROP-T are commonly used tests to identify patients with ACS next only to ECG. They are useful for both the diagnostic and prognostic value in ACS. They can individually asses the evaluation of patients with ACS.

Combination of these markers can even be more beneficial for diagnosis. Wide spread availability of more sensitive biochemical cardiac markers particularly TROP-T improves the diagnosis of myocardial infarction. It helps in differentiation of STEMI from non STEMI. The higher levels are also important prognostic marker in ACS.

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AIM OF OUR STUDY :

To assess the correlation of different cardiac Biomarkers' level with short term prognosis of ACS, and to evaluate their ability to predict long term outcome in patients hospitalized with an Acute Coronary Syndrome.

MATERIAL AND METHODS :

68 patients admitted to Medicine and Cardiology Ward of S.C.B. Medical College with diagnosis of ACS were taken into study.

Patients with previous history of AMI, Congestive heart failure on treatment, Congenital Heart Disease, Rheumatic Heart Disease , Collagen Vascular Disease and Chronic Renal Failure are excluded from the study.

After proper exclusion, patients selected are subjected to thorough clinical examination, Routine & special investigations like Hb, DC, TLC, FBS, Serum – urea, creatinine, lipid profile, urine (routine & microscopy) and 12 lead ECG are done in all cases. Cardiac bio markers like myoglobin, CK-MB, Trop-T, HS-CRP are also done in each cases.

They are observed closely for the development of any complication /requirement of any intervention during hospital stay.

The causes of death are assessed and after discharge, patients are followed up for 1 month then up to 6 months. The delayed and late complications of ACS are evaluated and causes of death wherever applicable are noted.

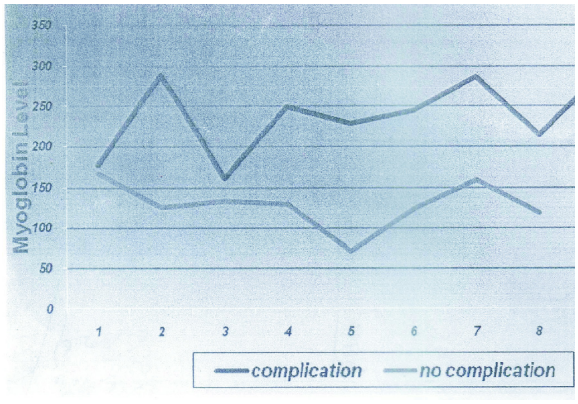
The relation between elevated serum biomarkers and complications are analysed by Pearson's Coefficient of correlation.

OBSERVATION & DISCUSSION :

In our study we have taken 44 cases of ACS, their prognostic aspects are correlated with the different serum cardiac biomarkers and evaluated.

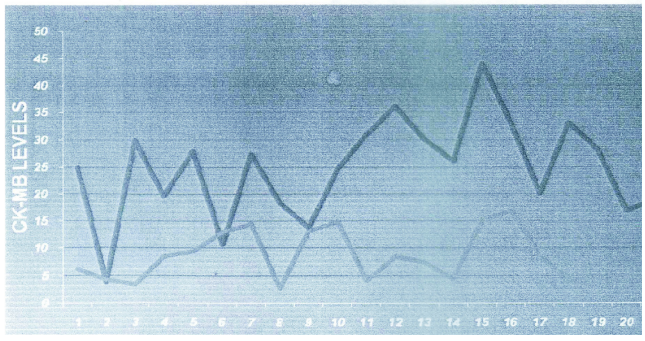
Out of 44 cases 26 (59.1%) are males and 18 (40.9%) are females.There are 23 STEMI cases and 21 cases of non STEMI. Complications developed in 25 (56.8%) cases and absent in 19 (43.2%). Out of 25 cases, where complications were seen 20 were STEMI (out of 23 STEMI cases) and 5 were non STEMI (23.8%) out of 21 NON-STEMI cases. The different complications were severe arrhythmia in 9 (36%), AV Block in 6 (24%), LVF in 5 (20%), cardiogenic shock in 6 (24%), others in 3 (12%) cases.

Correlation of Myoglobin with in Hospital Complications of ACS



Myoglobin level was done in all cases of ACS. The correlation of myoglobin level with inhospital complications of ACS showed mean – 180.300, SD – 65.9, correlation coefficient – 0.807 with p value – 0.000. This shows elevated levels of serum myoglobin is associated with increased chance of development of complication after ACS, the correlation coefficient was found to be 0.807 (p = 0.000). This finding corroborates with that in the study done by Lemos and Morrow et al[1], as part of the TIMI 11B and TIMI 18 studies, In a multivariate model adjusting for baseline characteristics, ST changes and CK-MB and cTnl levels, an elevated baseline myoglobin was associated with increased six – month mortality in TIMI 11B (adjusted odds ratio (OR) 3.0 (95% CI 1.8 to 5.0).

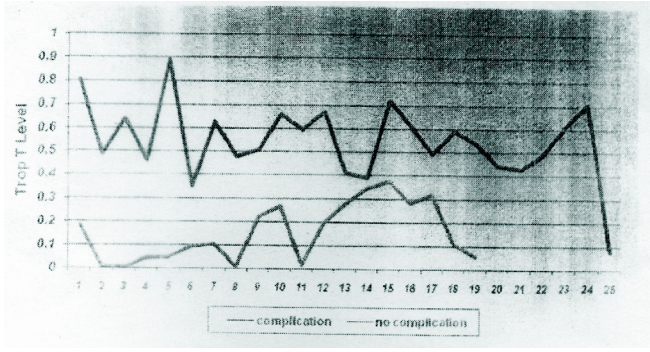
Correlation of CK-MB with in Hospital Complications of ACS



In this study correlation of CK-MB Level with in hospital Complication of ACS has been done. We have total patient (n = 44) with mean 17.155, sd – 10.54, correlation coefficient (r) – 0.609 with p value – 0.000 . Out of 44 cases STEMI were 23 having Mean – 22.26, SD – 9.75, C.C. – 0.425 with P. value – 0.043 and UA / NSTEMI (n = 21) showing mean – 12.5, SD – 9.3, C.C. – 0.803 with p. value 0.000. All the values are statistically significant.

Elevated level of CK-MB was associated with more chances of development of in-hospital complications or death following ACS, the correlation coefficient being 0.609 [p = 0.000]. The correlation was even stronger in NSTEMI [r = 0.803 (p = 0.000). This finding corroborates well with that found in the study by JM Galla, KW mahaffey et al[2], Regardless of total CK, elevated CK-MB was associated with a 25% to 49% increased relative risk of worse outcomes. Findings from the analyses were verified by the multivariable model. They had concluded that CK-MB remains a reliable marker for myocardial necrosis and a strong predictor of worse prognosis.

Correlation of Trop-T with in Hospital Complication of ACS



In our study we have done Co-relation of the Trop-T level with inhospital Complication of ACS : Out of Total 44 patients (n = 44) mean is = 0.39, SD – 0.24, C.C. – 0.773, p value – 0.000. In STEMI (n = 23). The mean – 0.52, SD – 0.16, C.C – 0.65, P. value – 0.001, UA / NON-STEMI (n = 21) showing mean – 0.23, SD – 0.25, C.C. 700, with P. value 0. 000.

From the above correlation, we have concluded that the elevated baseline Trop T level was strongly correlated with adverse clinical outcome 6 months after the index event [r = 0.676 (p = 0.000). This finding corroborates clearly with the study result of GD Kerr and DR Dunt[6]. In a prospective cohort study in which patients with suspected rest angina had a serum Troponin T estimation 14 hours after symptomatic onset and were classified using discriminator levels of serum Troponin T of 0.05 and 0.1 mg /L as well as a number of other variables. All patients were followed for six months to document any cardiac complications and a stepwise logistic regression analysis was conducted to determine independent risk factors of complications. They had concluded that in patients with suspected rest angina, dectable serum troponin T > 0.05 (mg /L) is an independent predictor of serious cardiac events during the six month follow up period although not during hospitalization. Another study by Heeschen C, Hamm CW et al[4] also revealed that elevated Trop T was independent predictor of mortality and recurrent MI at 6 months follow up.

We have done co-relation of hs-CRP level with inhospital complication of ACS. Our study showed statistical values of 43 total patient (n = 43) hs-CRP mean – 4.127, SD – 1.43, C.C – 0.436, with p value – 0.003. STEMI (n = 23) showing mean - 4.612, SD – 1.4, C.C – 0.197, with p. value 0;.368 and UA / NON-STEMI (n = 20) having mean 3.59, SD – 1.3, CC – 0.382 with p. value – 0.88.

Elevated baseline hs-CRP level, in our study, also showed positive correlation with adverse outcome 6 months after the index event [r = 0.341 (p = 0.049)]. This finding is corroborative with that obtained by Heescchen C, Hamm CW et al[4], mentioned above. They had evaluated C-Reactive Protein for predicting 6 months risk in patients with Unstable Angina. Baseline CRP values were taken in 447 patients with Unstable Angina enrolled in the placebo arm of CAPTURE trial, all the patients were followed up for 6 months. The study showed that CRP is an independent predictor of mortality and MI at 6 months of follow up. They also showed that the incidence of coronary restenosis during 6 months follow-up was significantly related to the CRP status (p = 0.03).

6 patients died in the Hospital. In our study we have correlated the average level of markers in those who died in hospital. The statistical values are Trop – T – mean is – 0.676, SD – 0.132, with p. value – 0.000, CK-MB – with mean – 29.72, S.D. – 9.91, p. value – 0.001, hs – CRP with mean 5.82, SD – 1.17, with p. value – 0.000. The mean Value of Trop – T, CK-MB, and hs – CRP of those patients who died in hospital were 0.676, 29.72 and 5.82 respectively.

The values are statistically significant. This shows there is a strong co-relation between the high level of the above cardiac bio-markers and development of complication and death.

SUMMARY & CONCLUSION :

Out of 44 patients of ACS evaluated, 23 were having STEMI and rest in the NSTEMI. 25 patients out of 44 had developed some complications during the period of their hospital stay where as 19 (43.2%) went uneventfully. 20 out of 23 patient of STEMI developed

complications where as 5 out of 21 of NSTEMI developed complications. The mean myoglobin level correlated strongly with development of in hospital complication of the ACS (r = 0.807 (p = 0.000).

The mean level of CK-MB was 17.155 with the SD being 10.54. It showed strong correlation with development of inhospital complications (r = 0.609 (p = 0.000). The mean level of Trop-T was 0.39 with the SD being 0.24. Trop-T also showed strong correlation with development of inhospital complications after ACS (r = 0.773 (P = 0.000). The mean level of hs CRP was 4.127 with SD being 1.43. hs CRP level failed to show any statistically significant correlation (p = 0.003) with complications.

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OBITUARY

We bow down in grief with loss of our great stalwards who had immense contribution in API activities

Late **Prof B.B. Tripathy** and **Prof D.B. Tonpe.**

Editor, OPJ

Original Article

JUVENILE RHEUMATIC MITRAL STENOSIS : A PROSPECTIVE STUDY

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

ABSTRACT

Objectives: *Follow up of patients with juvenile rheumatic mitral stenosis (MS) and study of natural history of the disease.* ***Methodology:*** *From 1990 onwards, we have followed up 129 cases of juvenile MS (onset below 20 years of age) prospectively. The mean follow up period was 6.1 +2 years.* ***Results:*** *The male to female ratio was 3:1. Forty one (31.7%) had previous history of rheumatic fever (RF), while 49(37.9%) were on regular penicillin prophylaxis. At the time of presentation, 26 patients (20.1%) had mild, 62(48.1%) had moderate and 41(31.8%) had severe form of the disease. Seven (5.4%) developed atrial fibrillation and one developed hemiplegia during follow up. Recurrent attacks of RF occurred in 53(41.1%). Thirty six (27.9%) developed new lesions like mitral regurgitation(MR) I aortic regurgitation(AR). Less than half (48%) could afford intervention. Nineteen (14.7%) died during the follow up period.* ***Conclusions:*** *We still come across cases of Juvenile MS. Considerable numbers of patients do not receive adequate penicillin prophylaxis. Many can not afford interventions. Closed mitral commissurotomy (CMC) is still a suitable alternative to balloon mitral valvotomy (BMV) because the former procedure is less costly.* ***Keywords :*** *Rheumatic heart disease, mitral stenosis, juvenile.*

INTRODUCTION

Rheumatic fever and chronic rheumatic heart disease (RHO) continue to be important public health problem ever in the new millennium. Chronic RHO is a common cardiovascular ailment, affecting children and young adults.[1] The disease once thought to be uncommon in India during early parts of the nineteenth century. became the commonest form of heart disease after the second world war and accounted for nearly 40% of cardiac cases seen in the hospitals? Between 1940-1983, school surveys estimated average prevalence of RHO to between 1.8 and 11/1000 school children (average 6/100); from 1984-1995 the prevalence was reported to be between 1-3.9/1000.[3] However, the data are not comparable, because the groups surveyed in the second period were small.[4]

Orissa is one of the few states in the country which continues to face the wrath of RF and RHO. A hospital based study has already shown that RHO is still highly prevalent with no recent significant decline in the percentage of such cases being admitted to a major Govemment Hospitals.

MATERIAL AND METHODS

From 1990 onwards, we have been following cases of juvenile mitral stenosis in order to ascertain their mode of presentation and natural history. A person was diagnosed to be suffering from juvenile rheumatic MS, if he/she was less than 20 years of age and had classical clinical and Achocardiographic features of MS. The cut-off age of 20 years was taken as per the definition of Roy et al.[6] We excluded those patients who had associated significant mitral regurgitation or aortic valve disease. All the patients, enrolled in the study protocol, were subjected to detailed clinical examination and echocardiographic assessment. Special care was taken to elicit history of rheumatic fever in the past and status of penicillin prophylaxis. During echocardiographic evaluation, assessment of mitral valve was done according to the scoring system devised by

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Wilkins et al.[7] Care was taken to exclude congenital causes of MS like parachute mitral valve. The patient was considered to have severe pulmonary arterial hypertension (PAH), if the acceleration time (AT) of the pulmonary artery was less than 70 miliseconds.[8]

All the patients were asked to present themselves annually once when the echocardiographic examination was repeated. If the patients did not turn up at the scheduled time. letters were sent to them to come for examination In the final analysis, we did not take into account those patients who could not be contacted or who failed to turn up on two consecutive occasions.

STATISTICAL ANALYSIS

The data were collected, and expressed as percentage, mean and standard deviation wherever applicable.

RESULTS

173 consecutive patients were initially recruited. As 44 patients did not report for their annual check up (on 2 consecL:tive occasions), their ultimate fate could not be known. Hence, their names were struck off from our follow up registry. Ultimately, 129 patients remained for final analysis. We started recruiting patients from 1990 onwards till the end of 2004. Mean period of follow up was 6.1 ± 2 years.

The baseline characteristics of the patient population have been presented in Table 1. The male to female ratio was 3:1. Forty one (31.7%) gave previous history of rheumatic fever and 49 patients (37.9%) were receiving regular penicillin prophylaxis.

Table 2 shows distribution of cases according to the age group. Majority of the patients (46.5%) were in the age group of 16-20 years. The youngest individual was 6 year old.

Table 3 displays the nature of initial presentation and follow up data of the cases. 59 patients (45.7%) had class II symptom of shortness of breath (SOB), whereas 70(54.3%) were class III/IV 3ymptomatic at the time of first presentation. Atrial fibrillation was present in 7(5.4%). One patient (0.8%) developed hemiplegia during follow up. Recurrent attacks of RF were recorded in 53(41.1%). Out of 26 cases of mild MS. 21 (80.7%) progressed to moderate disease during follow up. Out of 62 cases of moderate MS, 28(45.2%) ultimately developed severe form of the disease.

Table - 1
Baseline Characteristics

Total No. of Cases	**129**
Male : Female	97 : 32 (3:1)
Previous H/O RF	41 (31.7%)
Penicillin prophylaxis	49 (37.9%)

Table - 2
Age distribution of cases

Age (years)	**No. of Cases (%)**
6 - 10	23 (17.8)
11 - 45	46 (35.7)
16 - 20	60 (46.5)

Table - 3
Initial presentation and natural history

Characteristics	**No. of Cases (%)**
Symptomatology	
Class-II	59 (45.7)
Class - III/IV	70 (54.3)
Atrial fibrillation	7 (5.4)
Embolism	1 (0.8)
CCF	39 (30.2)
Recurrent attacks of RF	53 (41.1)
Progress of the disease	
Form mild to moderate	21/26 (80.7)
Form moderate to service	28/62 (45.2)
New lesions	
Mitral regurgitation	19 (14.7)
Aortic regurgitation	17 (13.2)
Interventions	
Balloon Mitral Valvotomy	27 (20.9)
Closed Mitral Commissurotomy	19 (19.7)
Deaths	19 (14.7)

Table - 4
Severity of MS at first presentation

Severity	No. of Cases (%)
Mild (1.5-2 cm^2)	26 (20.1)
Moderate (1-1.4 cm^2)	62 (48.1)
Severe (< 1 cm^2)	41 (31.8)

Table - 5
Echocardiographic Profile

Echo score (Mean ± SD)	7 ± 3
Calcification	6 (4.6%)
Severe PAH	57 (44.2%)

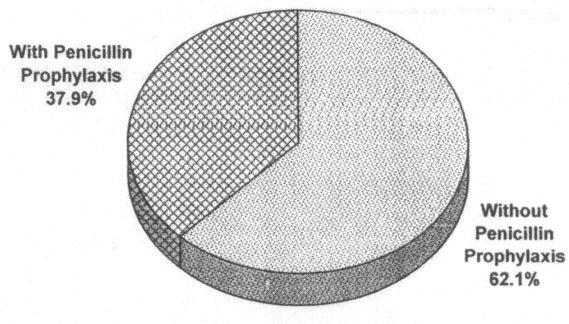

Fig. 1

LEGEND OF FIGURE

Fig.1 : Pie diagram showing penicillin prophylaxis status of the patients.

Additional lesions like mitral regurgitation and aortic regurgitation developed in 19(14.7%) and 17(13.2%) patients respectively during the period offollow up.

Altogether, 62(48%) underwent interventions like balloon mitral valvotomy (BMV) (20.9%) and closed mitral corr:missurotomy (CMC) (27.1%). 19(14.7%} died during the follow up. Commonest cause of death was congestive heart failure.

Table-4 shows severity of MS at first presentation. Twenty six (20.1%) had mild, 62 (48.1%) had moderate and 41 (31.8%) had severe MS.

Echocardiographic profile has been presented in Table-5. The mean echocardiographic score was 7±3. Calcification of the mitral valve was present in 6 (4.6%) and 57(44.2%) had severe pulmonary arterial hypertension.

DISCUSSION

Way back in 1963, S.B. Roy et al could realize the importance of MS affecting younger individuals and coined the term juvenile MS[6]. Since then, several studies from different parts of the country have endorsed the gigantic problem related to this debilitating disease.9-12 Sen, Bhayana et aI., and John.et al. have reported 30.5%, 42% and 21% of their respective series of MS to have juvenile rheumatic MS[1]D-12. However, very few data are available regarding long term follow up of juvenile MS patients in our country after 1980. This creates an impression that either the disease has become less common or it is no longer important. In this article, we present the clinical profile of 129 cases of juvenile MS. whom we have assiduously followed up since 1990.

The youngest individual was 6 years of age. T andon reported a case of MS who was 8 years old when first examined by him, though the diagnosis of MS was already made at 4 years of age elsewhere.[13]

The male to female ratio, in our series was 3:1. Predominance of male sex among cases of RHO has also been reported by Lalchandani et al. 14 Recent data suggest that large number of cases of RHO are still seen frequently in young children without any predominance of female sex, as was believed to be the predominant gender suffering from MS in the past. [6]

At the time of presentation, 70(54.3%) patients of this series were already having class III/IV symptom of S08. This indicates that majority of patients did not tum up to the hospitals unless they were severely symptomatic. Late presentation is due to poverty, illiteracy, and lack of awareness of serious nature of the disease. Orissa, from which the data is being

presented is one of the least developed states, where about 47.2% languish below the poverty !ine.[16] One disturbing aspect, revealed during our follow up was that hardly 1/3rd of total patients were receiving regular penicillin prophylaxis. This led to increased prevalence of recurrent attacks of RF (41.1 %). Padmavati has also reported high percentage of RF/RHO patients (42%) failing to receive any penicillin prophylaxis.[17] Penicillin prophylaxis is considered necessary because rheumatic fever has tendency of recurrence in those who have had rheumatic fever in the past[18]. Each new attack causes further damage to the valvular tissue making the disease worse than before[19]. ~till, most physicians are very reluctant to give benzathine penicillin injections 19. Figure-1 demonstrates penicillin prophylaxis status of the patients of our series.

Atrial fibrillation and embolic episodes were distinctly uncommon in the series. Rarity of AF in patients of juvenile MS has also been reported earlier.[20]

At the time of presentation, 41 (31.8%) patients had already developed severe MS. During the follow up period, 21(80.7%) progressed from mild to moderate form and 28(45.2%) progressed from moderate to severe form of the disease. In our observation, majority of juvenile MS cases had severe and crippling disease and is comparable to data published in the past.[14] The underlying reasons for severity of the disease process relates to recurrent and unrecognised streptococcal infection, lack of secondary prophylaxis and malnutrition.[21].[22] Echocardiographic examination revealed calcification of the mitral valves in 6(4.6%} patients only. As many as 57(44.2%) had sever PAH. Frequent occurrence of severe PAH and rarity of calcification are known classical features of juvenile MS.[23].[24]

Only 62(48%} underwent intervention like balloon mitral valvotomy (BMV) or closed mitral commissurotomy (CMC). BMV in juvenile MS cases is effective, safe and provides better immediate results than in adults particularty with regard to acute complications[25],26. However, in present series more patients were subjected to CMC than BMV, because the former procedure was less costly. Cost factor is important in a poor state like ours.

During the follow up, 19(14.7%) succumbed to their illness. Sanyal et al reported death rate of 20/ 1000 among children having RF/RHID[27]. However, Kumar et al reported very high mortality (case fatality rate of 16%) in a group of 257 RF/RHO patients with 1262.7 person-years of follow Up.28 High mortality reported by us also, is attributable to the late presentation of the patients with advanced form of the disease. Many patients also could not afford the cost of interventions.

CONCLUSION

With the ushering in of new millennium, focus of physicians has rapidly veered away from RHO to coronary artery disease and interventions associated with it like angioplasty and CABG. The problem of RHO has been sidelined and studies on its prevalence, treatment and prevention are receiving scant attention these days. Amidst this scenario, we present follow up data of 129 cases of juvenile rheumatic MS to refocus our attention on this debilitating disease. Many patients have already advanced form of the disease by the time they present to us. Considerable numbers of patients do not receive adequate penicillin prophylaxis. Progress of the disease is often relentless. Recurrent attacks of RF lead to involvement of other valves also. Many cases succumb to their illness because they are unable to afford the cost of interventional procedures. In such cases CMC may stilt be a viable alternative to BMV as the former procedure is less expansive. Nothing seems to have changed for our poor and illiterate patients. Thus, there should be no let up in ensuring adequate penicillin prophylaxis for all patients. Then only, we can conceive of stemming the tide of this debilitating disease.

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Original Article

A RANDOMISED CONTROLLED TRIAL OF THE EFFECT OF CITICHOLINE ON STROKE

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ABSTRACT

The present study was conducted in he department of Medicine SCBMCH cuttack for a period of one year.100 patients of both ischeimic and hemorrhagic stroke established by CT Scan of Brain presenting to the hospital with in 48 hours of onset were taken up for study. Out of the 100 patients, 50 patients were treated with citicholine along with standard stroke treatment and taken as cases. Other 50 with standard stroke treatment were taken as control. All the patient were studied at the base line with CANADIAN COMA SCALE. The patient were followed of at the end of first month and third month of the commencement of therapy and assessed by BARTHEL INDEX SCORE. The mean years of onset of stroke were 64.82 and 64.02 in both cases and Control group respectively. Analysis of categorized Barthel Index score showed that, there was significant difference between Barthel Index score of two groups of patients in the categories score (85-100). At 1st month follow up (0% in control group Vs 7 (14%) in citicholine group (p< 0.05) and 3rd month follow up 5(10%) in control group Vs 18(36%) in the citicholine group (p<0.05). Analysis in Barthel Index score in the category 85-100) at the end of 3rd month of the patients of haemorrhage sub group in both case and controls shows a significant difference 1(6.66% Vs 7 (31.81%) p value <0.05. ***Keywords :*** *Cerebrovascular accident, Ischemic stroke, Neuro protective agents, citicholine, stroke.*

INTRODUCTION

Stroke is defined as an abrupt onset of neurological deficit attributable to a focal vascular cause[1]. The WHO definition of stroke is rapidly developed clinical sign of focal or global disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause,other than vascular origin.[2]

Prevalence of stroke in India is 1.54 per 1000 population[3]**.** The total number of stroke in India in 2004 is 1.64 million.[4] The incidence of haemorrahagic stroke is 10%, infarct 87% and 3% SAH[5]**.** The primary aim in acute management of stroke is to improve the stroke outcome through improved early management, emergency treatment and acute intervention. Thrombolytics and control of intra cranial pressure and regulation of Blood Pressure have been the main therapeutic approach.

Within recent years large number of compounds that interfere with the biochemical mechanism that mediate ischemic brain injury have been demonstrated to be neuroprotective.

Citicholine (CDp choline) a compound normally present in all cells in the body is both a neuroprotective drug and act as a intermediate in membrane phospholipid synthesis.

Citicholine has been extensivey studied in >11,000 volunteers and patients with neurological conditions[6]**.** In clinical studies conducted in the United States and Canada with more than 1500 patients with ischemic stroke, citicholine was administered within 24 hours of a stroke, was well tolerated and showed significant treatment effects in key outcome measures used in stroke clinical research. Some important suggests that treatment with citicholine may reduce infarct growth after stroke and reduce rates of death or disability over a long term**.**[7]

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MATERIALS AND METHOD:

The present study was conducted in the department of Medicine SCB Medical College Cuttack for a period of one year from July 2008 to July 2009. 100 patients of both ischemic and haemorrhaegic stroke established by CT scan of Brain, presenting to the hospital within 48 hours of onset were taken for study.

Exclusion Criteria:

1. Critically ill patients with other systemic diseases.
2. End stage renal diseases
3. Advanced hepatic diseases
4. Presence of psychiatric illness
5. Cases of restrokes
6. Severe cardiovascular diseases with arrhythmia

After Exclusion, patients were alternatively randomised and one group of patients were treated with citcholine along with standard stroke treatment.

These patients were taken as cases and the other group of patients treated with standard stroke treatment were taken as controls.

Treatment protocol and follow up:

All the cases were treated with intravenous citicholine 1000 mg bd for 5 days followed by oral 500 mg bd for 25 days' comprising the whole treatment for 30 days. Medication like antihypertensive osmotic diuretic, lipid lowering statins and when necessary antithrombotics like clopidogrel were given to both cases and controls. All the patients were followed up at the end of first month and also third month by which time the required study was completed.

ASSESSEMENTS:

Baseline Assessments:

The age and sex of each patients were recorded and information was collected on the following variables, any history of hypertension, diabetes mellitus, hyper lipidemia, previous history of strokes, family history of strokes, CT Scan findings of diagnosed strokes,the type of stroke and the anatomical structures and vascular territory involved. The present study was conducted in both haemorrhaegic and ischemic stroke and Canadian Neurological Stroke scale was used to assess the severity of stroke.

Assessment of Outcome:

Primary outcome measure of this study was functional outcome as determined by Barthel Index at the end of 1st month and third month of commencement of therapy.For primary analysis Barthel Index * was classified into 6 stratas as death,0,5-40 ,45-60,65-80 and 85-10.statistical analysis was to be determined : i) whether there were significant differences between 2 groups in the distribution of patients in these six stratas specified. ii) assessment of mortality between 2 groups at the end of 1st month and 3rd month after the stroke onset.The statistical analysis was done by EXPINFO package (fishers exact test).

2. BARTHEL INDEX

FEEDING :

0 = unable

5 = needs help cutting, spreading butter, etc or requires modified diet

10 = independent

bathing

0 = dependent

5 = independent

grooming

0 = needs help wih personal care

5 = independent face/hair/teeth/ shaving (implements provided)

dressing

0 = dependent

5 = needs help but can do about half unaided

10 = independent (including buttons, zips, laces, etc)

bowels

0 = incontinent (or needs to be given enemas)

5 = occasional accident

10 = continent

bladder

0 = Incontinent, or catheterized and unable to manage alone

5 = needs some help, but can do something alone

10= independent (on and off dressing wiping)

toilet use

0 = dependent

5 = major help(one or two people, physical), can sit

10 = minor help (verbal or physical)

15 = independent

transfer (bed to chair, and back)

0 = unable no sitting balance

5 = major help (one or two people, physical) can sit

10 = minor help (verbal or physical)

15 = independent

mobility (on level surfaces

0 = immobile or <50 yards

5 = wheel chair independent, including corners, >50 yards
10 = walks with help of one person > 50 yards
15 = Independent (but may use any aid : for example, stick) >50 yards
stairs :
0 = unable
5 = needs help (verbal, physical, carrying aid)
Total = 0 - 100

OBSERVATION :

Table -1
AGE & SEX INCIDENCE (n = 100)

Age	Citicholine Group		Total	Control Group		Total
	Male	Female		Male	Female	
21-30	1	0	1	0	0	0
31-40	0	3	3	0	0	0
41-50	3	6	9	6	1	7
51-60	6	9	15	7	2	9
61-70	6	3	9	17	7	24
71-80	5	6	11	5	1	6
81-90	1	1	2	3	1	4
Total	**22**	**28**	**50**	**38**	**12**	50

Table –1 showed the age and sex distribution of patients taken for this study. It was observed that incidence of stroke was highest in the age group 51-60 in that is total 15 patients in Citicholine group and highest in 61-70 that is 24 in control group. Least no. of patients were in the age group of >80 years of age both in citicholine and control group. The mean age was found to be 64.02 in control and 60.04 in case group. It was also observed from the table that the incidence of stroke was more in males compared to females 60 : 40.

Table -2
INCIDENCE OF VARIOUS ASSOCIATED DESEASE (n = 100)

Disease	Control Group		Citicholine Group		Total
Diabetic Mellitus	4	8%	7	14%	**11(11%)**
Hypertension	22	44%	14	28%	**36(36%)**
Hyperlipidemia	5	10%	7	14%	**12(12%)**

Table – 2 showed 11 cases were diabetic (11%) and 36 were hypertensive (36%). 12 (12%) had hyperlipidemia.

TABLE - 3
INCIDENCE OF INFARCT AND HAEMORRHAGE IN CONTROL AND CITICHOLINE GROUP
(N = 100)

Side of Lesions	Control Group N=50		Citicholine Group N=50		Total
	Haemorrahage N=15	Infarct N=35	Haemorrhage N= 22	Infarct N=28	
Right	9(60%)	21(60%)	10(45.45%)	18(64.25%)	**58%**
Left	6(40%)	14(40%)	12(54.54%)	10(35.57%)	**42%**

Table – 3 showed incidence of infarct and haemorrhage in both citicholine and control group

Table - 4
Base Line Charateristics Of The Study Patients
(n = 100)

Characteristics	Control Group	Citicholine Group	P Value
Mean age	64.02	60.84	NS
Sex (M: F) (n)	22:28	38 : 12	NS
Stroke Hemisphere (L)	20	22	NS
Stroke Hemisphere (R)	30	28	NS
Base Line CNSS	5.88	5.26	NS
Pre-existing Medical Conditions	-	-	-
Hypertension	22	14	NS
Diabetes Mellitus	4	7	NS
Hyperlipidemia	5	7	NS

NS = Not Significant

Table – 4 showed the baseline characteristic of the patients. The age and sex match the hemisphere involved the baseline CNSS, history of hypertension, diabetes mellitus, hyperlipidemia.

Table - 5
Distribution of Patient's Barthel Index at 1st month FOLLOW UP.
(n = 100)

Categorized Barthel Index	Control Group (N=50)		Citicholine Group (N=50)	
Death	8	16%	6	12%
0	0	0%	0	0%
5-40	35	70%	22	44%
45-60	7	14%	6	12%
65-80	0	0%	9	18%
*85-100	0	0%	7	14%
Total	**50**	**100%**	**50**	**100%**

Table – 5 showed the distribution of Barthel index at 1st month follow up.
* = (p value < 0.05) in fisher exact tests

TABLE - 6
DISTRIBUTION OF BARTHEL INDEX AT 3RD MONTH FOLLOW UP
(N=100)

Categorised Barthel Index	Control Group of all patients (N=50)		Citicholine Group of all patients (N=50)	
Death	9	18%	9	18%
0	0	0%	0	0%
5-40	4	8%	1	2%
45-60	15	30%	7	14%
65-80	17	34%	15	30%
*85-100	5	10%	18	36%
Total	**50**	**100%**	**50**	**100%**

Table – 6 showed the distribution of Barthel index at 3rd month of follow up.
N= Number of patient
* = (p value < 0.05) by fisher exact test.

TABLE - 7
DISTRIBUTION OF BARTHEL INDEX OF THE PATIENTS OF INFARCTS
(3RD MONTH FOLLOW UP)
(N=63)

Categorised Barthel Index	Control Group (n=35)		Citicholine Group (n=28)	
Death	8	22.86%	7	25%
0	0	0%	0	0%
5-40	2	5.71%	0	0%
45-60	10	28.51%	4	14.28%
65-80	11	31.41%	7	25%
*85-100	4	11.41%	10	35.71%
Total	**35**	**100%**	**28**	**100%**

Table – 7 showed the distribution of Barthel index of the patients of infarcts at 3rd month follow up.
N= Number of patient
* = (p value > 0.05) by fisher exact test

Table -8
DISTRIBUTION OF BARTHEL INDEX OF THE PATIENTS OF HAEMORRHAGE
(3RD MONTH FOLLOW UP)
(N = 37)

Categorised Barthel Index	Control Group (n=15)		Citicholine Group (n=22)	
Death	1	6.66%	2	9.09%
0	0	0%	0	0%
5-40	1	6.66%	1	4.54%
45-60	6	40%	3	13.63%
65-80	6	40%	9	40.9%
85-100	1	6.66%	7	31.81%
Total	**15**	**100%**	**22**	**100%**

Table – 8 showed the distribution of Barthel index of the patients of haemorrhage at 3rd month follow up.
N = Number of patient * = (p value < 0.05) by fisher exact test

TABLE - 9
CORRELATION OF DEATH, MEAN CNSS AND DISTRIBUTION OF BARTHEL INDEX > 95 (1st MONTH FOLLOW UP)

	Control Group	Citicholine Group	P Value
Death	8	6	>0.05
Mean CNSS	5.35	5.26	> 0.05
Barthel Index > 95	0	2	>0.05

TABLE -10
CORRELATION OF DEATH, MEAN CNSS AND DISTRIBUTION OF BARTHEL INDEX > 95 (3rd MONTH FOLLOW UP)

	Control Group	Citicholine Group	P Value
Death	9	9	>0.05
Mean CNSS	5.35	5.26	> 0.05
*Barthel Index > 95	0	7	<0.05

* = (p value < 0.05) by fisher exact test

OBSERVATIONS:

Incidence of stroke was highest in the age group of 51-70 years. There were least number of patients in the age group > 81 years and < 21 years. The mean year of onset of stroke was 64.82 and 64.02 in both case and control group respectively. The incidence of stroke was more common in males 60:40 out of 100 patients studied. In citicholine group, there were 7(14%) diabetics, 14(28%) hypertensive and 7(14%) hyperlipidemic. In control group, there were 4(8%) diabetic, 22(44%) hypertensive and 5(10%) hyperlipidemic. Out of the 100 patients studied, 37(37%) were haemorrhage, 63(63%) were ischemic stroke and the right sided lesion were 58% compared to the left sided lesions 42%. In the control group 30(60%) were right sided lesions and 20(40%) left sided lesion. In the citicholine group 28(56%) were right sided lesion and 22(44%)were left sided lesion. The base line Canadian neurological stroke scale was 5.88 in control group and 5.26 in citicholine group. Base line characteristics including all that were prognostically important were distributed evenly among the two groups. There was no significant differences noted in terms of patients age, sex, hemisphere involved by the stroke, time of initiation of treatment and preexisting medical condition and baseline Canandian Neurological Stroke Scale(CNSS).

Mortality was equal in both groups of patients. 18% control group and 18% of citicholine group.

Analysis of categorized Barthel index score showed that there was significant difference between the Barthel index score of two groups of patients(in the category score 85-100) at 1 month follow up (0% in control group Vs 7(14%) in citicholine group (p<

0.05) and 3rd month follow up 5(10%) in control group Vs. 18(36%) in the citicholine group ($p<0.05$).

The analysis of Barthel index score in category >95) between the two group at 1st and 3rd months of follow up suggested that it was statistical significant(p value < 0.05).

Analysis of the categorized Barthel index of the infarct sub group at the 3rd month follow up stated that there were no significant difference of Barthel index(in category 85-100) between control 4 (11.41%) Vs citicholine group 10(35.71%) $p< 0.05$.

The analysis of Barthel index score (in the category 85-100) at the end of 3rd month of the patients of haemorrhage sub group in both case and controls shows a significant difference 1(6.66% Vs 7(31.81%) p value < 0.05.

CONCLUSION :

So it was concluded from the study that :

Treatment with citicholine (1gm iv bd x 5 days) followed by 500mg bd x 25 days total 30 days) in the patients of strokes presenting within 48 hours of onset increases the probability of complete recovery at 3rd month in haemorrhagic strokes. This benefit is less noticeable in case of ishaemic strokes.

Further clinical trials are needed to confirm the promising effect of citicholine in strokes.

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Original Article

NON-INVASIVE VENTILATION IN EXACERBATIONS OF COPD - A TEN YEAR EXPERIENCE

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ABSTRACT

208 cases of AECOPD were offered NIV as part of treatment for AECOPD between September 1999 and December 2009 in the intensive care unit of Kalinga Hospital, Bhubaneswar. 73 patients of AECOPD were mechanically ventilated as first choice. 23 more patients were intubated and mechanically ventilated due to NIV failure. The overall NIV failure rate in cases with COPD alone was 28%. Noninvasive ventilation has its best indication in moderate-to-severe respiratory acidosis in patients with AECOPD. Studies have confirmed it can be used in the ICU, HDU and wards to prevent endotracheal intubation and reduce mortality. ***Keywords :*** chronic obstructive pulmonary disease, non-invasive ventilation.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are periods of acute worsening which greatly affect the health status of those patients with an increase in hospital admission and mortality (Donaldson et al 2006). Estimates of in-patient mortality range from 4% to 30%, but patients admitted due to acute respiratory failure (ARF) experience a higher rate, in particular elderly patients with co-morbidities (up to 50%) and those requiring intensive care unit (ICU) admission (11%–26%) (American Thoracic Society Statement 1995). Many causes may potentially be involved in determining ARF during AECOPD, such as bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax and thromboembolism.

The ARF in the setting of an AECOPD is characterized by the worsening of hypoxemia and a variable degree of carbon dioxide retention and acidemia. The capacity of the patient to maintain acceptable indices of gas exchange during an AECOPD or the development of ARF depends both from the severity of the precipitating cause and from the degree of physiological dysfunction during the stable state and the subsequent physiological reserve. Worsening in ventilation to perfusion ratio (V/Q) mismatching is probably the leading mechanism in the occurrence of the hypoxemia by the enlargement of physiological dead space and the rise of wasted ventilation (Calverley 2003). The increase in airway resistance and the need of a higher minute ventilation may result in expiratory flow limitation, dynamic hyperinflation and related intrinsic Positive end expiratory pressure (PEEPi) with subsequent increased inspiratory threshold load and dysfunction of the respiratory muscles, which may lead to their fatigue (O'Donnell and Parker 2006). A rapid shallow breathing pattern may ensue in attempting to maintain adequate alveolar ventilation when these additional resistive, elastic and inspiratory threshold loads are imposed on weakened respiratory muscles, but despite increased stimulation of the respiratory centres and large negative intrathoracic pressure swings, carbon dioxide retention and acidemia may occur. Dyspnoea, right ventricular failure, and encephalopathy characterize severe AECOPD complicated by ARF (Ambrosino et al 1997). Arterial pH reflects the acute worsening of the alveolar ventilation and, regardless of the chronic level of arterial CO_2 tension ($PaCO_2$), it represents the best marker of the ARF severity (Plant and Elliott 2003).

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The optimum pharmacological treatment of the exacerbations of COPD is based on the so called "ABC approach", an acronym that reflects the three classes of drugs (antibiotics, bronchodilators, corticosteroids) commonly used. Controlled oxygen therapy and ventilatory support (invasive and non-invasive) are options able to improve symptoms and survival of the ARF patients by preventing tissue hypoxia and controlling acidosis and hypercapnia (Plant and Elliott 2003). While medical treatment works to maximize lung function and reverse the precipitating cause of the exacerbations, ventilatory support can lower the level of respiratory muscle load, thus reducing dyspnoea and respiratory rate, and improving arterial oxygenation, $PaCO_2$, and pH (Rodrìguez-Roisin 2006).

Some complications of invasive ventilation are related to the intubation or tracheotomy procedure; or to ventilation such as ventilator-associated pneumonia (VAP) and other nosocomial infections. Non-invasive methods of mechanical ventilation (NIV) may avoid most of the complications related to the invasive ventilation, ensuring at the same time a similar degree of efficacy (Girou et al 2000).

In selected invasively ventilated patients with AECOPD who had previously failed a weaning trial, NIV may be safely and successfully used after a few days of invasive ventilation in order to shorten weaning time, reduce ventilator-associated complications, and improve survival (Nava et al 1998; Girault et al 1999; Ferrer et al 2003). It has been demonstrated NIV is as able as invasive ventilation to unload respiratory muscles. (Vitacca et al 2001).

METHODS

The intensive care unit of Kalinga Hospital was started in December 1998 and the NIV service was started in September 1999. Initially we used the ICU ventilators which did not have option for NIV with nasal masks. Subsequently we bought two dedicated Home BiPAP machines and started using full face masks. Both Home BiPAP and ICU ventilators without NIV option are used according to the load of patients. Data of all cases undergoing NIV are kept as a part of audit. All cases admitted to Kalinga Hospital with acute exacerbation of Chronic Obstructive Pulmonary Disease(AECOPD) between September 1999 and December 2009 who needed Non-invasive Ventilation(NIV) have been analysed in this study.

RESULTS

In all 208 cases AECOPD were offered NIV as part of treatment for AECOPD between September 1999 to December 2009. Another 43 cases needed NIV for weaning from mechanical ventilation.

Table I. Severity of AECOPD.(n-139)

No.	Severity	Numbers	Failure	Intubation	Location	
				ICU	HDU	Ward
1.	pH<7.25 71	30	19	62	8	1
2.	pH 7.25-7.30 39	8	6	15	12	2
3.	pH 7.30-7.35 29	10	2	25	4	nil

Note: ABG was not available for all cases. NIV was used in many cases with pH > 7.35 but not analyzed here.

Table II. Location of NIV

No.	Location	Number
1.	ICU	149
2.	ICU & HDU	11
3.	ICU & Ward	4
4.	HDU	38
5.	HDU & Ward	1
6.	Ward	3

Note: ICU-Intensive care unit, HDU-High dependency unit.

Table III. NIV Failure (n-75)

No.	Failure	Number of failures	Total	%
1.	COPD without co-morbidities	45(total AECOPD-159)	28.3	
2.	Early	40	75	53.3
3.	Late	35	75	46.6
4.	With Pneumonia	4	8	50
5.	With Sepsis	4	4	100
6.	With renal failure	7	7	1.4
7.	With cardiac failure	2	6	33

Note: There were many other co-morbidities associated with COPD exacerbation which lead to NIV failure i.e. the total NIV failures do not add up to 75.

According to the pH the severity was divided into three grades(pH <7.25; pH 7.25-7.30; & pH 7.30-7.35). There were 71 cases who had pH <7.25 at the time of admission(most severe group). NIV was started in the ICU in 62 cases. In 8 cases NIV was started in High Dependency Unit(HDU) and in one case it was started in the ward. The NIV failure rate in this group was 42% but only 19 of them were intubated and mechanically ventilated. Many patients had poor quality of life, advanced age and many co-morbidities and decided against intubation and mechanical ventilation. Few of them were not intubated and mechanically ventilated for financial reasons.

In the second moderately severe group(pH 7.25-7.30) the failure rate was 20% and more number of cases were started NIV in the HDU. In the least severe group(pH 7.30-7.35) the NIV failure rate was higher, more number of patients were treated in the ICU and less number of cases were intubated and mechanically ventilated indicating that this group were more sicker, had more co-morbidities and poor quality of life(Table.I).

The overall NIV failure rates in cases with COPD alone was 28%. There were equal number of early(within<48 hours) and late(after >48 hours) failures. Patients with associated pneumonia, sepsis, renal failure had higher failure rates(Table. III)

Patients were started on NIV in the ICU, HDU, ward depending on the severity, monitoring capability, and skill of the team. With improvement many were shifted to lower levels of care(Table. II).

73 patients of AECOPD were mechanically ventilated as first choice. Another 27 patients of AECOPD were intubated and mechanically ventilated due to NIV failure. Out of these cases 43 patients were rapidly weaned from mechanical ventilation by using NIV. Three of them failed NIV during weaning and were re-intubated, mechanically ventilated and weaned again with NIV.

DISCUSSION

In a recent meta-analysis (Lightlower et al 2003) and summarized in a clinical commentary (Nava et al 2006) confirmed the clinical efficacy of NIV in the treatment of the ARF during AECOPD: compared to standard medical therapy alone the application of NIV improves survival, reduces the need for endotracheal intubation and the rate of complications, and shortens length of stay in hospital and in ICU.

In more severely ill patients (pH < 7.25), the rate of NIV failure was inversely related to the severity of respiratory acidosis, rising up to 52%–62% (Conti et al 2002; Squadrone et al 2004). The use of NIV in alternative to the invasive ventilation does not affect the mortality rate and the duration of ventilatory support, but the patients treated with NIV are subjected to a lower rate of complications (VAP, difficult weaning). In these patients, although exposed to high risk of failure, a NIV trial may be justified, if intubation is not strictly required because the need of protecting the airways, loss of consciousness or gasping (Conti et al 2002; Squadrone et al 2004; Nava et al 2006).

In patients with “mild” exacerbations, not complicated by respiratory acidosis, the use of NIV was investigated by few studies, including patients in large majority with pH > 7.35, who failed in demonstrate

a better effectiveness of NIV than standard medical therapy in preventing the occurrence of the ARF. No significant improvement in mortality and hospitalization duration was found, and the tolerance of the patients to the NIV was less than 50% (Bardi et al 2000; Keenan et al 2005).

In our study we have been able to use NIV successfully in 91 cases out of the 139 cases(65.5%) where ABG was available and pH was less than 7.35 and thus prevented intubation and its associated complications.

NIV failure occurs more frequently in the first hours of ventilation, and was reported to be predicted by the following clinical factors: severe acidosis, high severity score, severe impairment of consciousness, presence of co-morbidities and lack of improvement of arterial blood gases after 1–2 hours of initial ventilation (Ambrosino et al 1995; Nava and Ceriana 2004; Confalonieri et al 2005). Nevertheless COPD patients with severe ARF treated with NIV, particularly those with more severe functional impairment during the stable state, may have a late worsening (after > 48hrs), often requiring endotracheal intubation, despite an initial brief improvement (Moretti et al 2000).

In our study early failure was almost same as late failure, failure with severe respiratory acidosis, pneumonia, sepsis and renal failure were higher.

The only one randomized study including COPD patients with hypercapnic ARF and pneumonia (Confalonieri et al 2001) showed that NIV may reduce the rate of intubation and complications in comparison with medical therapy.

When acute exacerbation of COPD with hypercapnic ARF is due to cardiogenic edema the treatment with bi-level NIV has shown to reduce intubation rate (Nava et al 2003).

Absolute contraindications for NIV are as follows:

Cardiac or respiratory arrest

Severe encephalopathy

Severe gastrointestinal bleeding

Severe haemodynamic instability with or without unstable cardiac angina

Facial surgery or trauma

Upper airway obstruction

Inability to protect the airway and/or high risk of aspiration

Inability to clear secretions

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Severe encephalopathy with glasgow coma scale (GCS) <10 was considered a contraindication to NIV treatment based on the concern that a depressed sensorium would predispose the patient to aspiration. More recently some experiences of NIV treatment of patients with altered levels of consciousness, due to hypercapnic ARF, were reported. These observations need to be confirmed by randomized controlled trials but suggest the feasibility of NIV in such patients, with acceptable rates of failure and low rates of aspiration complications (Scala et al 2005).

We have used NIV successfully in GCS < 10 in many cases but the GCS was not recorded in our audit forms therefore the exact number is not available.

Nava during one of his deliberations in the ERS meeting in 2010 suggested the following criteria of severity and location where NIV can be started.

Location	**pH**	**P/F**
Indication		
Ward	<7.35	300
prevent progression		
HDU	<7.30	250
avoid intubation, bridge to extubation		
ICU	<7.25	200
need for intubation		

(Nava, ERS 2010)

There is evidence that some COPD patients with less severe ARF without failure of any other organ may be successfully treated with lower costs in the respiratory intermediate intensive care unit (RIICU) and even in the ward than in the ICU (Plant and Elliott 2003; Bertolini et al 2005). The skill of the health care team promotes proper NIV utilization and improves the patient outcome. Patients with severe acidosis or with altered levels of consciousness due to hypercapnic acute respiratory failure are exposed to high risk of NIV failure. In these patients a NIV trial may be attempted

in closely monitored clinical settings where prompt endotracheal intubation may be assured.

With acquisition of greater skill of our team we are able to use NIV in the HDU more frequently and even in the wards thus reducing the cost to the patients. In a paper presented at the Orissa Chest Society Annual meeting in 2009 the analysis of the above data showed that the average duration of NIV in AECOPD was 3-5 days and the average duration of mechanical ventilation in AECOPD was 7 days thus leading to a cost saving of 2 ICU days.

CONCLUSION

Noninvasive ventilation has its best indication in moderate-to-severe respiratory acidosis in patients with AECOPD. Studies have confirmed it can be used in the ICU, HDU and wards to prevent endotracheal intubation and reduce mortality. The skill of the health care team promotes proper NIV utilization and improves the patient outcome. Patients with severe acidosis or with altered levels of consciousness due to hypercapnic acute respiratory failure are exposed to high risk of NIV failure. In these patients a NIV trial may be attempted in closely monitored clinical settings where prompt endotracheal intubation may be assured. NIV in AECOPD reduces cost to the patient.. In future with the up gradation on emergency departments in Orissa NIV can be started in the emergency rooms also.

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Original Article

CHANGING CLINICAL PROFILE OF INFECTIVE ENDOCARDITIS

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ABSTRACT

Infective endocarditis is a disease caused by microbial infection of endocardial lining of intracardiac structures. The aim of our study was to compare the clinical profile of infective endocarditis over last five decades with the clinical profile of our patients who were admitted with infective endocarditis at IGH between 1st July 2006 and 30th June 2010. 47 cases were encountered during the above period of study; 14 female and 33 male. Commonest age group was 15-30 years. In cases of acute IE, fever with rigor was the commonest manifestation, whereas in subacute IE, loss of weight, petechiae and arthralgia were the commonest manifestation. 12 had developed heart failure at presentation, 8 more during treatment. Only 4 cases had embolization. 12 cases had renal dysfunction, 3 cases had first degree heart block. ***Keywords*** *: Infective endocarditis, clinical profile, complication.*

INTRODUCTION

Infective endocarditis is a disease caused by microbial infection of endocardial lining of intracardiac structures. Infection usually affects the valve leaflets but it may also affect the mural endocardium, chordal structure, and even myocardium or pericardium.

Despite significant advances in the diagnosis and treatment of Infective endocarditis, 6 month mortality approaches 25%.[1]

The earliest diagnosis of Infective endocarditis is attributed to Lazarey Riverius (1589-1655).[2] Sir William Osler[3] summurised his many advances in his famed lectures on malignant endocarditis in 1885.[3] 0sler made a true confession of diagnostic uncertainty in many cases.

AIM AND OBJECTIVE

To compare the clinical profile of Infective endocarditis over last five decades with the clinical profile of our patients who were admitted with Infective endocarditis at IGH between 1st July 2006 to 30th June 2010.

METHODS

Consecutive patients of Infective Endocarditis during the period of 1st July 2006 to 30th June 2010, meeting modified Dukes modified criteria[4] were included in the study. They were studied for the demographic pattern, clinical presentation and complications. All these patients were admitted under the Dept. of Medicine at Ispat General Hospital.

RESULT

We encounter total 47 cases of Infective endocarditis during the above period of study' 14 were female and 33 were male.

Age group	Number of cases
15 to 30 yrs	24
30 to 40 yrs	16
40 to 60 yrs	6
>60 yrs	1

Among all cases 5 were acute Infective endocarditis. Out of them 2 had VSD, 2 had Aortic regurgitation and one with i.v drug abuser using pentazocine injections. Among 42 cases of subacute Infective endocarditis aortic valve disease seen in 21 cases, VSD was observed in 3 cases, mitral valve in 12 cases, tricuspid valve in 5 cases, and one case in patient undergoing haemodialysis.

Surprisingly during these 4 yrs no case of Infective endocarditis was observed in patients who have undergone permanent pacemaker implantation nor in any patients with ICD. This is in contrast to finding of Cabel et al.[5]

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CLINICAL PROFILE OF ALL CASES

Clinical profile	Acute infective endocarditis	Subacute infective endocarditis
Fever	+++	+/-
Chill and rigor	++	-
Weakness	+	+
Loss of weight	+	++
Petechiae	+	++
Osler node	-	+
Roth spot	-	-
Clubbing (n=8)	-	+ (after 1 yr follow up)
Jaundice (n=12)	-	+
Splenomegaly (n=12)	-	+
Splenic rub/ tenderness	-	-
Arthralgia (n=32)	-	++
Hematuria (n=2)	-	+

COMPLICATIONS

Heart failure was observed in 12 cases as the presenting feature and 8 more cases during treatment. Reduced LV function was the commonest feature. Embolisation was seen in only 4 cases, all of whom presented with sudden onset hemiplegia. We did not observe Roths spot, Janeways lesion or splinter hemorrhage in any case. Mycotic aneurysms were not observed in any of our patient; probably because of non availability of cerebral angiography technique in our hospital. Renal dysfunction was observed in 12 patients in our series. Heart block was seen in 3 cases, all were 1^0 heart block. No patient had complete heart block requiring pacemaker implantation.

DISCUSSION

During this study we found that many signs those were described in the past are becoming obsolete now mainly due to early antimicrobial therapy. Many new conditions are arising that provides a nidus for infective endocarditis like devices in heart. Osler node, Roth's spot, Janeways lesion or splinter hemorrhage are becoming rare signs. Echocardiography has revolutionized the diagnosis of infective endocarditis and in many cases the most powerful tool to diagnose infective endocarditis infective endocarditis. There are several finding that suggest infective endocarditis. These are vegetation, evidence of periannular destruction and abscess formation, leaflet perforation, prosthetic valve dehiscence.[6]

TYPICAL 2DECHO FINDING IN INFECTIVE ENDOCARDITIS

Vegetation	Irregular in shape, adherent to endocardium, high frequency discrete movement, oscillatory mass.
Abscess	Thickened area or mass, no homogenous appearance, evidence of flow by doppler
Aneurysm	Echolucent space continuous with the cavity of origin
Fistula	Connection between two distinct cardiac blood spaces.
Leaflet perforation	Defect in the valve leaflet with evidence of blood flow.
Prosthetic valve dehiscence	Rocking movement of the valve with >150 excursion in any plane.

CULTURE REPORT

Acute Infective endocarditis (n=5)	Subacute Infective endocarditis (n=42)
Staph. Aureus - 3 Culture negative - 2	Strept. Viridans - 12 Staph epidermididis - 8 Enterococci - 7 Culture negative - 15

CONCLUSION

Patients of Infective endocarditis are an extremely heterogeneous group. They have variety of comorbidities, causative organisms and complications. Chu et al[7] analyzed 267 cases of Infective endocarditis and found that diabetes and staph aureus are the two independent risk factor for mortality.

There are a number of development in the field of Infective endocarditis that should improve diagnosis, treatment, and prevention of Infective endocarditis. New molecular methods, bacterial vaccines, antimicrobial agents like Daptomycin for Staph aureus Infective endocarditis[8] and colonizing resistant biomaterial are under development.

Most studies are small and are from single centre. To address the limitations the International Collaboration on Infective endocarditis was formed and is collectively prepearing data from a large cohort of Infective endocarditis patients at multiple centres..this may be beneficial to the patient of Infective endocarditis in near future.

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Original Article

EPIDEMIOLOGICAL PROFILE OF OCCUPATIONAL EXPOSURE, POST EXPOSURE PROPHYLAXIS AND OUTCOME

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

ABSTRACT

Background: *With increasing number of HIV positive persons accessing health care system the chance of transmission of HIV to health care personnels (HCPs) is increased. Universal Precautions (UP) and post exposure prophylaxis (PEP) can decrease the risk.* ***Objective :*** *To study the type and nature of occupational exposure, the categories of HCPs at risk and outcome of PEP for planning targets for awareness.* ***Methods:*** *The study involved health care personnel seeking PEP in VSS Medical college ,Burla between February 2008 to October 2010. Data related to exposure, the PEP regimens prescribed, their adverse effects and outcome were analysed.* ***Results:*** *Fifteen HCPs reported for PEP. Nine were males and six females. Nursing students (27%), resident doctors (20%) and laboratory technicians (20%) had greater exposure. Most reported for PEP between 2-24hrs after exposure. Needle stick injury occurred in 46.7% cases. Exposures were mild in most (60%) cases. Twenty six percent HCPs had exposure to high risk source. Zidovudine and Lamivudine were prescribed in 10 cases and 4 cases got expanded regimen including Indinavir or Lopinavir/ritonavir. Adverse effects were nausea, headache, fatigue, weakness, anorexia and unconjugated hyperbilirubinemia. Three cases discontinued PEP. Five cases were lost to follow up. No seroconversion was noted in other.* ***Conclusion:*** *Nursing students are at greatest risk of exposure. Knowledge about Universal Precautions is poor amongst HCPs.PEP was effective in preventing transmission in high risk exposure.****Key words:*** *Health care personnel, Occupational exposure, Post exposure prophylaxis.*

INTRODUCTION:

In present time more and more people living with HIV/AIDS (PLHA) are seeking health care for their illness either related or unrelated to HIV infection. The NFHS 3-2007 noted that only 10% of those infected with HIV knew their status.[1] Therefore practicing 'Universal Precautions' that prevent transmission of blood borne pathogens including HIV, HBV, HCV etc. to healthcare personnel(HCP) is of utmost importance.[2] However, awareness and practice of 'Universal Precautions' amongst HCPs is poor. In a random survey in our institute involving 10 nursing students, 9 interns, 18 PG students and 13 nursing staffs working in department of medicine, it was found that most of the interns and nursing students have little idea while post graduates and nursing staffs have incomplete knowledge about 'Universal Precautions' and post exposure prophylaxis (PEP) (Unpublished data). This leads to unsafe practices and accidental exposure to blood and other potentially infectious body fluids (semen, vaginal secretion, synovial, peritoneal and pericardial fluid, amniotic fluid, CSF)and exposure in the form of injury by sharps (needle stick injury) or splashes (blood, amniotic fluid)which puts the HCPs at risk of acquiring HIV infection. However, HIV infection is not an instantaneous consequence of exposure to HIV, leaving a 'Window of Opportunity' during which one can intervene to prevent its transmission to exposed persons.[3] The risk of transmission of HIV infection among HCPs reported average at 0.3% for needle stick injuries and 0.09% in case of exposure to splashes to mucous membrane or broken skin.[4,5] Animal and human case-control studies on post exposure prophylaxis

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(PEP) has supported efficacy in preventing transmission of HIV to the tune of 81% with a single drug when used within a critical period after exposure (72hrs) and for a specific duration (28days).[6,7,8] Therefore all exposed HCPs should report for post exposure prophylaxis and receive antiretroviral drugs, if eligible.

We studied the profile of health care personnel who sought PEP services at our institution and their outcome.

METHODS:

All health care personnels(HCPs) who sought post exposure prophylaxis(PEP) services at V.S.S. Medical college, Burla following exposure to blood or other potentially infectious body fluids while providing health care were included in the study from February 2008 till October 2010.The PEP services were provided without discrimination and confidentiality is maintained in each case.[1] Informed consent was taken in each case. HIV testing of exposed and source persons were performed according to NACO (National AIDS Control Organization) guidelines after due consent. Each HCP reporting for PEP was provided a form A2-PEP informed consent/refusal form for giving consent and another form is used by PEP provider (ART nodal officer/SMO ART centre) to record various details related to exposure(Form A2 accidental exposure to blood- medical notification form-2006).[1] This included the following- name, age, sex, occupation, date and time and place of exposure, time since exposure, nature of exposure(with blood or body fluids, by sharp or splash, percutaneous or mucocutaneous, intact or non intact skin, hollow or solid needle), circumstances of exposure, wound description, base line HIV status and Hepatitis B vaccination status of exposed, awareness about 'Universal Precautions, HIV status of source, other tests in exposed persons(HBsAg, anti HCV antibody, liver enzymes, CBC tests etc), PEP regimen prescribed, adverse effects noticed, information related to completion or discontinuation of PEP, other treatment or referrals, outcome of PEP by assessing HIV status in exposed at 3month and 6month. All HCPs were asked to report every week till completion of PEP. In case of nonadherence to follow up, the exposed persons were tried for contact by telephone and other means. All the HCPs who received PEP were studied for their clinicoepidemiological profile, adverse reactions related to PEP and outcome.

The health care personnel (HCP) in this study means any person paid or unpaid working in health care setting, including doctors, nurses, laboratory technicians, nursing and medical students, interns, resident doctors, biomedical waste handlers and cleaning staff. Occupational exposure was defined as exposure to blood and other body fluids while performing job duties.[1]

The PEP regimens were prescribed according to NACO guidelines. Basic regimen used was fixed dose combination of Zidovudine (300mg) + Lamivudine (150mg) twice a day for 28 days. In Expanded regimen i.e. Basic regimen plus a protease inhibitor (PI), either Indinavir 800mg thrice a day or Lopinavir (400mg) / ritonavir (100mg) twice a day were used for 28 days.

RESULT:

Fifteen numbers of health care personnel (HCPs) sought PEP services during the study period. In them male to female ratio was 3:2 (Table-1).Males (49%) between age 20 to 40 yrs and females (27%) of age < 20 years had maximal exposure. Exposure was more amongst nursing students (26.7%), resident doctors (20%) and laboratory technicians (20%)(Table-2). Maximum HCPs reported between 2 to 24 hours after exposure (60%) (Table-3) . Forty six percent of exposures were of percutaneous type (needle stick injury) and none with mucous membrane exposure were found (figure-1). One person (14%) had exposure by large bore hollow (18G) needle, four with medium bore hollow needle (57%) and two with solid needles (29% .Needle stick injury followed recapping in 4 cases (57.14%), guiding suture needle with finger in 2 cases and after collecting blood in a blood donation camp in one case. Exposure to blood occurred in 14 cases (93.3%) and one had exposure to serosanguinous exudation from non intact skin of a HIV positive source.

Type of exposure was mild in 9 cases (60%), moderate in 4 cases (26.7%) and severe in 2 cases (13.3%). Thirteen of the fifteen source patients were HIV positive (86.7%) of whom nine were asymptomatic.

Rest 2 sources had unknown status. Most exposed persons (93.3%) did not know the HIV status of the source at the time of exposure excepting one instance of exposure at CD4 laboratory. Fourteen HCPs (93.3%) received PEP. Ten of them (71.4%) received basic regimen and four (28.6%) received expanded regimen (Table-4). Of the cases who received PEP, nine (64.2%) completed 28 days, 3 (21.4%) discontinued and 2 are continuing PEP. Adverse effects were the reason for discontinuation of PEP. Various adverse effects observed following intake PEP drugs are mentioned in Table-5. In one case who received Indinavir developed unconjugated hyperbilirubinemia (serum bilirubin-9mg/dl) which subsided following change over to Lopinavir/Ritonavir. Eleven (73.3%) of the exposed persons provided consent for baseline HIV testing and all of them had a negative test. Eight HCPs were already vaccinated for Hepatitis B within last 5 years; rest seven were advised Hepatitis B vaccination. None of the known thirteen source patients were positive for Hepatitis B. Five cases (33.3%) were lost to follow up, 5 others had complete follow up with HIV negative status at 3rd and 6th month. One case who has completed 5 months after exposure was negative for HIV at 3rd month. In rest of the three cases follow up is yet to be completed. Eleven (73.33%) of the exposed were not having any knowledge about 'Universal precautions' at the time of exposure.

Table –1 : Age and sex distribution of HCP having exposure (N=15)

Age in years	Male no (%)	Female no (%)	Total no (%)
<20yrs	0 (0%)	4(26.7%)	4(26.7%)
20-40 yrs	6(40%)	2(13.3%)	8(53.3%)
40-60 yrs	3(20%)	0(0%)	3(20%)
Total	9(60%)	6(40%)	15(100%)

Table-2 : Category of HCP exposed (N=15)

Category	No	Percentage
Nursing student	4	26.7
Nurses	1	6.7
Medical students	1	6.7
Interns	1	6
Resident doctors (SR,JR)	3	20
Laboratory technicians	3	20
Attendants	1	6.7
Faculty	1	6.7
Total	15	100

Table-3 : Time since exposure till PEP is received (N=15)

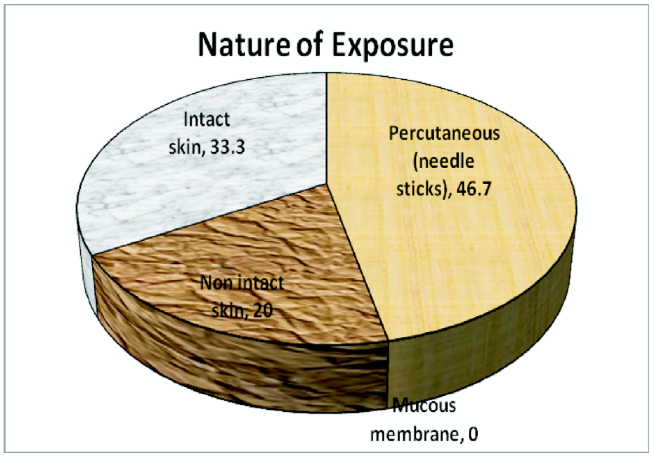
Time since exposure	No of HCW	percentage
<2hrs	2	13.3
2-24hrs	9	60
24-48hrs	4	26.7

Table-4 : PEP regimen prescribed to exposed persons (N=14)*

TYPES OF REGIMEN	Constituent of drugs in regimen	No of cases	percentage
Basic	Zidovudine+lamivudine	10	71.428
	Stavudine+lalmivudine	0	0
expanded	Zidovudine+lamivudine+ indinavir	2	14.285
	Zidovudine+lalmivudine+lopinavir/r**	1	7.143
	Zidovudine+lamivudine+indinavir(7days) followed by zidovidine+lamivudine+lopinavir/r	1	7.143

Table -5 : Adverse reactions of PEP drugs noted in the study (N=14)

Adverse effect	No of cases	Percentage
Nausea	6	42.857
Vomiting	6	42.857
Anorexia	9	64.285
Fatigue	8	57.14
Headache	6	42.857
Dizziness	7	50
Unconjugated hyper bilirubinemia	1	7.142



DISCUSSION:

In the present study 60 percent were of male sex and 40 percent of females with a ratio of 3:2. Similar finding was observed by Tetali S et al from three tertiary care hospitals in South India.[9] Males HCPs between 20 to 40 years and females less than 20 years were more exposed. The exposed HCPs were represented from various categories including nursing and medical students, interns, resident doctors, faculty, nurses, laboratory technicians and attendants. Among them nursing students had most exposures (Table-2). According to WHO, nurses were the most exposed,[10] whereas surgeons were most commonly exposed in the south Indian study.[9] In a study from a Mumbai Hospital (India) most needle stick injuries involved the nurses (44%) and attendants (23%).[11] In another teaching hospital from Pune interns were most vulnerable.[12] In teaching hospital like ours nursing students and interns are involved in drawing blood and giving injections, assisting deliveries and surgery, making them most vulnerable considering their lack of awareness and practice of universal precautions. Sixty percent reported between 2 to 24 hours exposure, indicating a reasonable awareness about PEP amongst those exposed. Timing of initiation PEP at earliest is of utmost importance in preventing transmission of HIV.[8] Needle stick injury accounted for 46 percent and rest were shared between contact with non-intact and intact skin. Needle sticks were responsible for 68% exposures in a study from south India.[9] No HCP with history of splash of blood or body fluids to mucous membrane were found in the present study. This could be due to lack of awareness about the related risk amongst HCPs. Various circumstances leading to needle stick exposure included recapping the needle after collecting blood or giving injection (while remaining unmindful), after collecting blood from donors (while hurrying) and while guiding suture needle with finger. One case included in the study was an attendant from a rural hospital who sustained injury by suture needle while assisting in bare hands, reflecting the state of poor awareness in rural set up about universal precautions.

Most exposures (60%) were of mild nature. In our study 13 of the 15 sources were HIV positive (88.7%)of whom nine were asymptomatic(69.2%). Mehta A et al reported HIV status as positive in 13 cases out of 254 known sources of exposure.[10] In the present study exposure to HIV positive source appears to be higher. This could be due to the fact that most HCPs here are reporting after knowing the source as positive for HIV. However most of them did not know the HIV status of source at the time of exposure. Most exposed of HCPs had no idea about "universal precautions" at the time of exposure. Most (93%) exposed HCPs received PEP. Zidovudine and Lamivudine were prescribed most often (71%) while expanded regimen including a protease inhibitor was prescribed in four cases (29%) (Table-4). In the study by Mehta A et al in Mumbai, the basic regimen was given to seven and expanded regimen two HCPs of the 13 exposed to HIV positive source.[11] PEP was discontinued by 3 of our cases. Discontinuation of PEP was associated with adverse effects like nausea, headache, fatigue, extreme weakness etc. One case

developed unconjugated hyperbilirubinemia after taking Indinavir in the expanded regimen. In a study conducted amongst HCPs between January 2003 to December 2005 in B. J. Medical college, Pune it was found that only 49.5% who received extended regimen completed 28 days treatment.[12]

In another study during 2001-2002 at AIIMS, New Delhi only 15 out of 35 cases prescribed PEP completed 28 days.[13] Reported rate of adherence to PEP in other parts of world varies between 70% to 80%.[3] Regimens combining newer nucleosides like Tenofovir with Emtricitabine are associated with less toxicity and improved adherence.[14] Similarly use of Ritonavir boosted protease inhibitors like Atazanavir, Lopinavir or Darunavir will strengthen the expanded regimen with less of toxicity.[3] Most exposed persons (73%) agreed for baseline HIV testing and all of them were negative. More than fifty percent HCPs were already immunized for Hepatitis B. Five HCPs who received PEP were lost to follow up, while 5 others had negative HIV status after 6 months. One more was HIV negative at 3 months, she has completed 5 months of follow up. In their study of 13 HCPs exposed to HIV positive source Mehta A et al reported that 3 HCPs were lost to follow up.[11] This indicates the need for improved counselling and more vigorous follow up. We have noticed no case of seroconversion as yet like others.[11,12,13] The risk of transmission noted was 0.3% following needle stick injury[4] and 0.09% in case of exposure to splashes of infectious material to mucous membrane or broken skin[5] but actual risk may vary depending on the type of exposure and viral load in HIV positive source.

CONCLUSION:

Transmission of HIV infection and other blood borne pathogens are a definite risk to HCPs. Full adherence to 'universal precautions' should be applied while dealing with blood and body fluids. The interns, medical students, nursing students, are at increased risk of exposure due to inexperience. They should be given priority in training regarding 'Universal precautions' and PEP in addition to all other HCPs on a continuous basis at the institutional level to reduce the risk of transmission.

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Original Article

DNA POLYMORPHISM OF PLASMODIUM FALCIPARUM AS A POSSIBLE PREDICTOR OF COMPLICATION

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ABSTRACT

Fifty cases of falciparum malaria were included in the study. 12 had some form of complication and out of them, 3 died. Many cases with uncomplicated course were negative for DHFR- a marker of drug resistance. DHFR when present in the allele C16, C51, C164 were of wild type. Genetic analysis by PCR can be handy in predicting the course of falciparum malaria. ***Keywords*** *: falciparum malaria, DNA Polymorphism, complication, prognosis.*

INTRODUCTION :

Epidemics like Swine Flu, Gastroenteritis, Dengue and Chickungunya attract attention. But the impact of malaria can never be disregarded in a state like Orissa. Researches continue, promising drugs are launched; but the disease status still remains lamentable. Adding to misery is the fact that percentage of Falciparum infection is on rise.[1] This is the subset of patients prone for complications and death.

When we examine the patient of Falciparum Malaria, it is difficult to predict whether he will land in complication or not. Parasite indices seldom help. Many patients with low parasite count in peripheral blood succumb. On the other hand, some patients with clinical features of malaria do not show parasite in peripheral blood.

Polymerase chain reaction (PCR) for plasmodium falciparum is a reliable test with sensitivity between 97-100% (2,3) Analysis shows that plasmodium Falciparum has different genotypes. Attempts was made to correlate the genotype with propensity for complication: so that it would be of predictive value regarding course of the disease.

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MATERIAL AND METHOD :

Fifty cases with clinical features of malaria and positive for plasmodium falciparum (by Slide, ICT, optimal or QBC) were included in the study. Approximately 2 ml of venous blood was collected from them. They were informed about the nature of the experiment and written informed consent was taken from each individual. Blood was collected in microfuge tube containing anticoagulant EDTA, stored at -20^{0}C on deep freezer and then transported to the laboratory of CIFA (Central Institute of Freshwater Aquaculture), Kaushalyagang, Bhubaneswar for PCR.

The patients were followed up, given antimalarial treatment and their clinical course was correlated with genotype.

OBSERVATION :

Out of fifty cases, 12 had some form of complication and out of them 3 died. Rest had uncomplicated course and recovery.

Table-1 shows the genetic analysis of plasmodium falciparum by PCR.

CSP = Circumsporozoite protein

A = 650 base pairs (bp)

B = 700 base pairs (bp)

MSA_1 = Microzoite surface Antigen-1

A = 350 bp

GENETIC ANALYSIS BY PCR

Sl. No.	CSP	MSA1	MSA2	KAHRP	Cg_{10}	DHFR				
						C_{16}	C_{51}	C_{59}	C_{108}	C_{164}
1.	A	B	A	A	M	W	W	M	M	W
2.	A	B	A	A	W	-	-	W	W	-
3.*	A	B	C	B	M	W	W	M	M	W
4.	-	A	B	-	ND	-	-	M	-	W
5.	B	A	B	B	M	W	-	M	W	-
6.	B	-	A	B	W	W	W	M	-	W
7.	-	-	B	A	M	W	-	W	M	W
8.	-	-	A	A	W	W	-	M	M	-
9.	B	A	A	A	ND	W	W	M	-	-
10.**	A	B	C	B	M	W	W	M	M	W
11.	B	A	B	A	H	W	W	M	M	-
12.	-	-	B	-	W	W	W	M	M	-
13.	A	-	B	-	M	-	-	M	-	-
14.*	A	B	C	B	M	W	W	M	M	W
15.	A	-	A	A	W	-	-	W	-	W
16.*	A	B	C	B	M	W	W	M	M	W
17.	A	-	A	-	M	-	-	-	-	-
18.*	A	B	C	B	M	W	W	M	M	W
19.*	A	B	C	B	M	-	W	M	M	W
20.	-	A	A	-	W	-	-	-	-	-
21.*	A	B	C	B	M	W	W	M	M	W
22.	B	A	B	A	M	-	W	W	-	-
23.	B	A	B	A	W	-	-	-	-	-
24.	B	A	B	A	M	-	-	-	-	-
25.	-	A	B	A	ND	-	-	M	W	W
26.*	A	B	C	B	M	W	W	M	M	W
27.	A	A	A	-	W	W	W	W	W	-
28.+	A	B	C	B	M	W	W	W	M	W
29.	B	A	A	-	ND	-	W	-	-	-
30.*	-	A	A	-	ND	-	-	M	-	-
31.	A	B	C	B	M	W	W	M	M	W
32.	A	-	B	A	W	-	-	-	-	-
33.	A	-	B	A	M	W	-	-	-	-
34.*	A	B	C	B	M	W	W	M	M	W
35.	B	A	B	A	W	-	-	-	-	W
36.	B	A	B	A	M	-	W	-	-	-
37.	B	A	A	A	ND	-	-	-	-	-
38.*	A	B	C	B	M	W	W	M	M	W
39.	B	-	B	-	M	W	-	-	-	-
40.**	A	B	C	B	M	W	W	M	M	W
41.	B	-	B	-	M	-	W	-	-	W
42.	B	-	B	-	W	W	-	-	-	-
43.+	A	B	C	B	M	W	W	M	M	-
44.	-	A	A	-	W	W	W	-	M	-
45.	-	A	A	A	ND	W	W	W	W	-
46.	-	-	A	A	ND	W	-	M	W	W
47.+	A	B	C	B	M	M	W	M	M	W
48.	B	-	A	A	M	W	W	W	W	W
49.	B	A	A	A	M	W	-	-	-	-
50.+	A	B	C	B	M	W	W	M	M	W

B = 450 bp

MSA_2 = Microzoite surface Antigen-2

A = 850 bp

B = 450 bp

C = 950 bp

KAHRP = Knob Associated Histidine Rich protein

A = 650 bp

B = 700 bp

DHFR = Dihydrofolate Reductase.

Cg 10/PFCRT = Plasmodium Falciparum Chloroquine Resistant Transfer Protein.

M = Mutant (Codon 76)

W = Wild Form

CSP, MSA_1, MSA_2 represent polymorphic markers for Pl. falciparum. DHFR is a marker of drug resistance. Cg10 is a marker of chloroquine resistance.

Amplification didnot occur for some genetic loci. It is proposed that antibiotics inhibit enzymes responsible for amplification. Concomitant use of antibiotics could be responsible for non-amplification.

Case no with * mark had complicated course. Case with '**' mark died. '+' marked cases had similar genotypes as complicated ones, but had uncomplicated course.

DISCUSSION :

It is interesting to observe that complicated cases had similar genotypes. But at the same time, there are some cases with similar genotype and they had uncomplicated course.

Outcome of falciparum infection depends upon two factors : host factor and parasitic factor.[1,4] It is difficult to measure host factors like host resistance, host response, beneficial immunoresponse, immunoresponse with deleterious effect etc. Probably better resistance or response in some cases protected them from virulent organism.

It is also remarkable that majority of plasmodium falciparum have chloroquine resistance gene. Many cases with uncomplicated course were negative for DHFR - a marker of drug resistance. DHFR when present in the allele C_{16}, C_{51}, C_{164} were of wild type.

Host factors are difficult to assess. So if the plasmodium falciparum has this form of genetic markets, they can be taken as potentially dangerous. On the other hand, healthy individuals may be presumed to have good host response. But this may be misleading. Genetic marker as well as presence or absence of drug resistance gene may guide for treatment.

CONCLUSION :

Falciparum containment still remains a mirage. It is difficult to predict who will have complicated course and who will be uncomplicated. On the otherhand, uncomplicated falciparum malaria is rather a retrospective diagnosis.

Genetic analysis by PCR can be handy in predicting the course. Because under treatment threatens life. On the other hand, treating all patients with available powerful drugs leads to drug resistance. Judicious evaluation is crucial.

However larger study is needed to justify such judgement.

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Original Article

PLATELET AGGREGATION, ELECTROPHORESIS & WESTERN BLOTTING IN ISCHEMIC STROKE – A PRELIMINARY STUDY

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ABSTRACT

Background and Purpose : *Platelet activation is a crucial mechanism in the pathophysiology of ischemic stroke. The aim of the study is to evaluate the status of platelet in ischemic stroke patients by studying their aggregation (spontaneous and induced), electrophoresis and western blotting.* ***Materials and Methods :*** *15 patients of ischemic stroke with equal numbers of age and sex matched control were included in the study. Platelet aggregation done in 15 cases. Electrophoresis and western blotting done in one case.* ***Result :*** *Spontaneous platelet aggregation was found in five cases of stroke and none among controls. Epinephrine induced peak platelet aggregation was found in 64.8 $\pm$3.67% compared with 43.06$\pm$3.88 in control subjects (p value <0.001). TRAP induced peak platelet aggregation was found in 78.8$\pm$6.06% in stroke patients in comparison to 44.6$\pm$ 3.66 in control subjects (P Value <0.001). The mean $t_{1/2}$ of peak platelet aggregation in TRAP treated platelet in stroke patients is significantly less in comparison to control. On platelet electrophoresis in the stroke sample a strong band of 190 KD was observed while it was not found in control. On western blotting of resting platelet similar pattern was observed in stroke and control. After two minute of aggregation tyrosine phosphrylated bands at 100 and 140 KD mw region became less intense in stroke sample indicating tyrosine dephosphorylation at these region.* ***Conclusion:*** *Spontaneous and induced platelet aggregation is enhanced in ischaemic stroke cases. Rate of aggregation in TRAP treated patients were higher in stroke cases. Electrotrophoretic profile of platelet proteins showing and additional band at 190 KD may be due to breakdown of cytoskeletal protein.. Western blotting show evidence of tyrosine dephosphorylation.* ***Keyword :*** *Stroke, Ischemic Stroke, Platelet Aggregation, Electrophoresis, Western Blotting.*

INTRODUCTION :

Platelet activation is a crucial mechanism in arterial thrombogenesis and therefore in the pathophysiology of ischemic stroke. Accordingly antiplatelet therapy plays a central role in secondary prevention of ischemic stroke. Assessment of platelet activation after ischemic stroke could be clinically valuable if platelet markers existed that predict the risk of recurrent events and reflect the effect of antiplatelet therapy. Recently developed techniques such as the detection of activation dependant neoantigens on the platelet surface by flow cytometry, the platelet function analyzer (PFA), or whole blood aggregometry represent methods that in the future could become helpful tools in stroke care.[1,2]

Increased platelet aggregation has been demonstrated following an acute ischemic insult eg. transient ischemic attack and cerebral thrombosis. Shear induced platelet aggregation is increased in patients with cerebral thrombosis. The share of platelet in the process of atherosclerosis and its thrombotic complication depend on their rate of activation. Neuronal damage that occur following cerebral arterial occlusion by thrombus are proposed to be due to substances secreted by platelets in addition to other factors. Very little is known regarding molecular, biochemical process of this platelet dysfunction. In this study an attempt has been made to study the status of platelet in ischemic stroke patient and a little insight into the mechanism of platelet activation.[3,4,5]

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AIMS & OBJECTIVE :

To study the status of platelet in ischemic stroke patients by studying their aggregation (Spontaneous and induced), Electrophoresis and western blotting .

MATERIAL & METHODS :

The study was conducted in 15 consecutive patients of stroke and 30 control subjects. All the patients were admitted in the Department of Neurology of S.S. Hospital, Institute of Medical Sciences, B.H.U., Varanasi. Controls were healthy age and sex matched relatives of the patients.

SELECTION OF PATIENTS

The patients presenting with acute hemiplegia with or without aphasia along with hypodense lesion of 15 mm in size or more in middle cerebral artery territory on a non-contrast cranial computerized tomographic (CT) scan, were selected. Patients presenting as infarcts in the regions supplied by anterior or posterior cerebral arteries were not included.

INITIAL EVALUATION AND INVESTIGATIONS

Patients and controls were evaluated on a preset proforma Apart from cranial CT scan, following investigations were performed in all the selected patients and controls viz. a complete Haemogram, glucose, creatinine, electrolytes and VDRL, liver function tests, complete urinalysis, ECG and X-ray chest.

Patients suffering from systemic illness, any cardiac illness likely to generate embolus, were excluded from the study. Similarly, patients receiving any pharmacological agent liable to affect platelet functions were also excluded from the study. Informed consent was taken from each patient.

SAMPLE COLLECTION

All the venepunctures were performed between 9-10 A.M. before breakfast. For platelet aggregation studies 9 volumes of blood was collected in 1 volume of 3.8% trisodium citrate in plastic tubes.

After collection, all the samples were transported to Cell Biology Laboratory, Department Biochemistry, Institute of Medical Sciences for platelet function studies

PLATELET PREPARATION AND FUNCTIONAL STUDIES

Materials used:

1. Buffers-(a)Buffer A (Platelet washing buffer),(b) Buffer B (Platelet resuspension buffer)
2. Epinephrine (1: 1000 w/v, NI Pharmaceuticals)
3. TRAP (SIGMA)

Preparation of Washed Platelets

The citrated blood samples were left in the capped plastic tubes for 15 minutes at room temperature and then they were centrifuged at 180 g for 20 minutes. The supernatant platelet rich plasma (PRP) was transferred into plastic tubes by plastic autopipettes to which citric acid (9 mM) and EDT A (5mM) were added. The remaining volume of blood was further centrifuged for 15 minutes at 800 g to obtain platelet poor plasma (PPP). Platelets from PRP were pelleted by centrifugation at 800 g for 15 minutes. Cells were gently suspended in 5 ml of buffer A, to which glucose and apyrase were added to final concentration of 5 mM and 0.6 ADPase units per ml, respectivley. Platelets were again pelleted and resuspended in 1 ml of buffer B, containing 5.5 mM glucose. Subsequently, aggregometry was performed at 37°C according to the turbidometric method with the use of platelet ionised calcium aggregometer (Model - 600).

MEASUREMENT OF PLATELET AGGREGATION

Aggregation was induced in PRP using epinephrine (1: 1 000) 10 um, and TRAP 10 um as agonist in the Chronolog platelet ionised calcium Aggregometer (model 600) at 37°C under stirring conditions (1000 RPM).Wherever epinephrine was used as stimulant, 10% (v/v) PPP was added to the washed platelets as a source of fibrinogen.

In addition to induced platelet aggregation studies' spontaneous platelet aggregation was also performed in each case.

ELECTROPHORESIS OF PLATELET PROTEINS

Washed platelets were mixed with 5x sample buffer in the ratio 4:1 (v/v) and heated for 2 minutes at 95°C in a dry bath. Platelet samples (80 µl) and prestained low range marker proteins (10 µl, Bio-Rad) were loaded into various lanes. Proteins were separated by overnight vertical electrophoresis of samples on 1.5 mm thick SDS polyacrylamide (11 %) slab gels (Balaji, India) at constant voltage of 50 Volts. (Biotech Power supply, India). Then the gel was destained and bands were identified

WESTERN IMMUNOBLOTTING

Platelet proteins were separated by 11 % SDS-PAGE and electrophoretically transffered on to the Hybond-C super Nitrocellulose membrannes (Amershan) using the horizontal Nova-Blot semidry blotting system (pharmacia by using a constant current of 0.8 mAmp/cm2). Blocking of the residual sites on the membranes was effected by incubating the blot for one hr. at room temperature with 5% non-fat dry milk in TBST buffer. Blot was incubated for one hour with monoclonal anti-phosphotyrosine antibodies. Following washing' the blot was incubated for one hr. with HRP-Iabelled anti-mouse secondary antibodies. Antibody binding was detected by using the enhanced chemiluminescence (ECL) system. (Amershan) on X-ray films (Kodak).

RESULTS :

PLATELET AGGREGATION IN STROKE

Spontaneous platelet aggregation was found in five cases of stroke and none among controls. Induced platelet aggregation with TRAP and epinephrine were studies in fifteen cases and equal number of controls. Epinephrine induced biphasic reaction in the control samples. However in the patients from stroke there was a qualitative difference in the aggregation profile. In stroke there was no primary wave and only strong secondary aggregation was observed.

Epinephrine is a physiological agonist for platelets. Next, we wanted to see whether the hyperaggregatory response of the platelets is partly contributed by the factors present in the plasma or it is intrinsic to the qualitative changes in the platelets in stroke. Hence platelets removed from the plasma, washed and suspended in a buffer was used for the study and thrombin receptor activating peptide(TRAP)rather than epinephrine was used as the stimulant. TRAP induced a considerably stronger aggregation in stroke in comparison to control platelets.

ELECTROPHORETIC PROFILE OF PLATELET PROTEIN IN STROKE

Platelets from stroke differ qualitatively from the normal counterparts. When the platelets from control and stroke patients were compared there was a striking difference at the region of about 190 KD. In the stroke sample strong band of about 190 KD was observed which was not found in control platelets. There were no apparent differences of other molecular weight regions. This 190 KD protein might be the Calpain mediated proteolytic products of cytoskeletal proteins. As this data represent a single experiment more experiments at different calcium concentrations should be. done to prove this point.

WESTERN BLOTTING

Washed platelets were prepared from the blood of the patients of stroke. Part of the cells was kept unstimulated and the other part was aggregated for two minutes with 10µm of TRAP. The proteins from the two groups of the samples were subjected to SDS PAGE followed by western blotting using antiphosphotyrosine antibody. The resting platelets from stroke had three prominent groups of antiphosphotyrosine band. The strongest band was around the region of 60 KD mw, where as other groups were about 100 and 140 KD mw regions. This picture is similar to the pattern observed in platelet from non stroke control subjects.

After two minutes aggregation the tyrosine phosphorylated bands at 100 and 140 KD mw region became far less intense than in the resting platelets, indicating tyrosine dephosphorylation at these regions.

Table-I: Results of peak platelet aggregation in percentage with epinephrine 10µm

Group	%Aggregation mean ±SD	t value	p value
Control (n=15)	43.06±3.88	15.86	<0.001
Stroke (n=15)	64.8±3.67		

There is a significant increase in epinephrine induced peak platelet aggregation in patients of stroke in comparison to control.

Table – II : Results of peak platelet aggregation in percentage with TRAP 10 µm.

Group	$t_{1/2}$(mean ± SD) in minutes	t value	P value
Control (n=15)	44.6± 3.66	18.8	<0.001
Stroke (n=15)	78.8±6.06		

With TRAP there is also significant increase of platelet aggregation in stroke patients in comparison to control.

Table-III : Result of $t_{1/2}$ of peak platelet aggregation in TRAP treated platelets

Group	$t_{1/2}$(mean ± SD) in minutes	t value	P value
Control (n=15)	1.92± 0.35	6.39	<0.001
Stroke (n=15)	1.22±0.29		

$t_{1/2}$ is the time taken in minute to reach 50% peak aggregation. The mean $t_{1/2}$ in stroke patients is significantly less in comparison to control suggesting an increased rate of TRAP induced aggregation of platelets in stroke patients.

Interestingly the bands at around 60 KD mw region were of similar intensity in resting and two minutes aggregated sample.

DISCUSSION : PLATELET AGGREGATION STUDIES

Platelet can be activated by a number of agonists such as epinephrine, thrombin, ADP, ristocetin and collagen etc. ADP and epinephrine being weak agonist induce a biphasic aggregation in the platelets. The primary wave of agggregation is weaker, reversible and is due to the integrine activation following some yet unexplained reasons. This also leads to stimulation of the thromboxane pathway. Release of thromboxane as well as ADP (from the dense bodies) further stimulate the platelets resulting in a secondary wave.[6,7,8,9]

First the platelets present in PRP were stimulated with epinephrine which closely simulated the physiological situation in vivo. As expected epinephrine induced a biphasic aggregatory response. However, platelets from stroke exhibited a single and stronger secondary response. Two reasons could be attributed to this observation. One, the thromboxane pathway is

already activated in the circulating 'resting' platelets in stroke. Therefore, epinephrine induced only a stronger secondary response. Secondly, platelets from stroke could have been already sensitised with a low threshold of agonist stimulation. This could lead to a stronger response to the similar epinephrine concentration as in the control. These observations also supported the spontaneous aggregation already reported in cases of stroke.

In the next experiment washed platelets were induced to aggregate with TRAP as agonist. The aggregation was also stronger in platelets from the stroke. In the previous experiment platelet hyper responsiveness could have been attributed to some factors present in the plasma. However, this subsequent experiment ruled out this possibility as the cells were washed and suspended in a buffer than in the plasma. This also supports our conclusion that platelet hyperactivity is due to changes intrinsic in the cells themselves rather than the external factors.

Primary aggregation is a short wave due to weak contact between the platelets. The secondary aggregation is induced only upon the synthesis and secretion of thromboxane A2 which is stronger agonist. Thromboxane synthesis is initiated by activation of enzyme cyclooxygenase. Presence of secondary wave of aggregation in stroke platelets indicates that the synthetic pathway remains intact and unaffected in their platelets.

Several studies have demonstrated that acute cerebral ischaemia is associated with a transient lowering of threshold for platelet aggregation to ADP and epinephrine in vitro and a temporary increase in circulating platelet aggregate are formed in vivo. Increased platelet aggregability has been demonostrated in recent TIA or within 7 days of acute stroke in aged patients in comparison to young controls. Single cerebral ischaemic attack only temporarily activated platelet, those parameters were restored to normal in 10 days to several week after the acute insult.Spontaneous platelet aggregation in cerebrovascular disease has been demonstrated.[7,8,9,10]

Our study corroborates with most of the studies mentioned above. Many factors enhance platelet aggregability in stroke including stress, elevated plasma lipids and free fatty acids and associated smoking. Increased circulating catecholamines while weak direct platelet agonists augments platelet aggregability by other agonists, oppose the effect of natural antiplatelet factors such as prostacyclines. Increased catecholamine levels in stressful situation such as acute stroke increases the level of plasma fibrinogen, factor VIII and vWF' both important factors for platelet activation. Increased plasma fibrinogen level is an independent risk factor for stroke, perhaps in part through its stimulatory effect on platelet aggregation.

ELECTROPHORETIC PROFILE OF PLATELET PROTEINS IN STROKE

As the platelets from stroke were found to be different functionally from the control cells, possibility of any change in the electrophoretic profile of the protein was studied subsequently. There was appearance of a band at about 190 KD region in the platelets from stroke. No other striking difference was observed at other molecular weight regions between the two samples. There is a strong possibility that this 190 KD protein could be the proteolytic break-down product of the high molecular weight cytoskeletal proteins. It is known that in stimulated platelet the calcium dependent thioprotease calpain gets activated which degrades the 3 prominent cytoskeletal proteins namely, Fillamin, Talin and Myosin heavy chain. It results in the appearance of proteolytic products at lower molecular weight regions. Hence, it could be argued that the activated cells circulating in the stroke patients have higher basal calcium as well as stimulation of calpain activity in comparison to the control counterparts. However the possibility of the appearance of unidentified protein thrombospondin, could not be ruled out.[14]

WESTERN BLOTTING

The strong tyrosine phosphorylated band at 60 KD mw region relates to the *Src* family of tyrosine kinases present abundantly in the platelets. The identification of tyrosine phosphorylated protein at 100

and 140 KD mw region remains unknown. However, it is interesting to find that these proteins appears to be dephosphorylated on tyrosine at 100 and 140 KD mw regions. This can be attributed to either decreased tyrosine kinase activity or enhanced tyrosine phosphatase activity in TRAP stimulated platelets from stroke. Such a picture is not observed in platelets from non stroke control humans where two minutes aggregation increased tyrosine kinase activity in general. However more number of samples need to be studied under varying experimental condition to establish this fact.[11,12,13,14]

CONCLUSION :

To conclude ischemic stroke is a very common problem in neurologic practice. Platelet dysfunction is an important association as found in this study. From studies around the globe there is mounting evidence linking platelet dysfunction to ischemic stroke. Modifying or altering platelet function may have an important role in the prevention of the disease.

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Original Article

UTILITY OF PLASMA N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE (NT-proBNP) TO DISTINGUISH BETWEEN CARDIAC AND NON-CARDIAC CAUSES OF ACUTE DYSPNOEA

S. Sahu,* S.C. Singh, M. Patnaik,** S.N. Rautray,*** P.C. Mohapatra,**** S. Das*******

ABSTRACT

AIM : *The present study is designed to assess plasma NT-pro BNP level in differentiating Dyspnoea from Cardiac and Non-Cardiac causes.* ***MATERIALS AND METHODS:*** *84 cases of acute dyspnoea with above 15 years of age were included in the study . Dyspnoea due to chest trauma, Renal insufficiency (serum Cr.>2.5 mg/dl),Previously known Valvular Heart Diseases and Severe coronary ischemia identified as >0.1 mV ST-segment elevation or ST depression on 12 lead ECG were excluded from the study. After enrolment history, clinical examination , routine blood test, electrocardiography, chest x-ray were done and additional blood sample was collected for NT-pro BNP measurement.* ***RESULTS :*** *84 cases were studied, Male=55(65.4%) and Female=29(34.6%). 40 (47.6%) had acute cardiac dyspnoea and 44 (52.4%) had non cardiac dyspnoea. The mean NT-pro BNP concentration of cases with acute cardiac dyspnoea (4539 pg/mL) were significantly higher than the cases non cardiac dyspnoea (136.613 pg/mL),(P <0.001). On evaluation of acute Heart Failure, 3 (7.5%) had NYHA Class II symptoms, 10 (25%) had Class III symptoms and 27(67.5%) had Class IV symptoms demonstrates the significant relationship between NYHA symptom severity and NT -pro BNP levels(P < 0.001). The median NT-proBNP level was 1150 pg/mL (IQR 675–3070 pg/mL) in patients with LVEF e"50% and 4558 pg/mL (IQR 1900–25000 pg/mL) in those with LVEFd" 50% (P < 0.001).* ***SUMMARY AND CONCLUSION****: The serum NT- pro BNP measurement is a useful parameter for diagnosing cardiac causes of dyspnoea and also acute heart failure as per NYHA class. It can be used for early detection and management of acute heart failure.* ***Key Words:*** *plasma N-terminal pro-brain natriuretic peptide, Acute Dyspnoea, Coronary ischemia, Valvular heart disease.*

INTRODUCTION

Early detection and accurate diagnosis of heart failure remains a huge clinical challenge in patients with acute dyspnoea. Though ECG and chest X-ray merely serve as baseline investigations, the diagnosis is eventually only confirmed by a 2D- echocardiogram coupled with Doppler flow study. Biomarkers of left ventricular dysfunction are being studied to differentiate cardiogenic from noncardiogenic dyspnoea. BNP is a leading biomarker.[1] Brain Natriuretic Peptide (BNP) is a group of Natriuretic peptides that are involved in the regulation of diuresis , which antagonizes the vasoconstrictor effects of RAAS.[1] BNP is produced by cardiac myocytes in response to increased left ventricular wall stretch .[2] It is derived from an intracellular 108 amino acid precursor protein ,which is cleaved in to 2 fragments and released by myocytes yielding NT-proBNP(1st 76 Aminoacids the inactive form) and BNP (32 Aminoacids active form).[1,3,4] A close correlation exists between these peptide levels. However in patients with left ventricular dysfunction,the proportional and absolute increase of NT-proBNP exceeds that of BNP.[4,12,13] Also NT-proBNP has longer half life(120min) than BNP(20min) increases specimen stability and more robust results. Patient presented with acute dyspnoea may be due to cardiovascular causes(CHF , ACS) or Respiratory causes(COPD acute exacerbation , Asthma , Bronchitis , Pneumonia) or Mixed or Other causes (anxiety, fever, sepsis etc.)

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Diagnostic uncertainty in patients with complaints of acute shortness of breath presenting to hospital may cause delay in treatment and proper care. In patients with shortness of breath due to Heart failure increased plasma levels of NT-proBNP can be demonstrated. The use of NT-proBNP as a biomarker for heart failure in patients with acute dyspnoea might improve care and reduce length of hospital stay.[5]

AIM OF THE STUDY

The present study is designed to assess plasma NT-proBNP level in differentiating Dyspnoea from Cardiac and Non-Cardiac causes.

MATERIALS AND METHODS

84 cases of acute dyspnoea with above 15 years of age were included in the study .Dyspnoea due to chest trauma, Renal insufficiency (serum Cr.>2.5 mg/dl),Previously known Valvular Heart Diseases and Severe coronary ischemia identified as >0.1 mV ST-segment elevation or ST depression on 12 lead ECG were excluded from the study. After enrolment history, clinical examination, routine blood test, electrocardiography, chest x-ray were done and additional blood sample was collected for NT-proBNP measurement. **NT-proBNP analysis:** NT-proBNP analysis was performed with a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana) on an Elecsys 1010 analyzer according to established methods. This assay is reported to have <0.001% cross reactivity with bioactive BNP. Briefly, 20 µl of the sample was incubated with biotinylated polyclonal capture antibodies and polyclonal ruthenium-complexed detection antibodies, which were directed against NT-proBNP. After incubation,the captured NT-proBNP, which was bound to streptavidin-coated paramagnetic microparticles, was quantified by electrochemiluminescence.

RESULTS :

84 cases were studied, Male=55(65.4%) and Female=29(34.6%). 40 (47.6%) had acute HF and 44 (52.4%) had non cardiac dyspnoea.The mean NT-proBNP concentration of cases with acute HF (4539 pg/mL) were significantly higher than the cases without HF (136.613) pg/mL,(P <0.001)(Figure 1). On evaluation of acute HF, 3 (7.5%) had NYHA Class II symptoms, 10 (25%) had Class III symptoms and 27(67.5%) had Class IV symptoms (Figure 2) demonstrates the significant relationship between NYHA symptom severity and NTproBNP levels(P < 0.001). The median NT-proBNP level was 1150 pg/mL (IQR 675–3070 pg/mL) in patients with LVEF e"50% and 4558 pg/mL (IQR 1900–25000 pg/mL) in those with LVEFd" 50% (P < 0.001).

SUMMARY AND CONCLUSION:

The serum NTpro-BNP mesurment is a useful parameter for diagnosing cardiac causes of dyspnoea

Figure 1: Mean serum NT pro-BNP level between patients of acute HF and noncardiac causes of acute dyspnoea.

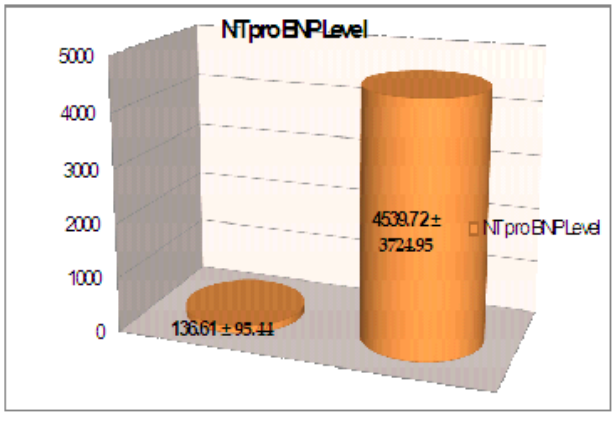
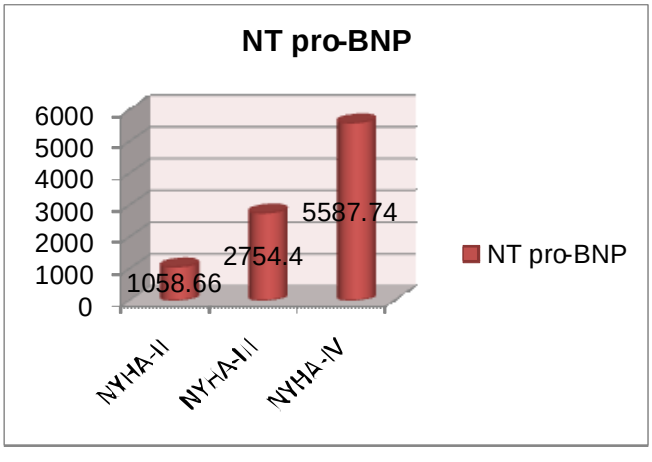
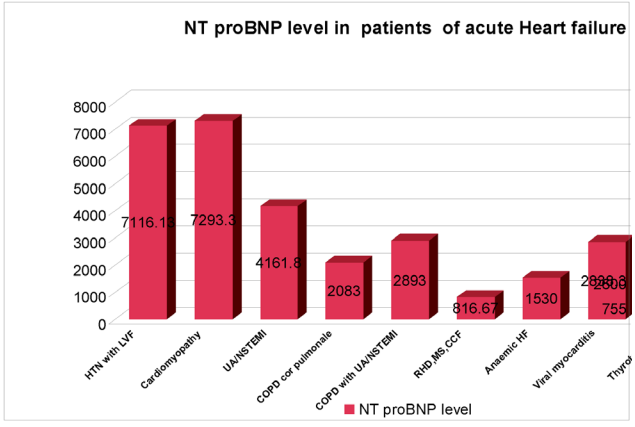
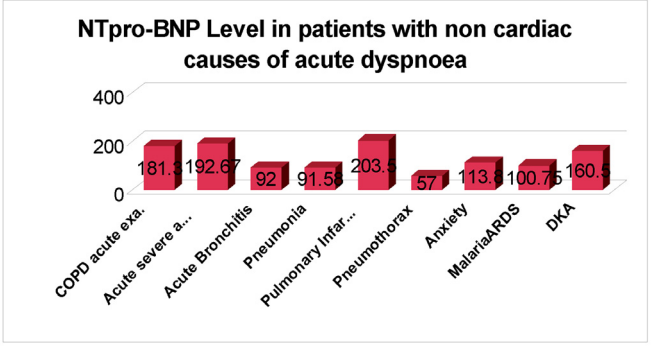


Figure 2: Mean serum NT pro-BNP level between patients of acute HF in order of their NYHA class.







and also acute heart failure as per NYHA class. It can be used for early detection and management of acute heart failure.

CONCLUSION:

Studies suggest that Serum NTpro-BNP measurement will be intrinsic in the future management of CHF. It has been observed that increased NT pro-BNP is associated with acute HF severity and increased morbidity and mortality. For clinicians, there is still a multitude of questions in understanding quantifications on an individual patient basis. Brain natriuretic peptide detection using a POC platform makes testing accessible to more health care providers and multicenter trials easier to initiate. Continued research will elucidate how to best utilize BNP and its role in the future of health care.

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Original Article

EFFECT OF DPP-IV INHIBITOR (VILDAGLIPTIN) Vs. OTHER OADS (GLIMEPERIDE & METFORMIN) ON INSULIN RESISTANCE & B-CELL FUNCTION IN TYPE – 2 DIABETES MELLITUS

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ABSTRACT

*Purpose of this study is to compare the effect of DPP-IV inhibitors (VILDAGLIPTIN) as monotherapy, with glimeperide-metformin combination on insulin resistance and Beta-Cell function in type 2 DM of vildagliptin and to determine the efficacy as monotherapy in managing Type 2 DM. 60 case of newly diagnosed type 2 DM were taken for this study, they were divided into group A who received vildagliptin and group B who received glimeperide and metformin combination and followup for a period of 6 months with serial estimation of FPG, HbAIC, FPI, HOMA-B, HOMA-IR at baseline, at 3 months & at 6 months. It is concluded that, glycemic control and insulin resistance significantly improved in both groups but significant improvement in beta-cell function was observed only in group-A.**Key words** : Type-2 Diabetes Mellitus, DPP-IV Inhibitor, Insulin resistance, Beta-cell function.*

INTRODUCTION

When the food is ingested it reaches the intestine. The carbohydrate moiety of the nutrient stimulate the secretion of gastrointestinal hormones (incretins) from the K-Cells of jejunum and L-Cells of ileum. The incretins are G.I.P. & GLP-1. The main function of the incretins are to regulate insulin & glucagon secretion. Besides they also have other metabolic effect like delaying of gastric emptying, inhibition of food intake, regulation of several energy storage & disposal mechanisms.

Non-human models indicate that incretins are also involved in pancreatic B-cell proliferation & inhibition of B-cell apoptosis.

Incretin effect refers to the amplification of insulin response to glucose when delivered orally as opposed to intravenously.

Patients with type-2 DM have reduced concentration of active GLP-1. This impairment exacerbate a defect in insulin & glucagon secretion that is characteristic of type 2 DM. GLP-I normally acts to stimulate glucose sensitive insulin secretion & suppresses glucagon release.

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Di-Peptidyl-Peptidase-4 is a serine protease that is widely distributed throughout the body. The target peptides for DPP-IV in the gut include incretins (GLP-1 & GIP). As a result of cleavage by DPP-IV more than 50% of circulating GLP-I is inactivated within 1to2 minutes.

This effect on GLP-1 has proven to play key role in the incretin activity & glucose homeostasis. By inhibiting DPP-IV, incretin activity can be prolonged leading to increased level of incretins (GLP-I). As a result the insulin glucagon imbalance can be corrected. So that insulin secretion from the B-Cell is increased & glucagon secretion from alfa-cell is suppressed.

Vildagliptin is a selective DPP-IV inhibitor which increases the plasma level of GLP-I & GIP. It increases the insulin level and suppresses the glucagon level.

The sensitizers only act on the insulin receptors & the secretagogues previously used stimulate the B-cells. In type-2 DM as time goes on B-cell apoptosis continues. The insulin secretion from the B-cell falls significantly and the conventional sensitizers and the secretagogues become ineffective & the patient ultimately depends on insulin for glucose homeostasis.

DPP-IV inhibitors are a group of novel oral

agents which through incretins act on both alpha cells & B-cells of the pancreas for maintaining glucose homeostasis & help in the improvement of B-cell function & prevention of apoptosis.

MATERIAL & METHODS

60 newly detected Type-2 DM cases were included in the study. Out of 60 cases, 38 cases are males and 22 cases are females.

Subject eligibility criteria are age within 30 years, FBS 126-250mg/dl and HbA1C – 7-10%.

These cases were divided into two groups, Group A and Group B. Group A patients was given vildagliptin and Group B patient given metformin and glimeperide. Both group of patients were subjected to follow up for a period of 6 months with blood examination of FPG, HbA1C, FPI, HOMA-B, HOMA-IR at baseline at 3 months and at 6 months period at SCB Medical College, Cuttack in the Dept. of Medicine.

OBSERVATION

Baseline data

Parameters	Group A (Vildagliptin)	Group B (GLIM+METFORMIN)
Age	42.9±7.92	46.5±6.66
Sex	M (20): F(10)	M(18) : F(12)
BMI	25.68±1.70	25.92±1.146
FPG	186.9±22.56	196.6±35.358
HbA1C	9.23±0.729	9.5±0.320
FPI	10.53±5.46	10.461±6.733
HOMA-B	32.68±22.38	31.89±26.58
HOMA-IR	4.77±2.237	4.909±2.871

At 3 months follow-up:

Parameters	Group A 3 MONTHS FOLLOW UP	Group B 3 MONTHS FOLLOW UP
Age		
Sex		
BMI	25.008±1.44	24.86±1.39
FPG	140.35±17.55	136±10.68
HbA1C	7.55±0.416	8.4±1.8
FPI	9.559±3.053	10.54±2.65
HOMA-B	46.845±20.34	35.86±18.98
HOMA-IR	3.33±1.22	3.53±1.34

At 6 months follow-up:

Parameters	Group A 6 MONTHS FOLLOW UP	Group B 6 MONTHS FOLLOW UP
BMI	24.76±1.56	24±0.87
FPG	111.2±10.13	115.4±7.98
HbA1C	6.46±0.587	7.5±1.002
FPI	11.572±3.89	8.4±2.3
HOMA-B	89.031±36.92	50.84±12.76
HOMA-IR	3.161±1.41	3.0±1.06

DISCUSSION

Diabetes mellitus (DM) refers to a group of common metabolic disorders which shares the phenotype of hyperglycemia. Several distinct types of DM exist and occurs by a complex interaction of genetic and environmental factors. The metabolic dysregulation associated with DM causes secondary pathologic changes in multiple organ system that include end stage renal disease and cardiovascular diseases. DM will be a leading cause of morbidity and mortality for the foreseeable future.

Advances in the therapy of type 2 DM have generated considerable enthusiasm for oral glucose-lowering agents that target different pathophysiologic process in type 2 DM. DPP-IV inhibitors represent a new class of oral agents that inhibit degradation of native GLP-1 and thus enhance incretin effect. These

Comparison of Group A at 3 months and 6 months follow-up:

Parameters	Group A (VILDAHLIPTIN) 0 MONTH	Group A 3 MONTHS FOLLOW UP	GROUP A 6 MONTHS FOLLOW UP	P VALUE 0&6 MONTH	P VALUE 0&6 MONTH
BMI	25.68±1.70	25.008±1.44	24.76±1.56	0.103	0.033
FPG	186.9±22.56	140.35±17.55	111.2±10.13	<0.0001	<0.0001
HbA1C	9.23±0.729	7.55±0.416	6.46±0.587	<0.0001	<0.0001
FPI	10.53±5.46	9.559±3.053	11.572±3.89	0.398	0.398
HOMA-B	32.68±22.38	46.845±20.34	89.031±36.92	0.012	<0.0001
HOMA-IR	4.77±2.237	3.33±1.22	3.161±1.141	0.003	0.0009

Comparison of Group B at 3 months and 6 months follow-up:

Parameters	Group B (GLIM+ METFORMIN)	Group B 3 MONTHS FOLLOW UP	GROUP B 6 MONTHS FOLLOW UP	P VALUE 0&6 MONTH	P VALUE 0&6 MONTH
AGE	46.5±6.66				
SEX	M(18):F(12)				
BMI	25.92±1.146	24.86±1.39	24±0.87	0.0021	<0.0001
FPG	196.6±35.358	136±10.68	115.4±7.98	<0.0001	<0.0001
HbA1C	10.005±1.103	8.4±1.8	7.5±1.002	0.0017	<0.0001
FPI	10.461±6.733	10.54±2.65	8.4±2.3	0.952	0.118
HOMA-B	31.89±26.58	35.86±18.98	50.84±12.76	0.508	0.008
HOMA-IR	4.909±2.871	3.53±1.34	3.0±1.06	0.020	0.0012

agents (e.g. Vildagliptin) promote insulin secretion in absence of hypoglycemia and weight gain.

In this study, out of 60 newly diagnosed type-2 DM, 38 were male and 22 were female patients. They were divided in to Group-A (30 patients-Male-18, Female-12) Group-A was treated with vildagliptine as monotherapy and Group-B patients were treated with metformin and Glimeperide combination. These patients were followed up at base line, at 3 months and 6 months with blood investigation like FPG, HbA1C, FPI, HOMA-B and HOMA-IR.

At baseline Data - Group A patients shows FPG-186. 9I 22.56, HbA1C 9.23±0.729, FPI 1053±5.46, HOMA - B 32.68±22.38, HOMA- IR 4.77±2.237 and Group B patients shows FPG 196.6±35.358, HbA1C 9.5±0.320, FPI 10.461±6.733, HOMA B 31.89±26.58 and HOMA IR 4.909±2.871 respectively (P Value FPg 0.210, HbA1C 0.683, FPI 0.965, HOMA - B 0.901, HOMA- IR 0.835).

At 3 months follow up – Group A patients shows FPG 9.559±3.053, HbA1C 7.55±0.416, FPI-9.559±3.053 HOMA- B 46.845±20.34, and HOMA IR 3.33±1.22 and in Group B patients shows FPG 136±10.68, HbA1C 8.4±1.8, FPI 10.54±2.65, HOMA B 35.86±18.98 and HOMA IR 3.53±1.34 respectively (P Value FPG 0.250, HbA1C 0.015, FPI 0.189, HOMA B 0.034 and HOMA IR 0.547).

At 6 months Follow up – Group A patients shows FPG 111.2±10.13, HbA1C 6.46±0.587, FPI 11.572±3.89, HOMA B 89.031±36.92 and HOMA IR 3.161±1.141 and in Group B patients shows FPG 115.4±7.98, HbA1C 7.5±1.002, FPI 8.4±2.3, HOMA B 5084±12.76 and HOMA IR 3.0±1.06 respectively (P Value- FPG 0.079, HbA1C 0.001, FPI 0.003, HOMA B <0.001 and HOMA IR 0.573).

Observations at 6 months follow up showed in both group a significant improvement in blood glucose values (FPG and HbA1C) and Beta-cell function (FPI, HOMA B & HOMA IR) particularly in Group A patients who were on monotherapy with vildagliptin.

CONCLUSION

It is observed that, the glycemic control with vildagliption as monotherapy is as effective as combination therapy of metformin & glimeperide.

Beta cell function was significantly improved in Group A patients who were on vildagliptin, in comparison to metformin and glimeperide.

Insulin resistance was significantly decreased in both groups.

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Pictorial CME

FAHR DISEASE

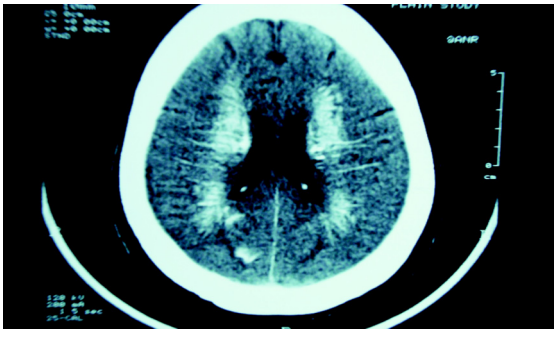
N. Mohapatra*, CBK. Mohanty, R. Mohanty,*** B.N. Mohapatra***, P.Jena,***
A. Sahu**, S. Ghosh*****, N. Mohanty*****

A 56 yr old lady presented with progressive mental deterioration and dysarthria. for 10 days without any history of fever, convulsions, or head injury. She had a past history of altered behavior and forgetfulness for last five years. She was neither hypertensive nor diabetic. Neurological examination revealed mental confusion, dysarthria, ataxia, bilateral resting tremor of hands without any focal motor or sensory deficit or meningeal signs. Blood examination showed normal serum levels of Na, K. Ca Phosphorus glucose and parathormone. LFT and RFT were normal. CT scan brain revealed bilateral symmetrical non-enhancing hyperdense lesions s/o calcification involving globus pallidus, putamen. caudate nucleus, internal capsule, thalami and cerebellum. These CT findings when correlated with typical clinical features and normal blood chemistry was suggestive of Fahr disease.

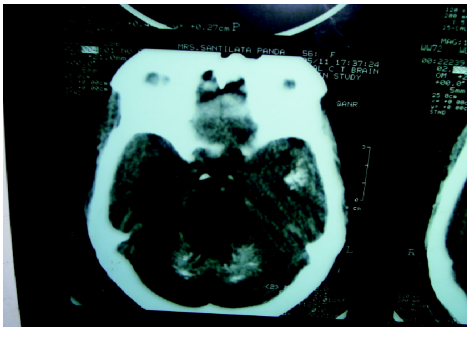
Fahr Disease, first described by Karl Theodar Fahr in 1930,is a rare degenerative neurological disorder, which refers to sporadic or familial idiopathic bilateral basal ganglia calcification that is associated with many neuropsychiatric abnormalities. The most common site of calcification is globus pallidus, but other sites are putamen, caudate nucleus, internal capsule, dentate nucleus, thalamus, cerebellum, and cerebral white matter. Calcium deposits occur in the extracellular and extravascular spaces.

Age of onset of symptoms is typically 30 to 60 years. Clinical features include dysarthria, extrapyramidal tremor, ataxia, progressive deterioration of mentality, loss of motor functions, symmetrical spastic paralysis, athetosis, seizures and optic atrophy.

There is neither a cure nor a standard course of treatment for Fahr Disease. Prognosis is variable and unpredictable.



CT Scan Brain :
Calcification involving globus pallidus, putamen. caudate nucleus, internal capsule, thalamus



CT Scan Brain :
Calcification involving cerebellum

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Pictorial CME

A CASE OF UNILATERAL MILIARY TB

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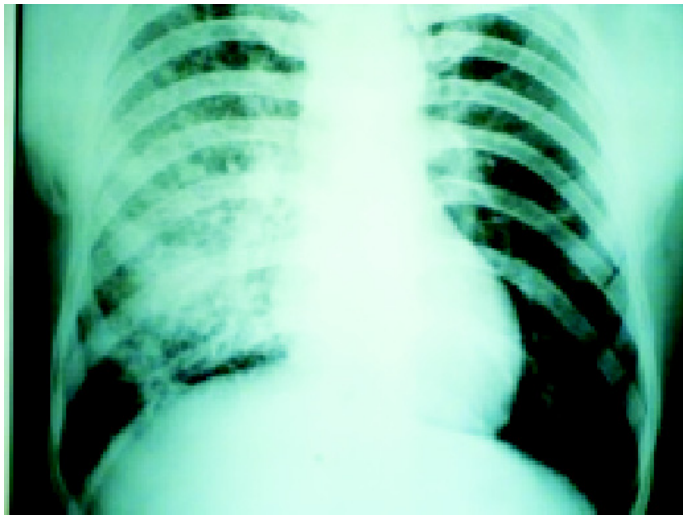

Chest X-Ray PA View showing miliary shadows involving only the right lung

A 35 year old male presented with low –grade fever,anorexia,weight loss with non-productive cough for 2 months.General Examination revealed a febrile patient with mild pallor,pulse rate-80/min and BP-96/66mm Hg. Examination of resp. system revealed no abnormal finding. Abdominal examination revealed mild hepatomegaly. Lab. investigations were otherwise normal except for Hb-9gm%, ESR-80 mm/hr. Mantoux test was negative. Chest X-ray done on next day revealed typical miliary shadows involving only the right lung.

This is the most unusual manifestation of miliary TB never described before in literature. Explanation of this could be due to a TB focus in a right hilar node eroding into the relatively low pressure right pulmonary artery leading to hematogenous dissemination into the right lung fields only.

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Review Article

LONE ATRIAL FIBRILLATION, AN UNKNOWN ENTITY

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INTRODUCTION :

Atrial fibrillation (AF) is the most common cardiac arrhythmia[1] and involves the two atria. Its name comes from the word "Quivering" of the muscles of the heart, instead of coordinated contractions. Electrocardiographic detection is by absence of 'P' waves with irregularly irregular R-R intervals. Risk for AF increases with age with 8% of people over 80 years having AF.

People with AF usually have a significantly increased risk of stroke (upto 7 times the general population). Stroke risk increases due to formation of clots in the poorly contracting atria and appendage. The American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend in their guidelines the following classification system based on simplicity and clinical relevance.[2]

AF Category	Defining Characteristics
First detected	only one diagnosed episode
Paroxysmal	recurrent episodes that self terminate in less than 7 days.
Persistent	recurrent episodes that last > 7 days.
Permanent	an on-going long-term episode.

In addition to the above four AF categories which are mainly defined by episode timing and termination, the ACC/AHA/ESC guidelines describe additional AF categories in terms of other characteristics of the patient.

LONE ATRIAL FIBRILLATION (LAF) :

Absence of clinical or echocardiographic findings of other cardiovascular disease (including hypertension), related pulmonary disease, or cardiac abnormalities such as enlargement of the left atrium and age under 60 years.

NON VALVULAR AF :

Absence of Rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair.

SECONDARY AF :

Occurs in the setting of a primary condition which may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia or other acute pulmonary disease.

LONE AF :

The diagnosis of lone AF requires the exclusion of cardio pulmonary disease, other causes of AF, such as hypertension valvular abnormalities, cardiomyopathy, cardiac ischaemia diabetes and thyroid disorders.[3] Therefore the diagnosis of lone AF is essentially a diagnosis of exclusion and should be preceded by careful evaluation.[4]

INCIDENCE AND CLINICAL COURSE :

The overall prevalence of AF IS 0.4%-1% m the general population.[5] Among that group, lone AF occurs in 1.6 - 11.4% of all cases of AF.[6,7,8]

A high prevalence of over 30% of lone AF was reported in the ALF A study. (Etude an Activite Liberale de La Fibrillation Auviculaie) of French patient population. This study had important limitations in that it was designed to define the clinical characteristics and out comes of patients with A F and not the incidence of AF. The second limitation was that this study underestimates the relative frequency of asymptomatic

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AF and 24 hrs ambulatory ECG recording was not done. The following table summarises some of the epidemiological studies of lone AF (Table-1). Many of these patients have a paroxysmal form of the arrhythmia with an estimated progression to permanent AF as high as 29% over 30 years (Table-2), with a relatively low risk of mortality, heart failure and thomboembolic complications[1]. The prognosis of patients with paroxysmal lone AF appears to be good, given this may primarily be an electrical problem (related to pulmonary vein foci) where as patients with chronic lone AF are at increased rise of embolic events and higher mortality. Thus chronic lone AF is not a benign disorder and receives more attention than paroxysmal AF.[11]

Lone AF patients probably need careful follow up with repeated evaluation of risk factors and comorbidities as underlying conditions may change. In one study lone AF patients with normal atrial size had a benign course throughout while those with increased left atrial volume experience more adverse outcomes such as cerebral infarction, myocardial infarction and CHF[I2]. Approximately 44% of patients with an initial diagnosis of lone AF may represent occult cases of arterial hypertension. In these patients hypertension may influence outcomes and treatment options.[13]

Other multiple factors of a medical, genetic or habitual nature that are crucial for the development of 'lone AF' may not be included is the list of typical risk factors. Thus 'Idiopathic AF' (i.e. without any cause) may not be the same as 'lone *AF'*. One recent review of this field even proposed an un-official term of 'not-so-Ione AF' to emphasise the potential influence of these factors.[l4]

RISK FACTORS FOR LONE AF :

Epidemiological data show a male predominance with men comprising upto 78% of patients[10]. This sex difference has been further investigated showing that proportion of males was greater among sporadic lone AF and possibly familial probands.[15]

A familiar incidence of lone AF has been described with autosomal dominant pen trance. First degree relatives of lone AF have AF more frequently. Genetic mutations that contribute to lone AF have been described, including mutations in genes (KCNE3, V17M, SCN5A) for potassium and sodium channels, connexins, components of the renin angiotensin-aldosterone system and mink gene.[16,17,18]

Obesity is associated with an increased incidence of AF as a whole with a 3-8% increased risk of incidence of AF with each unit increase in Body Mass Index (BMI).[19,20] However concrete data linking BMI to lone AF are lacking with some studies suggesting that lone AF patients are statistically taller and leaner than other patients with AF.[21]

Socio economic factors are seen to play some role in lone AF. A type A behaviour and acute life stress may precipitate AF with reversal to sinus rhythm on removal of stress.[22] High coffee consumption and obesity were associated with an increased risk of persistent AF.[23]

Alcohol consumption has also been associated with lone AF. The holiday heart syndrome was associated with symptoms of paroxysmal AF following high amounts of alcohol intake. However in the Framingham study, long term alcohol consumption showed a weak correlation with AF, unless high consumption was taken into account (>36 gms/day).[24] Contrarily in another study high alcohol intake in men was found to increase the risk of AF.[25]

Endurance sports (eg. Marathon running) has been associated with lone AF[26]. In such people there was a significant association of increased left atrial volume and incident lone AF. The proportion of patients with lone AF who report current sports practice (31%) is higher than that observed in controls (14%).[27] In fact current sports practice seems to be associated with higher prevalence of lone AF.

Another factor that has been related to lone AF is sleep apnoea syndrome (SAS). This is probably due to SAS's influence on autonomic imbalance and various haemodynamic factors leading to increased incidence of lone AF.[28]

TABLE -1

EPIDEMIOLOGICAL STUDIES OF LONE AF

	Year of Publication	Number of LAF Patients	LAF as a percentage of the whole AF population	Sex	Age (range / mean, years)	Duration of follow- up (range / mean, years)
Brand et al[3]	1985	43	11.5%	74% M / 26% F	- / 70	- / 10.9
Onundarson et al[85]	1987	8	32%	-	-	- / 14.2
Kopecky et al[2]	1987	97	1.7%	80% M / 20% F	15-60 / 44	- 14.8
Davidson et al[86]	1989	32	4.6%	59% M / 41% F	30 – 55 / 46.8	2-16 / 4.9
Scardi et al[7]	1999	145	1.93%	81% M / 19% F	- / 43.4	1-35 / 10.4
Osranek et al[8] (Olmsted population)	2005	46	-	83% M / 17% F	- / 45.8	- / 27
Jahangir et al[14] (Olmsted population)	2007	76	-	78% M / 22% F	- 44.2	2.5 – 42.2 / 25.2

AF, atrial fibrillation; F, female; LAF, lone atrial fibrillation; M, male

TABLE -2

MORTALITY AND MORBIDITY ASSOCIATED WITH LONE AF

	Number of LAF Patients	Sex	Age (range / mean, years)	Paroxysmal and persistent / chronic AF (%)	Recurrence rate (%of paroxysmal LAF patients)	Progression to chronic LAF (% of paroxysmal LAF patients)	Risk of thromboembolic events(number per 100 person-years	Cardiovascular death (number per 100 person-years)
Band et al[3]	43	74% M	- 70	0/100	-	-	2.4	-
Onudarson et al[85]	8	-	-	0/100	-	-	0	0
Kopecky et al[2]	97	80% M	15–60/44	78/22	58%	16%	0.55	0.97
Davidson et al[86]	32	59% M	30-55/46.8	94/6	56%	-	0.64	0
Scardi et al[7]	145	81% M	-/43.4	86.2/15.8	-	23%	1.26	0.23
Osranek et al[8] (Olmsted population)	46	83% M	-/45.8	100/0	-	-	0.54	0.69
Jahangir et al[14] (Olmsted population)	76	78% M	-/44.2	93/7	-	29%	0.9	0.63

AF, atrial fibrillation; F, female; LAF, lone atrial fibrillation; M, male

Drug induced lone AF should be considered given that there as some specific groups of medicines that may induce AF. Eg dopamine, adenosine, 5flurouracil, anticholinergics antidepressants, antimigraine drugs, drugs for erectite dysfunction magnesium sulphate.[29]

Natriuretic Peptides :

One group biomarkers of potential importance in terms of diagnosis, prediction and recurrence of and treatment monitoring of lone AF are the natriuretic peptides of which Brain natriuretic peptide (BNP) has been most thoroughly researched.

Plasma BNP concentrations in lone AF patients is significantly higher than healthy matched controls. Age, left atrial diameter and history of AF were independent predictors of elevated BNP.[30] Lone AF vs sinus rhythm, atrial volume index, pulmonary artery systolic pressure and 'E' mitral velocity all independently correlated with higher BNP level in lone AF[31]. ANP levels on the other hand are not elevated in patients of lone AF and this discordant finding of elevated BNP with normal ANP may represent an underlying subclinical predisposition to lone AF especially in patients with sinus rhytlun.[32]

Apelin :

This is an endogenous peptide hormone that appears to have a physiological role in counter regulation of the angiotensin and vasopression systems. In subjects with lone AF mean Apelin levels were significantly lower when compared with subjects in sinus rhythm.[33]

Inflammation :

An interesting association between inflammation and lone AF was found in specimens of endomyo cardial biopsies taken of the right atrial septum and of the two ventricles. All lone AF atrial biopsy specimens showed severe hypertrophy with vacuolar degeneration of the atrial myocytes and ultrastructural evidence of fibrinolysis, lymphomononuclear infiltrates with necrosis of the adjacent myocytes. Ventricular biopsies showed inflammatory infiltrates but in only 25% of patients.

An association between higher CRP levels and lone AF has been found.[34] hs CRP seems to predict recurrent AF, in lone AF patients who are not taking antiarrhythmic drugs.

MANAGEMENT :

For all patients of AF there are two general treatment strategies: rhythm and rate control. For younger individuals especially those with paroxysmal lone AF, rhythm control appears to be a better approach.[5] In patients with symptomatic lone AF, a beta blocker may be tried first (cardio selective preferably) but other agents such as flecainide, propafenone and sotalol are particularly effective[15,35]. In patients with adrenergic ally mediated AF, β blockers represent first line treatment, followed by sotalol and amiodarone.

Regardless of the rate versus rhythm control strategy, the need for anticoagulation is based on stroke risk factors. In lone AF the risk of thromboembolism is low without treatment. Therefore long term anti coagulation is not recommended for primary prevention of stroke in patients with lone AF without any risk factor for thromboembolism. The precise recommendation for anticoagulation in lone AF according to the ACC/ AHAIESC guidelines is Aspirin (81-325 mg/day) or no therapy (class-1)[4] Protection against thromboembolism is not recommended even during pregnancy for patients with lone AF and/or low thromboembolic risk.[4]

In patients with lone AF nonantiarrhythmic agents like statins have been efficacious in maintaining sinus rhythm in patients with persistent lone AF. Recurrence risk is also reduced by use of statins after cardioversion.[36,37] There is some data showing the usefulness of ACE inhibitors addition to antiarrhythmic therapy in maintenance of sinus rhythm after cardioversion.[37]

Other options for treatment of lone AF are catheter ablation and beating heart pulmonary vein isolation.[4,39]

CONCLUSION :

Patients with lone AF form a group that is distinct from AF with underlying cardiovascular disease. The

therapeutic approach is different particularly is terms of anticoagulation.

Although lone AF by definition has no underlying cause it may be associated with other medical, habitual and social factors. Clearly there is a need for further research and lone AF patients need careful follow up.

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Current Concept

MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

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INTRODUCTION:

Acute promyelocytic leukemia (APL), a distinct subtype of acute myeloid leukemia (AML), is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion between the promyelocytic leukemia (PML) gene and retinoic acid receptor α (RARα). Variant of chromosomal translocations [e.g. t(11:17), t(5:17)] can be detected in no more than 2% of APL patients. Since, the first description of APL case in 1957 by Dr. Hillestad till date, the important milestones in this field are as follows:

- Hillestad, Swedish author, 1957: First case
- 10 – 15% of all AML
- Bernard et al 1973: CR with Dauno
- ATRA: 1985 : 5 year girl in Shanghai children's hospital, China
- ATRA + CT : Early 1990s
- ATO : Early 1990s
- Maintenance CT / Adjuvant Therapy
- Cure rate of 80 – 90%: who survive induction/ consolidation.

MOLECULAR PECULIARITIES:

It arises from more committed stem cell; absence or low expression of MDR protein; presence of coagulopathy; sensitivity of leukemic cells to ATRA / CT / DAUNO.

DIAGNOSIS:

***Morphology*:** All patients should have a marrow aspirate. This may be omitted only when the peripheral blast count is very high and the patient is to be considered for palliative treatment only. A trephine biopsy is required only in the case of a dry marrow aspirate and where no abnormal cells are present in the peripheral blood (PB) to allow a morphologic and molecular diagnosis. Morphologic studies require Leishman stain, myeloperoxidase, etc. Immunophenotyping by flow cytometry can increase the accuracy of morphologic diagnosis. APL blast cells are CD34 –/+ heterogenous, CD 117 –/+ dim, HLADR –/+ dim, CD13 +/++, CD11b– and abnormal low levels of CD15. Blasts of hypogranular variant form of APL (M3V) frequently coexpress the T linkage affiliated marker CD2 with myeloid markers CD13 and CD33.

***Karyotyping*:**

FiSH Analysis: FiSH analysis of PML/RARA can be carried out using standard methods and commercially available fluroscently labeled probes. This methodology is highly specific and sensitive, and much less expensive and time-consuming than karyotyping.

RT–PCR: RT–PCR analysis of PML–RARA is carried out on RNA extracted from bone marrow (BM) and blood samples. It is highly specific, sensitive and is "gold standard". It is essential for monitoring of minimal residual disease (MRD).

Immunostaining: Immunostaining with anti-PML monoclonal antibodies on dry smear of BM or PB (provided circulating blasts are present) is helpful to achieve a rapid diagnosis. This test is highly specific and can be completed in 2 hours.

Prognostic indicators are TWBC at initial presentation, age, TPC, abnormal creatinine, increased peripheral blast, presence of coagulopathy, FLT_3 mutation – 35% of APL cases, bCr_3 isoform of PML – RARα, CD56 expression.

Risk Stratification for Relapse:

Low Risk : WBC 10 x 10^9/L & Platelet > 40 x 10^9/ L

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Intermediate Risk: WBC ≤10 x 10^9/L & Platelet ≤ 40 x 10^9/L

High Risk: WBC > 10 x 10^9/L & Platelet ≤40 x 10^9/L

TREATMENT: will be discussed in the following headings:

- Induction
- Consolidation
- Maintenance
- Supportive

Induction C-T:Aim is to achieve complete remission (CR). Regimens available are ATRA :High CR, high relapse; ATRA + Anthracycline ; ATRA + Anthracycline + Ara–C ;Arsenic Trioxide (ATO).

Chemotherapy (CT) Vs ATRA + CT: European APL Group(Blood 1993: 3241-49),North American inter group(NEJM 1997: 1201-08). It showed a better outcome in ATRA + CT; Low relapse while CR, Early death remained the same.

a. ATRA + CT Vs ATRA →C-T (Sequential):

Cooperative Group	C–T	n	C–R n (%)	CIR %	OS %
GIEMA *Mandelli et al, 1997; Blood: 1014*	ATRA + Idar	253	229 (95)	NA	87 (2yr)
European APL *Fenaux et al; Blood 1999: 1192*	ATR + Daun + Ara–C	99 163	NA (94) NA (90)	11 (24) 29 (24)	84 (2yr) 77 (2yr)
MRC *Burnett AK et al 2000; Leukomia: 1362*	ATRA + Dauno + Ara–C	120	NA (87)	20 (44)	71 (4yr)
GAMLCG *Lengfelder et al 2000: Leukemia: 1362*	ATRA + Dauno + Ara–C + Thioguanine	51	47 (92)	NA	88 (2yr)
PETHEMA *Sanz et al 1999; Blood: 3015*	ATRA + Idar	123	109 (89)	NA	82 (2yr)
PETHEMA *Sanz et al 2004; Blood: 1237*	ATRA + Idar	251	227 (90)	7.5 (34)	85 (3yr)

b. Role of Ara–C:

Study	Regimen	Benefits
European APL JCO 2006: 5703	ATRA + Dauno Vs ATRA + Dauno + Ara–C	CR : Same Relapse – Yes
Bunnett AK et al; Blood 2007: 181a	ATRA + Idar Vs ATRA + Idar + Ara–C	CR, Relapse, OS – Same Increase death in Ara–C
Sanz et al; Blood 1999: 3015	-do-	No difference

Controversy continues to exist. Recommended to be added in high risk category.

a. Choice of Anthracyclin: Any of Daunorubicin, Idarubicin, Mitoxanotrone. No prospective studies conducted.

b. Recommendations:

Low and Intermediate Risk :

ATRA – 45 mg/m^2/day till CR or 90 days
Plus Anthracycline
Daunorubicin – 60 mg/m^2/day – 1-3 days Or
Idarubicin – 12 mg/m^2/day on days 2, 4, 6, 8

High Risk: Same as above Or
With Ara–C – 200 mg//m2/day – 1 to 7 days

Consolidation C-T: 90% of newly diagnosed APL cases will achieve CR, but 25 to 30% will relapse if consolidation and maintenance C–T are not administered. Thus, both consolidation and maintenance C.T are now routinely recommended. The objective of consolidation C–T is to achieve molecular remission (MR).

a. ATRA: Benefit of adding to CT – not demonstrated in randomized studies ,GIMEMA (2004) and PETHEMA (2004, 2008);better outcome if ATRA added for 15 days to CT; low relapse rate

ATRA – For 15 days is recommended in consolidation CT.

ARA–C:

Study	Benefit
PETHEMA (LPA – 99) Vs European APL – 2000 (Blood, 2008: 1078)	Yes (High Risk)
GIEMA (Blood 2004: 3920)	Yes
MRC 15 Trial (JCO 2000: 2620)	No
German AML Study (Leukemia 2000: 1362)	Yes
PETHEMA (LPA – 99 Vs 2005) (Blood, 2010, 115 (25): 5137)	Yes (High Risk)

N.B.: Controversial / Should be added to high risk category in patients < 60 yrs

a. RECOMMENDATION:

Low and intermediate risk

1st Month: ATRA – 15 days + DNR – 60 mg/m^2/day x 3 days.

2nd Month: Repeat DNR – 45 mg/m^2/day x 3 days

High risk

1st Month: ATRA + Dauno + Ara–C – 200 mg/m^2/day – 7 days.

2nd Month: ATRA + Dauno (45 mg/m^2/day – 3 days) + Ara–C – 1 gm/m^2/12 hr – 4 days.

3rd Month: If no MR.

ATRA + MTZ (10 mg/m^2/day x 5 days)

Maintenance C.T: Aim is to prevent relapse. Several PCR negative cases at the end of the consolidation CT will ultimately relapse especially in high risk category (WBC > 10 x 10^9/L at presentation). Randomized trials prove its beneficial effect only in high risk category. Thus, until further studies are

completed, maintenance C-T should be administered for 2 years in all the cases.

a. Benefit:

Study	Benefit
NAIS – 10129	Yes
APL 93	Yes
GIMEMA	No
JALSG – APL 97	No
European APL – 2009	Yes (High Risk)

b. Maintenance Therapy: Recommended in all cases for 2 yrs unless toxicity develops .

ATRA – For 15 days every 3 months

6 MP – 50 mg/m^2/day continuously

MTX – 15 mg/m^2/day weekly

Monitoring, dose modification – like ALL

SUPPORTIVE THERAPY: Most important and directly proportionate to the success rate. Complete blood count (CBC) and coagulation parameters should be done twice daily and once a day respectively. Liberal use of red cell, cryoprecipitate, fresh frozen plasma, platelet supports and other supportive measure are essential to maintain various parameters as follows : Hb > 9 gm%; TPC > 30 to 50 x 10^9/L; Fibrinogen > 150 mg/dl; PT, aPTT – As close as control value.

Liberal use of Red cell / FFP / Cryo / Platelet support; heparin, tranexamic acid, anticoagulant & antifibrinolytic therapy – Should not be used. Myeloid growth factor should not be used in induction. Other general supportive care are to be continued.

ADVERSE EFFECTS OF ATRA:

ATRA / APL differentiation syndrome : Add Dexamethasone – 10 mg BD x 2 weeks ;stop ATRA time being, if required ; prophylaxis with dexamethasone if WBC > 30 x 10^9/L

Sweet syndrome: Erythematous or pustular rash usually on elbows on 18th day after initiation of ATRA. Histology shows inflammation of subcutaneous tissue.

ASH PROTOCOL FOR DEVELOPING COUNTRIES:

Arsenic Trioxide (ATO): ATO helps in both differentiation and apoptosis of abnormal promyelocytes and blast cells in APL.

a. Benefit: Various studies proved its efficacy.

Remission Induction all patients)	DNR 60 mg/m^2/day (days 2,4,6 and 8)* ATRA 45 mg/m^2/day§ (day 1 until CR) Dexamethasone 2.5 mg/m^2/12h × 15 (if WBC > 5 × 10^9/L)			
Consolidation risk-adapted)	**Low-risk** (WBC ≤ 10 × 10^9/L Platelets > 40 × 10^9/L)	**Intermediate-Risk** (WBC ≤ 10 × 10^9/L Platelets ≤ 40 × 10^9/L)	**High-Risk** (WBC >10 × 10^9/L Platelets ≤ 40 × 10^9/L) **≥ 60 years old**	**< 60 years old**
	DNR 25 mg/m^2/day (days 1,2,3,4) ATRA 45 mg/m^2/day × 15	DNR 35 mg/m^2/day (days 1,2,3,4) ATRA 45 mg/m^2/day × 15	DNR 35 mg/m^2/day (days 1,2,3,4) ATRA 45 mg/m^2/day × 15	DNR 25 mg/m^2/day (days 1,2,3,4) Ara-C 1000 mg/m^2/day (days 1,2,3,4) ATRA 45 mg/m^2/day × 15
	MTZ 10 mg/m^2/day (days 1,2,3) ATRA 45 mg/m^2/day × 15	MTZ 10 mg/m^2/day (days 1,2,3) ATRA 45 mg/m^2/day × 15	MTZ 10 mg/m^2/day (days 1,2,3) ATRA 45 mg/m^2/day × 15	MTZ 10 mg/m^2/day (days 1,2,3,4,5) ATRA 45 mg/m^2/day × 15
	DNR 60 mg/m^2/day (day 1) ATRA 45 mg/m^2/day × 15	DNR 60 mg/m^2/day (days 1,2) ATRA 45 mg/m^2/day × 15	DNR 60 mg/m^2/day (days 1,2) ATRA 45 mg/m^2/day × 15	DNR 60 mg/m^2/day (day 1) Ara-C 150 mg/m^2/8 h (days 1,2,3,4) ATRA 45 mg/m^2/day × 15
Maintenance all patients)	**2 years** ATRA 45 mg/m^2/day × 15 (every 3 months) Methotrexate 15 mg/m^2/day (weekly) 6-Mercaptopurine 50 mg/m^2/day			

Drug	Author	N	CR %	MR %	EFS %	OS %
ATO + ATRA	Liu Y F et al 2004 (Blood: 2359)	60	93.3	ND	94.2 (44)	98 (4yr)
ATO + ATRA	E Stey E et al 2006 (Blood: 3469)	44	86.6	100	90 (24)	90 (2yr)
ATO + ATRA	Ravandy F et al 2009 (JCO: 504)	82	90	100	80 (24)	85 (2yr)
ATO	Ghavamzadeh A et al (Ann Oncol 2006: 131)	111	85.6	92	63.7 (24)	87.6 (3yr)
ATO	Mathews B et al, 2006 (Blood: 2627)	72	86	76	74.8 (34)	86.1 (3yr)
ATO	George B et al 2004 (Leukemia: 1587)	11	91	100	81.3 (54)	91 (5yr)
ATO	Jin Zhou et al 2010 (Blood: 1697)	19	89.5	ND	72.7 (54)	83.9 (5yr)

a. Current Status of ATO: Drug of choice for resistant / relapse cases ; High risk: In consolidation following ATRA + Dauno ; in induction and consolidation with ATRA where anthracyclines are contraindicated; persistence of MRD after consolidation; in induction in high risk – doubtful efficacy; cheap / can be used for poor patients .

b. Precaution during ATO Therapy:

i. QT interval assessment by ECG: withheld ATO, if > 500 msec.

ii. Electrolyte: Maintain K^+ > 4.0 mEq/L Mg^{++} > 1.8 mg/dl

MONITORING OF THERAPEUTIC RESPONSE:

CR: At the end of induction CT: Mandatory

Molecular Remission: RT-QPCR;no relevance after induction CT;at the end of consolidation: mandatory.

During and after maintenance: RT-QPCR once every 3 – 6 months upto 3 yrs after completion of consolidation CT.

Relapse / Resistant APL:

Induction of CR_2 (1,2) 2 x 25 day course of ATO followed by 4 courses of intrathecal therapy.

Consolidation (3,4):

If M.R. – High Ara–C →Autologous HSCT

If no CR – Allogenic HSCT

4 additional course of ATO if not eligible for HSCT

Clinical Trial

SPECIAL SITUATION:

Older Patients (> 60 yrs):Reduce dose of anthracycline; no Ara–C; ATO

Patients with severe comorbidities: ATO

Children & Adolescent: ATRA – 25 mg/m^2/day

CNS Relapse : CT for relapse cases + IT →Twice weekly until CSF clearance. Weekly for 4 wks, monthly for 4 to 6 months.

Therapy related APL : Essentially same, but consider the use of prior CT.

Pregnancy : Avoid ATRA in 1st trimester; Avoid ATO in all trimester; No breast feeding if ATO/C–T.

FUTURE THERAPY: The following regimens in phase – II and phase – III trials looks promising in future.

ATRA + ATO

ATRA + Oral ATO

Tamibarotene (AM–80) + Oral ATO

Gemtuzumab ozogamicin

CONCLUSION:

APL – a distinct sub-type of AML with t (15:17) (PML – RARα) as molecular hallmark. It is a

medical emergency which requires urgent treatment. Liberal use of blood components to correct coagulopathy & other supportive measures are very important. ATRA + Anthracycline based C-T are standard care for both low & intermediate risk groups at present. Maintenance for 2 yrs with intermittent ATRA, MTX & continuous 6MP are routine. Ara–C should be added in consolidation phase for high risk group. ATO – increasingly used both in resistant / relapse & new cases. A long journey since 1957 from highly fatal to highly curable disease (80% to 90% cure).

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Case Report

PATENT DUCTUS ARTERIOSUS AND CONGENITAL AORTIC STENOSIS - A RARE CO-EXISTENCE : CASE REPORT

M.Manjula,* D. K.Saw,* P.K.Rathor, N.Dhal,**S.N.Das,*** D.N.Moharana******

ABSTRACT

A 22 years old female patient presenting with features of Patent Ductus Arteriosus and severe Aortic stenosis-a rare entity. ***KEY WORDS****: Patent Ductus Arteriosus (PDA), Aortic stenosis (AS)*

INTRODUCTION:

Congenital heart diseases are the most common birth defects.While most cases undergo palliative or corrective surgery during childhood,some complex lesions may sometimes be first diagnosed in adolescence or adulthood . PDA is the most common type of extracardiac shunt and is defined as persistent patency of the ductus beyond 3 months of life .Congenital AS can occur at valve level (75%) sub valvular (23%) or supra valvular level(2%). The valve may be unicuspid, bicuspid or tricuspid. It usually runs a benign course till adulthood . The rare associated lesions with congenital AS are Coarctation of aorta , PDA and Peripheral Pulmonary artery stenosis .Here we have reported a case who has remained asymptomatic for 22years with features of PDA and severe AS .

CASE REPORT:

A 22 yr old LM presented with cough of 8 days duration which was non-productive in nature and not associated with fever, breathlessness or palpitations.There was no documented history of any cardiac illness in the past. There was no history of cyanotic spells or squatting episodes during childhood. On examination, patient was of average body built and nourishment, pulse rate was 90/min, normal volume and character, regular and no brachio-femoral or radio-radial delay. Blood pressure was 100/70 mmHg in right arm and 90/70 mm Hg in left arm, 110/70 mmHg in both lower limbs. Cardiovascular system examination: shape of the precordium was normal with prominent suprasternal and right carotid pulsations seen. Apex was located in left 7th intercostal space along anterior axillary line and was forceful, well sustained in character. There was a palpable systolic thrill in left 1st& 2nd intercostal space (along parasternal border), aortic area and also over the right carotid. Auscultation revealed a continuous murmur with multiple sounds interspersed within heard over left 1st and 2nd intercostal space along the parasternal border. Aortic component of the second heart sound was diminished and an ejection systolic murmur of grade 5/6 was heard in aortic area which radiated to the right carotid artery and was also heard all over the chest. Respiratory system, Gastrointestinal and Nervous system examination was normal.

INVESTIGATIONS:

Blood investigations were normal. ECG showed LVH pattern CXR showed Cardiomegaly. 2D Echo revealed Congenital heart disease- PDA with L to R shunt (4mm) and Severe Aortic stenosis (Gradient 113 mmHg, Tricuspid Aortic valve, AV area – 0.9 sq.cm).

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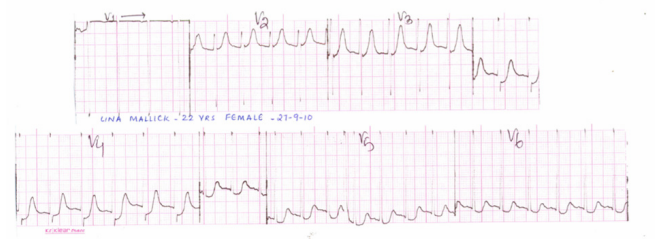

Fig: 1 ECG showing LVH

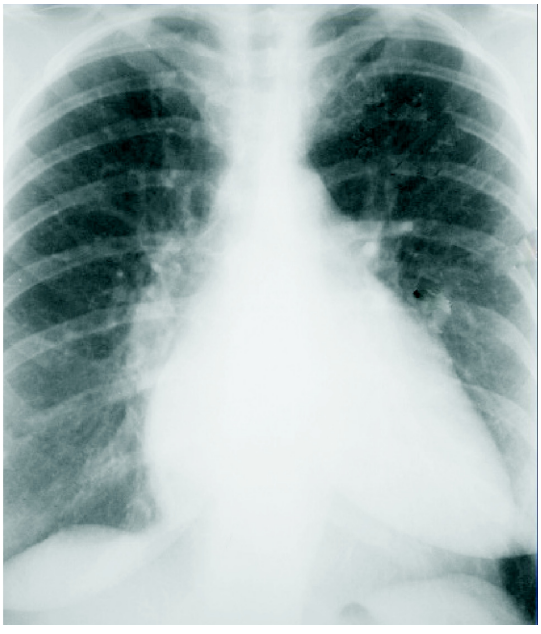

Fig: 2 Chest X-ray Pa View Showing Cardiomegaly

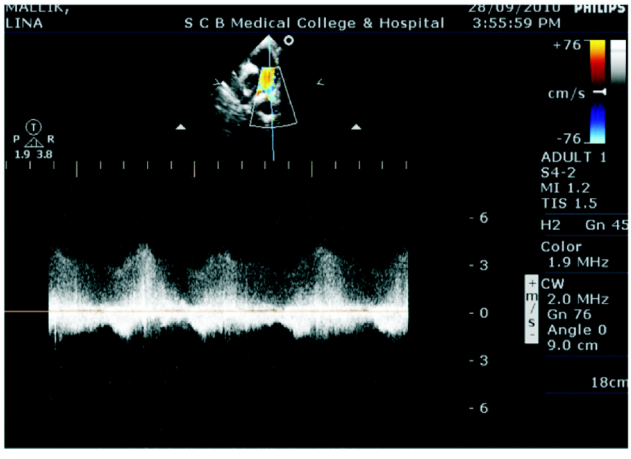

Fig: 3 Colour Jet Showing Flow In PDA (4 Mm) From Aorta To Pulmonary Artery

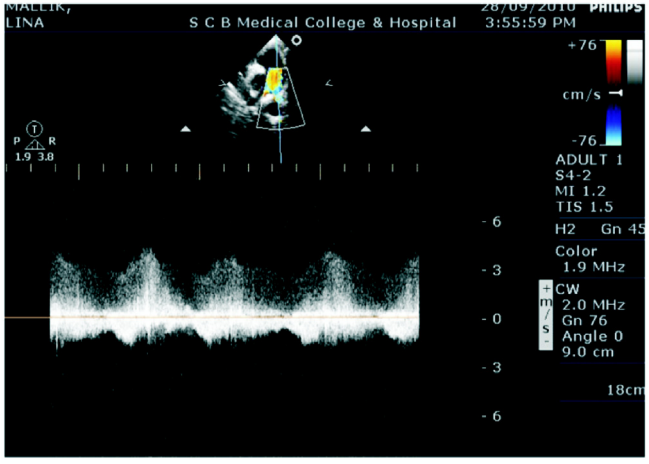

Fig: 4 Continous Doppler Flow Of PDA

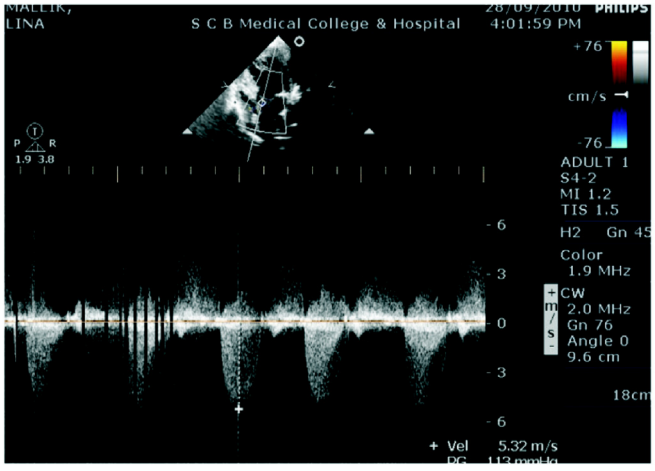

Fig: 5 Apical 5 Chamber View. Continuos Doppler Across Aortic Valve Showing Gradient Of 113 Mm Hg

Discussion:

Coexistence of PDA and AS is exceedingly rare with only 11 cases previously reported. Abnormalities of the left ventricle, aortic valve or aorta may sometimes lead to the ductus remaining open (complex hemodynamics). The hemodynamic effect of PDA and AS on each other has been elaborated by Bruckheimer and Colleagues in 1998. Assessment of PDA size and morphology with a coexistent severe AS in adults is usually by Colour Doppler or may rarely require cardiac catheterisation or multidetector row CT scan .It seems

likely that in our patient the dominant lesion - severe AS has masked the other lesion PDA. The stenotic aortic valve has ameliorated the flow across the PDA (relatively oligaemic lung field) and thus the patient has remained asymptomatic since birth. The prominent carotid pulsations in a case of severe AS may be explained by the Coanda effect where the powerful jet is directed straight into the innominate artery so as to build high pressure in the right carotid artery. Surgical management of the previously reported cases was done both in a single stage operation or a 2 stage procedure.

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Case Report

UNUSUAL PRESENTATION OF TUBEROUS SCLEROSIS AS END STAGE RENAL DISEASE

L.K. Meher*, J. Sarangi, S.N. Jali***, Suryanath K.R.******

ABSTRACT

A case of tuberous sclerosis who presented as end stage renal disease without any apparent neurological involvement is reported here with review of literature giving special emphasis on renal involvement. ***Key word :*** *Tuberous Sclerosis, Renal Disease.*

INTRODUCTION

Tuberous sclerosis (TSC) is a rare heredofamilial disease characterised by hamartomatous lesions in brain, skin, retina and viscera. Clinical diagnosis is easy when patient presents with classical triad of seizures, mental retardation and adenoma sebaceum. However due to incomplete penetrance, symptomatology may range from isolated organ involvement as in milder form to involvement of multiple organs. A case of tuberous sclerosis who presented as end stage renal disease without any apparent neurological involvement is reported here with review of literature giving special emphasis on renal involvement.

CASE REPORT

A 25 year old male was admitted to our medicine ward with complaints of , nausea, vomiting and decreased apetite of 3 months duration and high grade fever with chills and rigors for three days. There was no history of any convulsions.

On physical examination, there was moderate pallor and was detected to have hypertension with BP 160/110 mm Hg. There were multiple papulonodular

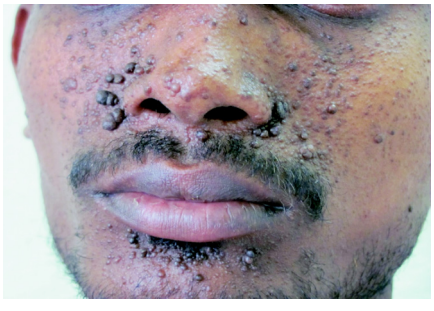

Fig 1 Adenoma Sebaceum

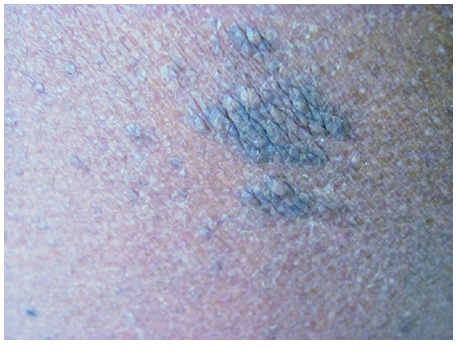

Fig 2. Shagreen Patch

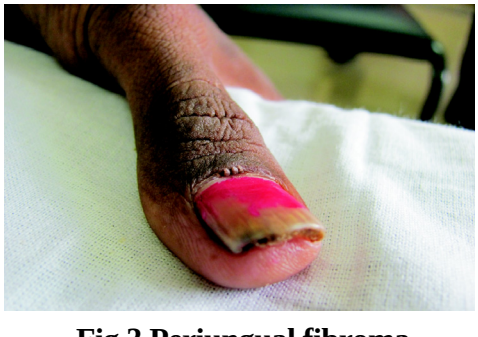

Fig.3 Periungual fibroma

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lesions over face mainly over nasolabial folds, which were angiokeratomas (Fig. 1). Shagreen patches(Fig.2), two in number, measuring 3 x 1 cm in size each were present over right lumbar region and left scapular region. Multiple periungual fibromas(Fig 3) were present over fingers and toes.

His abdominal examination revealed bilateral renal masses firm in consistency with irregular surface, which were ballotable. His higher mental functions were normal with normal intellect. No other abnormalities were present in CNS examination.

With the features of adenoma sebaceum , shagreen patches, peringual fibromas along with bilateral palpable renal masses, a provisional diagnosis of polycystic kidney disease in association with tuberous sclerosis was made.

Laboratory investigations showed,

Hb 7.6mg/dl, total count- 12400cells/cumm, DC N_{80} L_{17} E_2 M_1 B_0 , Peripheral smear – normocytic normochromic anemia with neutrophilic leukocytosis urine albumin ++, Urine microscopy- RBC- plenty, pus cells 20-25/HPF,

Urine culture revealed E.coli which was sensitive to ceftriaxone and Amikacin. FBS – 80mg/dl

S.urea – 158mg/dl, S. Creatinine 11 mg/dl,

Serum sodium – 135 meq/l and serum potassium – 5meq/l

GFR was 10ml/mt.

Ultrasonography of abdomen revealed multiple cysts of variable sizes in both cortex and medulla of both kidneys.

Plain CT scan of abdomen showed bilateral polycystic kidney with a fatty SOL of 6x4 cm size in left renal parenchyma lower pole suggestive of angiomyolipoma. Contrast CT was deferred due to higher creatinine level of patient.

Plain CT scan of brain showed multiple subependymal calcifications near both lateral ventricles with candle dripping appearance suggestive of tuberous sclerosis. Echocardiography was normal.

Patient was managed with antibiotics, antihypertensive drugs and hemodialysis.

DISCUSSION

Tuberous sclerosis , also known as Bournville's disease is an autosomal dominant multi system disease characterisesd by hamartomatous lesions in various organs of the body. The incidence of tuberous sclerosis in general population is about 1 in 6000 to 1 in 15000.[1] Although this neurocutaneous syndrome is well known for its skin lesions, seizures and mental retardation , it may present in multitude of guises, and affect almost any organ of the body which may vary from very mild (a few skin lesions, a specific neuroradiological finding of TSC on CT scan , but no evidence of fits or mental retardation) to severe (with fits that are difficult to control, or mental retardation and severe skin and visceral involvement) .

TSC exhibits locus heterogenecity with clinically indistinguishable disease being caused by mutations in two different genes, with one gene on 9q34,TSC1, and second gene on 16p13.3,TSC2. TSC1 gene product Hamartin and TSC2 gene product tuberin have been found to function as negative regulators of mTOR signalling pathway. TSC1/2 complex may modulate activity of Transforming growth factor â, and act as a tumour suppressor gene. The loss of function of this tumour suppressor gene may account for higher incidence of tumours in tuberous sclerosis.

The diagnosis of tuberous sclerosis is usually based on clinical and radiological findings devised by Roach etal,1999.(Table 1).[2]

Table 1 Diagnostic criteria for tuberous sclerosis (modified from Roach et al)

Definite diagnosis: Two major features or one major plus two minor features
Probable diagnosis : One major and one minor feature
Possible diagnosis: One major feature

Major features

Facial angiofibromas or forehead plaque
Periungual fibroma, nontraumatic ungula
Hypomelanotic macules, three or more
Shagreen patch
Multiple retinal nodular hamartomas
Cortical tuber[a]
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Renal angiomyolipoma or pulmonary lymphangiomyomatosis[b]

Minor features

Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter radial migration lines[a]
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
'Confetti' skin lesions
Multiple renal cysts

a) When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.

b) When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned.

This was a case of TSC, in view of 5 major features which included facial angiofibroma, periungual fibroma, shagreen patch, subependymal nodules,and renal angiomyolipoma and one minor feature,multiple renal cysts. He also had features of chronic renal failure with urinary tract infection.

Renal involvement is much frequent in tuberous sclerosis. Angiomyolipomas (AMLs) are the most common renal manifestation of TS developing during later childhood and adolescence. As the name implies, they are composed of blood vessels, smooth muscle and adipose tissue. The majority of adults have multiple bilateral lesions which are usually asymptomatic but can cause life-threatening haemorrhage or occasionally impaired renal function.

Renal cysts are also a common finding. They are usually asymptomatic except in the rare case of patients with both TSC and polycystic kidney disease owing to contiguous deletions of the TSC2 and PKD1 genes,which are located on chromosome 16p13.3. These individuals usually present with severe, early onset renal cystic disease (contiguous gene syndrome)[3] and progress to end-stage renal failure by early adult life. Renal cysts have a characteristic histology in TSC. They are lined with a hyperplastic epithelium consisting of eosinophilic, columnar cells with a "piled up" appearance. This allows them to be differentiated from both autosomal recessive and autosomal dominant polycystic kidney disease. They can arise from all portions of the nephron and are characteristically bilateral, multiple, and of variable size.

Patients with TSC also appear to have an increased risk of renal cell Carcinoma.

Not much studies have been conducted about prevalence of renal disease in TSC. According to the Cook et al study, prevalence of renal involvement in TSC was 61%. Angiomyolipomas were detected in 49%, renal cysts in 32%, and renal carcinoma in 2.2%. The prevalence of angiomyolipoma was positively correlated with age, compatible with a two hit aetiology. Renal cysts were the commoner lesion in young children, and their prevalence did not appear to be age related.[4]

Renal involvement in TSC is usually asymptomatic. Although renal disease is a frequent manifestation of tuberous sclerosis (TSC), chronic renal failure is rare. Initial presentation as chronic renal failure without neurological manifestations is extremely rare as occurred in our case and we came across only one case of TSC with initial presentation as chronic renal failure in literature.[5]Incidence of end stage renal disease is 1% in patients with TSC and normal intellect.[6]ESRD is much rare in TSC, but does contribute to significant morbidity and mortality.

The underlying renal pathology in TSC contributes to renal failure by a variety of mechanisms. Compression and/or replacement of the normal renal parenchyma by cysts, angiomyolipoma, or carcinoma; reduction in amount of normal tissue as a result of invasion by tumour or surgery.; or in cystic disease , hyperfiltration of the remaining glomeruli creating focal glomerulosclerosis.[6]

In patients with tuberous sclerosis, chronic renal failure is much more likely when renal cystic changes are present (with or without hamartomas) than when renal hamartomas are present alone,[7]as was our case which presented with both cystic disease and angiomyolipoma.

In our patient,angiomyolipoma was diagnosed based on CT findings. Angiomyolipoma tends to be small and multiple when associated with TSC. But in our patient, there was only a single angiomyolipoma of size 6x4cm which is rare, its large size making it prone for spontaneous haemorrhage requiring exploration. The majority of patients with AMLs remain asymptomatic. Intervention may be required for significant haemorrhage or suspicion of malignancy. Arterial embolization is effective in stopping haemorrhage. If surgery is required, preservation of renal tissue is an important consideration.

In older children and adults ultrasound scanning at 1–3 yearly intervals has been recommended to monitor the development and progression of renal AMLs[8], particularly with a view to elective embolization of AMLs exceeding a particular size (larger than 4 cm in one study[9]). However, the indications for treatment of asymptomatic AMLs are not well established and further studies are needed to confirm the benefits of screening and validate the criteria for intervention.

In children with polycystic kidney associated with TSC and in adults with extensive renal involvement, regular monitoring of renal function tests should be undertaken to assess the renal status which may help in prompt intervention and in retarding progress to end stage renal disease. Regular monitoring and control of blood pressure is also recommended in patients with renal involvement in tuberous sclerosis for prevention of complications.

Patients with TSC developing ESRD eventually require renal replacement therapy in the form of dialysis and renal replacement. Binephrectomy after starting dialysis and before renal transplantation is recommended, given the risk of cancer and bleeding related to angiomyolipomas.[10]

CONCLUSION

Though rare, ESRD can be a presenting manifestation of tuberous sclerosis and major predisposing feature is presence of cystic disease of kidney.

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Case Report

RAMSAY HUNT SYNDROME WITH 8TH CRANIAL NERVE PALSY IN A DIABETIC PATIENT

S. Patro,* G.C. Misra, L. Toppo,*** P. Khatua,******

ABSTRACT

Ramsay Hunt syndrome is a rare complication of herpes zoster in which reactivation of latent varicella zoster virus infection occurs in the geniculate ganglion causing otalgia , vesicular eruption on the external, middle and inner ear and a lower motor neuron weakness of the seventh (facial) cranial nerve. Because these symptoms are not always present at the onset, this syndrome can be misdiagnosed. The onset of a motor neuropathy involving VII cranial nerve makes it inherently different from the more typical presentation of shingles, which predominantly causes a sensory neuropathy. Around 10% to 20% of individuals will be affected by herpes zoster during their lives. Ramsay Hunt syndrome accounts for about 3% to 12% of all types of facial palsy, which is usually unilateral and complete and full recovery occurs in only about 20% of untreated patients. This syndrome commonly affects elderly, diabetics and immune deprived patients. Herpes zoster infection becomes severe in diabetic patients and can be a cause of unilateral facial palsy and unilateral Ramsay Hunt syndrome with involvement of adjacent cranial nerves. In this article, a case of diabetes mellitus with unilateral Ramsay Hunt syndrome is described where involvement of VIII cranial nerve was also observed. This patient was treated with regular insulin, labyrinthine sedatives, and acyclovir having a good recovery. ***Keywords:*** *Ramsay Hunt syndrome, varicella zoster, geniculate ganglion, otalgia, diabetes , labyrinthine, acyclovir.*

INTRODUCTION:

Herpes zoster has been described in all age groups, and lifetime risk is estimated to be 10%-20%. The incidence of herpes zoster is about 150-300 cases per 100 000, with the incidence dramatically increased in patients older than 60 years. Ramsay Hunt syndrome is much less common, approximately 5 cases per 100 000 population; nevertheless, it is the second most common cause of atraumatic facial paralysis. Herpes zoster oticus (Ramsay Hunt syndrome) accounts for about 3% to 12% cases of the facial palsy.Compared with Bell's palsy, Ramsay Hunt syndrome generally has more severe paralysis at onset, paralysis is usually complete, patients are less likely to recover completely and full recovery occurs in only about 20% of untreated patients.

Ramsay Hunt syndrome is a viral infection involving external, middle and inner ears resulting from aggravation of varicella - zoster virus (VZV), present in a latent state within the sensory ganglion of facial nerve. Some precipitating factor may reactivate it especially when immunity of patient wanes leading to Herpes zoster, a sporadic disease. Classical clinical presentation includes pain on pinna, followed by vesicular eruption on external canal and pinna. Facial paralysis, if present, characterizes Ramsay-Hunt syndrome, and almost accompanies the surge of cutaneous blisters. A variable degree of involvement of the 8th cranial nerve, manifested by auditory and vestibular symptoms (hearing loss and vertigo) are

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present in approximately 20% of the cases. In 1907, James Ramsay Hunt described a syndrome of otalgia, auricular vesicles and peripheral facial paralysis. At that time, it was well accepted that infection of ganglia and skin by a herpes virus produced a characteristic dermatomal distribution of pain and vesicular rash. Hunt hypothesized that this syndrome was a result of herpetic infection of the geniculate (seventh nerve) ganglion. He also described other accompanying signs and symptoms including tinnitus, hearing loss, nausea, vomiting, vertigo and nystagmus. It is now known that reactivation of varicella zoster virus (VZV) after primary varicella infection precipitates Ramsay Hunt syndrome **(Box 1)**.

Box 1. Clinical features of Ramsay Hunt syndrome

Key clinical features

- Acute peripheral facial paralysis
- Vesicles occurring anywhere along the sensory distribution of the facial nerve, including the anterior two-thirds of the tongue, the pinna or the external auditory canal
- Otalgia

Additional clinical features

- Tinnitus
- Hearing loss
- Vertigo
- Nausea
- Vomiting
- Nystagmus
- Change in taste perception

Case report:

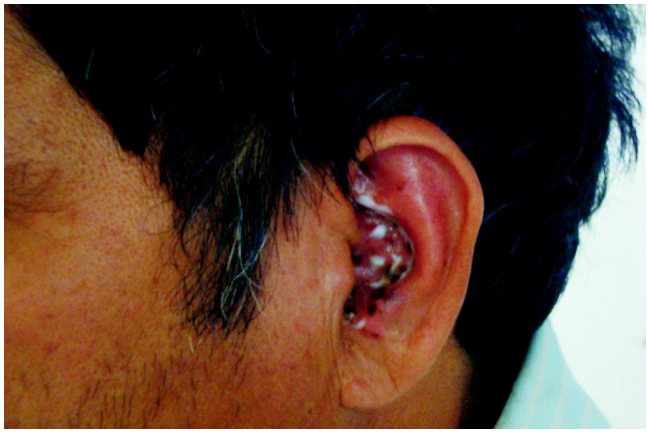
A 47 year old diabetic male on OHA presented to us with history of pain in left ear for the last 6 days. Twenty-four to forty-eight hours after the onset of otalgia, patient developed deviation of angle of mouth to right side along with vesicular eruptions on left concha and in left external auditory meatus. It was associated with reeling of head, left-sided facial droop, inability to close the left eye and numbness on the left side of the face. There was no numbness, tingling or weakness in his extremities. He was complaining of dribbling of saliva from the angle of mouth on the left side. On the day of reporting to us, the patient was having unilateral facial weakness, impaired taste sensation, dryness of left eye along with vertigo and discharge from left ear. Since last 2 months he was under stress for certain family problems.

On examination, he had good general health and was afebrile. There was unilateral lower motor neuron facial palsy which was complete. Bell's phenomenon was present on left side (**FIG 3)**. Left pinna and left external auditory canal had hyperemia and multiple vesicular lesions, some of them already ulcerated. Tympanic membrane was intact. The oral cavity and oropharynx were normal, with no vesicles. No nystagmus was noted. His pupils were normal in size, equal, round, and reactive to light. Extraocular movements were intact. Fundoscopic examination of both the eyes revealed no abnormality. Other systemic examinations including a thorough neurological examination were unremarkable excepting for impaired taste sensation from anterior two third of tongue. The patient was admitted and investigated. His postprandial blood sugar was 290 mg%, HbA1c was 12.2 %. Pure tone audiometry was showing mild to moderate unilateral sensorineural hearing loss on the left side with loss of stapedial reflex on tympanometry on the same side. ELISA and Western Blot tests for HIV infection were negative. Liver function tests, renal function tests and thyroid function tests were all within normal limits. Lumbar puncture revealed normal pressure. Glucose, protein and white blood cell count were all within normal limits in CSF. Plain X-ray views of mastoid, internal auditory meatus and chest were normal. Computerized tomography of brain stem, cerebellopontine angle, temporal bone and skull base were normal. This diagnosis was confirmed by detection of IgM antibodies to Varicella-Zoster virus by ELISA test.

Blood sugar was controlled with regular insulin. Oral acyclovir was given in a dose of 800 mg. five times daily for 7 days. Steroids were avoided in this patient due to diabetes, but NSAIDs were given. As the patient was having vertigo at the time of admission,

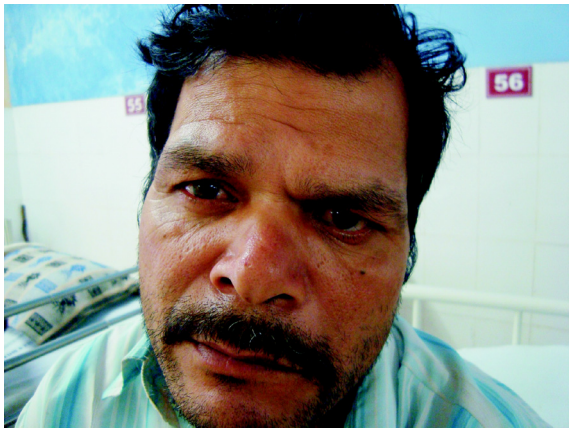
labyrinthine sedative was started after consulting otorhinolaryngologist. Topical antibiotic was applied to the lesions in the external ear to prevent further secondary infection locally. All along his treatment physiotherapy was continued. After 1 week of treatment and diabetes control, patient started improving clinically. Pure tone audiometry showed improvement in hearing. Eight weeks later in the follow up, patient was able to close his eyes completely and facial nerve functions of left side recovered.

(**Figure 1**)



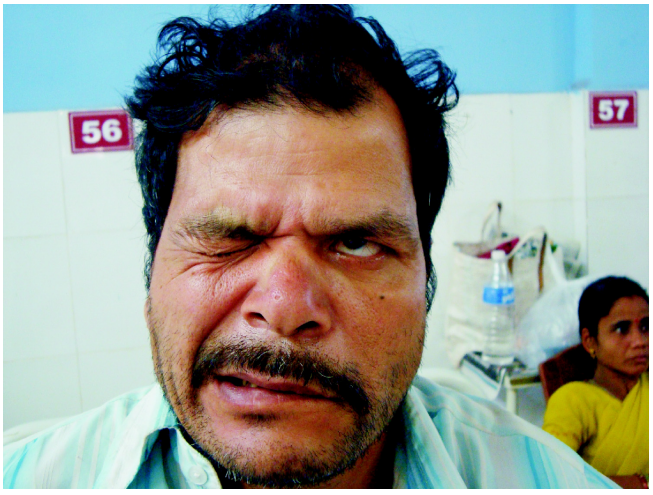
Patient at time of presentation, photograph showing left pinna and left external auditory canal showing hyperemia and multiple vesicular lesions, some of them already ulcerated.

(**Figure 2**)



Upper part of face (Lt.) does not escape – infranuclear type of facial nerve palsy (Lt.)

(**Figure 3**)



Upper part of face (Lt.) does not escape – infranuclear type of facial nerve palsy (Lt.)

Patient at time of presentation, photograph showing unilateral lower motor neuron type of facial palsy and presence of Bell's phenomenon.

DISCUSSION:

After primary infection with VZV, latent infection is established in the sensory dorsal root ganglia. A decline in host immunity, usually in elderly, diabetics and immunocompromised individuals, results in reactivation of the virus from latency. This is followed by the spread of reactivated virus to the skin through axons, causing a radicular pain and rash in the form of vesicles on an erythematous base with characteristic dermatomal distribution. Dermatomal pain may precede lesions by 48-72 hours and total disease duration may be 7-10 days. Reactivation of VZV from the geniculate ganglion, can cause peripheral facial weakness as well as rash around the ear, known as Ramsay Hunt syndrome.[1] Severity and incidence of herpes zoster increases in elderly and in immunocompromised states like in AIDS, lymphoproliferative disorders, disseminated carcinomatosis, diabetes, during steroid therapy and during radio or chemotherapy.[2,3] Rarely in such patients zoster may successively involve further dermatomes. In severe cases of herpes zoster oticus (Ramsay Hunt syndrome), involvement of vestibulocochlear nerve leads

to sensorineural hearing loss in 10% and vestibular symptoms in 40% patients. The same was also observed in our case. Concomitant involvement of multiple sensory ganglia by VZV was first noted by Hunt in 1910. He remarked the typical Ramsay Hunt syndrome along with the eighth nerve features including tinnitus, hearing loss, nausea and vertigo. Likewise, Sharpe et al reported atypical cases of Ramsay Hunt syndrome in which upper cervical dermatomes and multiple cranial nerves were simultaneously involved. Nonetheless, the term "*Ramsay Hunt Syndrome*" is commonly believed to be used for those with involvement of the external auditory canal, but not for the cases with involvement of other cranial or cervical nerves or ganglia.[1]

The diagnosis is based on history and physical examination. Gadolinium-enhanced magnetic resonance imaging and cerebrospinal fluid examination have no diagnostic or prognostic value. Polymerase chain reaction (PCR) can detect VZV in saliva, tears, middle ear fluid and blood mononuclear cells, but it is not necessary to establish the diagnosis.[4] In addition, the appropriate serologic assays (VZV IgM and IgA antibodies) on CSF, serum and vesicular fluid may also detect VZV infection.[1] Ramsay Hunt syndrome can be misdiagnosed at initial presentation, particularly in the absence of skin lesions. In approximately 10% of cases, there is no vesicular rash with the facial paralysis, but there is either a 4-fold rise in antibody to VZV or the detection of VZV DNA in skin, blood mononuclear cells or middle ear fluid. This condition is known as Ramsay Hunt syndrome sine herpete.[5]

Kubeyinje EP.(1995) reported that varicella runs more aggressive course in diabetic patients as compared to otherwise healthy individuals.[6] Neu I et al (1977) in their study found basal metabolic disorders especially diabetes of particular significance in activation and in primary and secondary manifestations of varicella zoster virus.[7] Muller C. et al (1989) concluded that metabolic derangement in diabetes leads to reversible disturbance in certain cellular immune functions which can be normalized by good metabolic control achieved by insulin treatment.[8] During admission to the medicine ward the patient had had a PPBS of 290 mg. %. His blood sugar was controlled by regular insulin with titration of blood sugar two hourly. Patient was also under severe psychological stress for the last 2 months. Psychological stress is identified as a potential risk factor for zoster that might operate by suppressing cell-mediated immunity.[9] So uncontrolled diabetes and psychological stress were two risk factors present in this patient, making him prone for infection of herpes zoster.

Good metabolic control of diabetes improves leukocyte functions and overall immune status of patient, so insulin was started and dose was adjusted to achieve good metabolic control.[8]As incidence of severe and disseminated infections of Herpes zoster is more common and severe in diabetes and as the patient was able to take orally, oral acyclovir was given. Recent reports suggest that treatment with acyclovir decreases the incidence of permanent facial nerve palsy in Ramsay Hunt Syndrome. Prompt diagnosis and management improves the outcome in Ramsay Hunt syndrome. Importantly, no statistically significant outcome differences were noted between patients treated with intravenous or oral acyclovir. A large prospective study demonstrated that combination therapy with acyclovir and steroids led to better recovery of facial nerve function than either of the drugs used alone, but glucocorticoid therapy was avoided in our patient due to uncontrolled diabetes.[3]

Published trials typically administered acyclovir at 800 mg by mouth 5 times a day for 7-10 days, but there are no existing data describing outcomes with other antiviral agents.[4] According to study reports, acyclovir has proved to reduce significantly the duration of the disease, pain and ocular complications. Early treatment with acyclovir showed to be effective in herpes zoster infections and in preventing complications. The early start of therapy with anti-viral agents is likely to have contributed to the good progression of our case.

Ramsay Hunt syndrome patients should have ophthalmology assessments to evaluate them for ocular complications of facial nerve palsy, since incomplete

eye closure exposes the cornea to drying and foreign body irritation. Mild facial paresis usually does not require therapy, but moderate to severe deficits require a corneal moistening regimen consisting of artificial tears during daytime and lubricating ointment at night. Taping of the lower eyelid to the lateral canthus can also be used to improve lid closure.[4]

CONCLUSION:

Ramsay Hunt syndrome can have variable clinical presentation. Physicians need to be aware that the peripheral facial paralysis, vesicular rashes and otalgia do not always present at the same time and may take time to evolve before declaring themselves as Ramsay Hunt syndrome.

Herpes zoster can cause severe infections in diabetic patient and can cause unilateral or bilateral Ramsay Hunt syndrome. It should be treated with appropriate metabolic control, NSAIDS and intravenous/ oral acyclovir at the earliest preferably within 72 hrs from start of the disease. Early treatment of infection enables a favorable progression of the case, preventing disabling motor nerve sequelae. Glucocorticoids should be avoided in Herpes zoster patients having uncontrolled diabetes.

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Case Report

RECURRENT REVERSIBLE JAUNDICE, DEMENTIA, NEUROPSYCHIATRIC MANIFESTATION AND CEREBELLAR ATAXIA – A RARE MANIFESTATION OF VITAMIN B12 DEFICIENCY

Parhi L*

ABSTRACT

This is a case of an adult who presented as recurrent dementia with cerebellar Ataxia, always preceded by jaundice and was found to have severe vitamin B12 deficiency with positive antiparietal cell antibody. ***Keywords:*** *Dementia, jaundice, cerebellar ataxia.*

INTRODUCTION:

Vitamin B12 deficiency had varied neurological manifestations including neuropathy, myelopathy, cerebellar ataxia, optic neuropathy, dementia, neuropsychiatric manifestations occurring alone or in any combination.[1,2,3]

The neurological manifestation may be episodic or progressive depending upon the etiology and intake of B12. There are few cases reported in literature showing recurrence of symptoms in B12 deficiency[2]. Here I am reporting an interesting case who presented with two episodes of mild to moderate jaundice, followed each time by dementia and cerebellar ataxia. Investigations revealed severe B12 deficiency with positive antiparietal cell antibody and biopsy of stomach showed chronic gastritis with metaplasia. Patient responded dramatically to injection vitamin B12.

CASE REPORT:

This 36 year old Hindu male, born of a nonconsanguious marriage, a vegetarian and who had completed engineering and presently engaged in business, had history of yellowish discoloration of Conjunctiva and urine 3 years back. It was not associated with fever, loose motion, steatorrhoea, itching, pain abdomen, swelling of abdomen, hematemesis, melena or vomiting. He took some medication for jaundice. After 1 month of this symptom, he had bilateral incoordination of limbs associated with slurred speech. It was associated with forgetfulness mainly to recent things with change of personality and behavior, resulting in gross impairment of previous level of function. It progressed over few weeks after which it was static. The treating physician at that time suspected him to be suffering from Wilson's disease and investigated accordingly. C.T. Scan of head, serum ceruloplasmin, 24 hour urine copper estimation and EEG done at that time was within normal limit and KF ring was negative. He was put on levodopa and trihexyphenidyl. There was no definite evidence of treatment with B- complex. His symptoms completely improved after 3 months and patient continued to take trihexyphenidyl and vitamin E. At that time serum B_{12} estimation and MRI cranium was not done. There was no history of alcohol intake or any significant drug intake.

One and half months back, again he had yellowish discoloration of conjunctiva and urine. It was not associated with fever or signs of liver failure. After 15 days he had again developed similar forgetfulness, change of behavior, insomnia and in-coordination of all limbs which progressed over few weeks and then became static. On examination he had lcterus, but not associated with pallor, lymphadenopathy and KF ring was negative and there was no hepatosplenomegaly. On higher mental examination he had MMSE(mini

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mental state examination) of 20/30(recall was 0/3). He had impaired judgement, recent memory and calculation. Speech and language was normal. Fundus was normal. All deep tendon reflexes were exaggerated but plantar was flexor. Bilateral knee-heel test and finger-nose test was abnormal and there was no truncal ataxia. There was no nystagmus, saccadic or pursuit abnormality and also there was no pendular jerk or hypotonia. Investigations revealed hemoglobin of 9.1 gm%, MCV = 103.1 fl, reticulocyte count of 4.8%. Total serum bilirubin was 7.7 mg% with indirect bilirubin of 6.6 mg% and direct bilirubin was 1.1 mg%. SGOT,SGPT were within normal limit. HBsAg, HCV, HIV, was negative. Bone marrow examination showed megaloblastic picture. Ultrasound of abdomen was normal. MRI cranium showed mild diffuse cerebral atrophy. Serum B12 level was 67 pg/ml and homocysteine level was 60 nmol/ml. Antiparietal cell antibodies were positive and gastric biopsy revealed feature of chronic gastritis with metaplasia

Patient was given injection vitamin B12 (optineuron), 1000 mg intramuscular daily for 7 days, followed by alternate day for 2 weeks, weekly once for 2 months followed by once in a month. He had started improvement after 1 week of treatment, with complete resolution of symptoms after 1 month.

DISCUSSION

Low levels of vitamin B12 associated with dementia, neuropsychiatric manifestations and cerebellar ataxia either alone or in combination have been documented in various cross-sectional studies in literature[1]. In fact being an important treatable cause one must be prompt in identifying this cause.

The present case was rather unusual in that, each time patient had jaundice for about a month, followed by dementia and cerebellar ataxia. With the above clinical symptomatology, Wilson's disease, chronic liver disease, recurrent drug/toxin exposure were the obvious causes which were thought initially. However, complete resolution of symptoms after each attack without any documented copper chelating therapy made Wilson's disease unlikely. Biochemical parameters for Wilson's disease were normal and KF ring was absent. Patient was a non alcoholic, with no preceding history suggestive of any chronic liver disease, drug or toxin exposure or any associated endocrinopathy. The above were adequately excluded on basis of clinical and appropriate biochemical investigations.

Presence of predominantly unconjugated hyperbilirubinemia, a decreased hemoglobin level with macrocytosis, complete resolution of symptoms every time and patient being a pure vegetarian prompted us to investigate the patient for vitamin B12 deficiency, which was found to be significantly low with a concomitant rise in level of serum homocysteine. Bone marrow revealed megaloblastic changes, antiparietal cell antibody was positive and stomach biopsy revealed features of chronic gastritis with metaplasia, all corroborating our diagnosis. Also, so high serum bilirubin (total of 7.7 mg% with indirect bilirubin of 6.6mg%) is probably not reported in B12 deficiency previously.

CONCLUSION

This case highlights the importance of recognizing vitamin B12 deficiency as an important inexpensive treatable cause in patients presenting with recurrent reversible jaundice, dementia and ataxia. Our patient had dramatic improvement with complete resolution of symptoms after one month with vitamin B12 injections. Hence the importance for prompt evaluation and early starting of treatment to achieve maximal possible benefit of this potentially treatable condition cannot be underestimated.

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Case Report

SNAKE BITE PRESENTING AS PANHYPOPITUITARISM

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ABSTRACT

Panhypopituitarism is a rare endocrine manifestation of snake bite (Russell's Viper). Patients usually presents months to years after the snake bite with – weakness, loss of secondary sexual hairs, loss of libido, amenorrhoea, testicular atrophy, sheehan's syndrome, hypothyroidism, hypoglycemia, shock etc, due to haemorrhegic infarction of anterior pituitary/adrenal gland following a vasculotoxic (Russell's viper) snake bite[1,2]. We report here a patient of snake bite who presented with hypothyroidism and shock and responded to Thyroxine and hydrocortisone treatment.

Keywords : *Panhypopituitarism, shock, hypothyroidism, snake bite (Russell's viper).*

INTRODUCTION

There is a wide range of endocrine manifestation following a vasculotoxic snake bite (Russell's viper) including hypopituitarism (Loss of libido loss of secondary sexual hairs, testicular atrophy, hypothyroidism), Adrenal insufficiency (shock), pancreatic insufficiency etc. Earlier acute pituitary/ adrenal insufficiency following Russell's viper bite have been reported in South East Asia. Panhypopituitarism is one of the chronic manifestation of the endocrine disorder following the viper snake bite[1,3].

CASE REPORT

A male patient of 35 years presented with pain abdomen, vomiting and altered sensorium for 5 days there was no history of fever, convulsion, loose motion. He had past history of snake bite 1 years back, who was admitted to SCB Medical College & hospital with pain and swelling of right leg with excess bleeding from the wound, epistaxis and hematemesis & melena and subsequently develops acute renal failure and shock for which he was treated with Anti-snake venom and conservative measures and dialysis. There was past history of repeated hospital admission within last 1 year with vomiting and altered sensorium which improved with I.V. fluids. He had not past history of Diabetes, hypertension, asthma & other bleeding disorders.

On examination, he was found to have moderate pallor, afebrile, pulse : 106/min, blood pressure : 80/60 mmHg. On neurological examination patient was stuporous with no focal neurological deficit and no meningeal signs. Chest and cardiovascular examination revealed no abnormality and abdominal examination was normal.

Laboratory investigation shows Hb%-8gm/dl, TLC-6,500/cmm, Serum urea-22 mg/dl & creatinine 0.9 mg/dl, serum Na+ - 116 meq/L & K+ 2.9 meq/L, CT scan of brain was normal. Thyroid function test shows - FT3- 2pg/ml, FT4-0.2ng/ml & TSH- 0.06µu/ml and serum cortisol (Morning) - 2 µgm/dl.

Thus it was diagnosed as a case hypopituitarism. Patient was put on injection hydrocortisone 2ml 6hourly and thyroxine (Thyrox) 100 µgm daily, intravenous fluids and other supportive measures for 7 days. Patient regained consciousness with improvement of blood pressure. The patient was

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discharged with oral prednisolone (5mg and 2.5mg) and thyrox (100 µgm) daily and advised for follow up.

DISCUSSION

The diagnosis of panhypopituitarism was confirmed in this patient by history of vasculotoxic snake bite with bleeding manifestation, with laboratory features of hypothyroidism and low cortisol with clinical features such as shock.

The pathophysiologic mechanism of panhypopituitarism may result from haemorrhagic infarction of the anterior pituitary gland following vasculotoxic snake bite (Russell's viper).

Patient responded quickly to intravenous hydrocortisone, oral thyroxine and other supportive measures.

Thus it is concluded that panhypopituitarism is one of the rare chronic endocrine manifestation of snake bite, especially in vasculotoxic snake (viper) bite.

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Case Report

GUILLAIN BARRE SYNDROME FOLLOWING FALCIPARUM MALARIA

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ABSTRACT

An adult male who was admitted for plasmodium falciparum malaria and was recovering after treatment, developed acute lower motor neuron type of quadriparesis. Clinical examination and Nerve conduction studies confirmed the rare association of Guillain Barre Syndrome (GBS) following falciparum malaria. ***Key words :*** *Guillain Barre Syndrome, Falciparum Malaria.*

INTRODUCTION :

Acute inflammatory demyelinating polyneuropathy or GBS following falciparum malaria is rare. Neurological complications frequently seen following falciparum malaria are cerebellar disturbances, extrapyramidal tremor, bulbar paralysis, cranial nerve lesions and transient paranoid psychosis[1].

Only sporadic cases of acute polyneuropathy following plasmodium falciparum and vivax infections have been documented.[2,3,4,5,6]

We are reporting here a case of GBS following plasmodium falciparum malaria.

CASE REPORT:

A 62 years old male was admitted for fever with chills and rigor for 5 days and altered sensorium for 1 day. He had no headache, vomiting, jaundice, seizure or any weakness. He was neither diabetic nor hypertensive. There was no history of any other recent illness or recent vaccination.

On examination, he was febrile, pulse -108/min, BP- 100/70 mmHg, resp.rate- 24/min. Neurological examination showed that he was drowsy, without any focal neurological deficit or meningeal signs. Plantar response was extensor bilaterally. Respiratory, cardiovascular, and gastrointestinal system examination revealed no abnormality.

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His haematological examination showed ring forms of Plasmodium falciparum and antigen test (ICT) was strongly positive for Plasmodium falciparum. His Hb-10gm%, TLC-4400/cmm, DLC-N50, L-41, E-9, ESR-38, FBS-88mg/dl, Blood urea-85mg/dl,S.creatinine-2.4mg/dl, S.Na-138mEq/l,S.K-3.8mEq/l and normal LFT. So a diagnosis of severe falciparum malaria with renal failure was made and he was treated with Artesunate. He underwent haemodialysis once and on the third day he started improving. He became fully conscious and ambulant on the fourth day.

On the fifth day(10 days after onset of fever) he developed weakness of lower limbs followed by upper limbs which progressed over the next three days and he became bed-bound. There was no facial weakness and no bladder or bowel disturbances. On examination of the CNS, higher functions were normal, cranial nerves were intact and there was lower motor type of quadruparesis. Muscle power was reduced to grade 2/5 in lower limbs, and 3/5 in upper limbs. There was hypotonia but no fasciculation. All deep tendon jerks were absent. Plantar response was flexor bilaterally. Nerve conduction studies of bilateral common peronial and posterior tibial nerves showed prolonged distal latencies, grossly diminished amplitude and diminished velocities. Sensory nerve conduction in both upper and lower limbs was absent. F wave latencies were diminished in both upper and lower limbs. This was suggestive of mixed demyelinating and axonal neuropathy involving both motor and sensory nerves and radiculopathy,which was consistent with a diagnosis

of GBS. As the patient could not afford IVIG, he was not given any specific treatment. He improved gradually and was discharged after12 days when his muscle power was4/5 in all limbs.

DISCUSSION:

Viruses are the most common organisms responsible for causing GBS. P.falciparum and P.vivax infections have documented to cause GBS in very few sporadic cases. In our patient P.falciparum infection was confirmed and the features of acute polyneuropathy developed after 10 days of infection. Nerve conduction studies confirmed the diagnosis of GBS and therefore a causal relationship between P.falciparum and GBS is assumed, as there was no other history of illness or vaccination in the recent past.

A review of 14 cases (13 previously reported and the present one) revealed that 10 cases had preceding falciparum malaria and 4 had vivax infections. Eleven of them had distal symmetric sensory deficits. Paralysis was mild in 9 cases (3 due to P.vivax and 6 due to P.falciparum) and recovered completely in 2-6 weeks without any specific treatment. 4 patients with falciparum malaria developed severe paralysis with respiratory failure and 3 patients died. There was one case of severe GBS following P.vivax infection requiring ventilatory support and IVIG therapy[3].

The exact pathogenesis of GBS following malaria infection is not known, but is likely to be immunogenic like that occurring after bacterial or viral infections[7]. Other mechanisms suggested for the development of polyneuropathy following a parasitic infection include parasitic emboli obstructing vasa nervosum, release of neurotoxins, associated metabolic and nutritional disturbances, immune mediated capillary damage, release of free radicals and tumor necrosis factor[4,8,9].

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Case Report

TUBEROUS SCLEROSIS - AN UNUSUAL CAUSE OF HYPERTENSION

S. Khadanga*, T. Karuna**

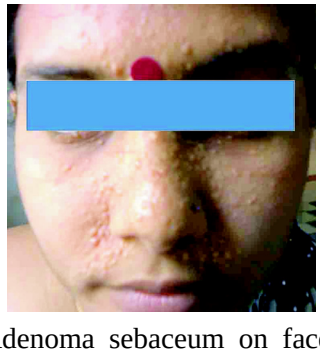
ABSTRACT

A case of Tuberous Sclerosis who presented with hematuria and hypertention without any apparent neurological involvement is reported herewith : an unusual presentation. ***Keywords :*** *Tuberous Sclerosis, Hypertension.*

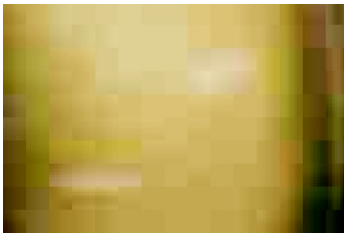
CASE REPORT :

A 22 years old female presented with red urine. She was a known case of hypertension for 7 years on Telmisartan (40) mg per day. On examination, pulse -normal, BP-146/84 mg(with treatment). On general examination, there was adenoma sebaceum and shagreen patches. On investigation, CT scan of brain was normal. USG findings showed angiomyolipoma of both the kidneys. Urine examination revealed RBC >100/hpf.

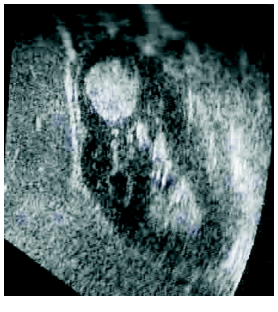
Tuberous sclerosis is an autosomal dominant neurocutaneous disorder characterized by presence of Hamartomatous lesion in multiple organs. Classically 2/3rd of the cases present with EPILOIA (Epilepsy, Low intelligence, Adenoma sebaceum). Up to 20% of the cases don't present with Epilepsy or any radiological CNS features. Renal involvement may present with hematuria and/or hypertension. Radiologically there may be simple cysts, angiomyolipoma or renal cell carcinoma[1]. AML is the commonest renal manifestation with a frequency of 55% to 75% in tuberous sclerosis patients and conversely 20% of patients with renal AML have tuberous sclerosis[2]. An angiomyolipoma is defined as a benign lesion that demonstrated imaging characteristics of fat.



Adenoma sebaceum on face



Shagreen Patches on skin



Angiomyolipoma of kidney

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Case Report

EARLY ONSET NEUROPATHY IN INSECTICIDE POISONINGS

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ABSTRACT

Early onset neuropathy can occur as a complication in setting of different acute insecticide poisonings. Here we present three cases, that we had come across in last 1yr, of neuropathy occured in 1st week of acute intoxication of different insecticide poisonings, namely one case of danadar (organophosphorus) poisoning and two cases of endosulfan poisoning. NCV and EMG was done in all three cases. Radiculoneuropathy (mixed demylinating and axonal neuropathy) and mixed sensory-motor polyneuropathy was found respectively in danadar and endosulfan poisoning.
Keywords : *Insecticide Poisoning, Neuropathy.*

INTRODUCTION

Neurotoxicity of inseticides is known since long. Many cases have been reported in acute orgonophosphorous poisoning. These are Intermediate Syndrome and Delayed Neuropathy(OPIDP). Intermediate syndrome develops 24-96hrs after acute intoxication. It is due to defect in neuromuscular junction. It present as ocular, bulbar, neck, respiratory and proximal muscle weakness(1). Delayed neuropathy occurs 2-3wks later, which is predominantly motor axonal neuropathy(2,4). But early onset neuropathy has rarely been reported.

Endosulfan is neurotoxic, producing convulsion, psychosis and organic brainstem syndrome. The predominant toxic effect is due to over-stimulation of the central nervous system (CNS), by inhibiting Ca- and Mg-ATPase and antagonising chloride ion transport in gamma-aminobutyric acid (GABA) receptors with little or no peripheral component(8).

Here we present some cases of early onset neuropathy, that we have came across in last one year, in different acute insecticide poisonings.

CASE REPORT

CASE -1 : A 20 years old female admitted after intake of danadar. Stomach wash was done immediately in local PHC and was repeated at casualty of SCB Medical college hospital. Patient was treated with pralidoxime 9gm/day and atropine. Patient was adequately atropinised having psychosis, pupil fully dilated and pulse rate being maintained at100- 120/min. Serum cholinesterase was 2080u/l. Atropine was being tapered gradually. On day-5 patient complain of weakness of both lower limb. Next day she developed weakness of both upper limb. O/E- hand grip was weak. Power around elbow and shoulder joint was 3/5. Power around hip and knee joint 2/5 with weakness of flexor and extensor of foot with hypotonia and absence of deep tendon reflexes. Sensory system examination was normal. Bladder & bowel were not involved. There is no involvement of facial, bulbar, ocular and neck muscle. Single breath count was 30. Repeat serum cholinesterase was 2273. NCV revealed radiculoneuropathy(mixed demyelinating and axonal neuoropathy).

CASE-2 : A 16 years old male admitted after intake of endosulfan. There was no convulsion or altered sensorium. Heart rate was 80/min. Blood pressure was 120/80. Chest was clear. Stomach wash was done. He was kept under observation with medication of pantoprazole and ondansetron. On day-3 he developed foot drop. O/E- there was weakness of both flexor and extensor of ankle joint, power around rest of the joint being normal. B/L Ankle jerk absent. Rest of deep tendon reflex normally elicited. Definite sensory loss over both feet. No involvement of bladder and bowel.

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Serum cholinesterase was 7008U/L. NCV revealed bilateral symmetrical mixed sensory-motor polyneuropathy with axonal degeneration. Patient was discharged with tablet methyl-cobalamine. On follow up, at 3month, patient recovered showing normal power of flexor and extensor of ankle joint with normal NCV study.

CASE-3 : A 25years old male admitted as a case of endosulfan poisoning without any h/o convulsion or altered sensorium was kept in observation. On day 3 he developed difficulty in walking. O/E- high stepping gait. Weakness of flexor & extensor with ankle jerk being absent. Power around rest of joint being normal. There was sensory loss over B/L foot. No bladder-bowel involvement. Serum cholinesterase was 5432U/L. NCV reveal bilateral symmetrical mixed sensory-motor polyneuropathy, predominantly motor with distal axonal degeneration. Patient was discharged with tablet methyl-cobalamine. On follow up, at 1& 4month, patient show persistence of weakness with improvement.

DISCUSSION

Like delayed onset polyneuropathy(2,4) , early onset neuropathy is predominantly motor, mostly due to axonal degeneration. Probable same mechanism play role in pathogenesis of disease i.e. inhibition of neuropathy target esterase.

Unlike intermediate syndrome, which is a defect in neuromuscular junction, prolonged action of acetyl choline on the nicotinic receptors definitely does not play a role in pathogenesis in early onset neuropathy in organophosporous poisoning(1). It is evident from NCV-EMG study, which denotes neuropathy rather than neuromuscular junction defect.

Dose of organophosporous and role of pralidoxime in induction of early onset polyneuropathy is debatable.

Both organophosphorus and carbamate can inhibit neuropathy target esterase and hence may induce neuropathy(4). But mechanism by which endosulfan , which is a organochlorine, can induce neuropathy is difficult to explain.

CONCLUSION

Early and delayed onset polyneuropathy in organophosphate compound poisoning are probably different spectrum of same pathogenetic process, differ by time of onset .

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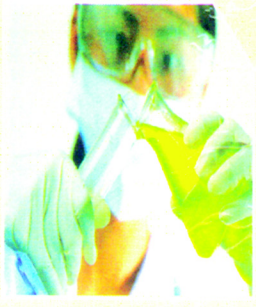

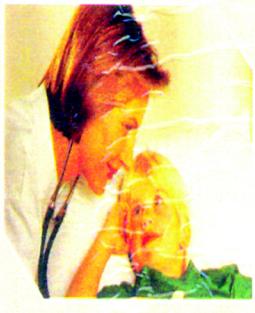

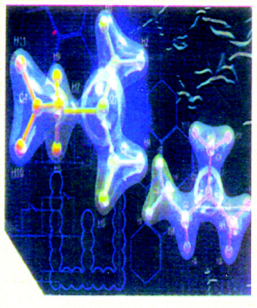

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