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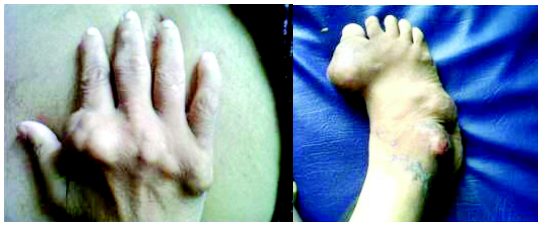

ANNOUNCEMENT

Articles, preferably original articles and case reports are invited from honourable members of API, Orissa State Branch to be published in the ORISSA PHYSICIANS' JOURNAL, volume IX, in the month of May 2012. The last date for submission of articles is March 31st, 2012.

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CONTENTS

Editorial

VENTILATOR ASSOCIATED PNEUMONIA : CRITICAL IN CRITICAL CARE

B.L. Parija, M.R. Behera

Ventilator associated pneumonia (VAP), is the most complicated health care acquired infection and is an important source of morbidity and mortality in critically ill patients . Risk factors for development of VAP are male gender, trauma, severity of underlying illness, colonisation of aerodigestive tract with pathogenic bacteria (prior use of antibiotics / treatment with H-2 receptor antagonists) & aspiration.

VAP tends to affect the most critically ill and vulnerable hospitalised patients, estimated to be between 5 to 25%[1]. According to the study done by Padhi et al. the incidence is 12% (24/200), almost similar to various other observations. The crude mortality rate of patients of VAP ranges from 30 to 50%[2]. In this study, the mortality rate is 37% in ICU and 42% during the hospital stay. Mean age of patients is 58 years and male patients are more prevalent.

Common organisms associated for VAP are MRSA (42%) and Pseudomonas species (21.2%). Others being Klebsiella, Haemophilus, Enterobacter, Streptococcus pneumoniae and Acenetobacter[3]. The present study has showed that the commonest organisms being Pseudomonas spp., Staphylococcus aureus, Acenetobacter species and Klebsiella. Specific bacterial pathogens isolated by various observers are usually institution specific. More accurate, higher quality invasive diagnostic sample obtained methods like bronchoalveolar lavage, bronchial biopsy probably facilitated the greater recovery of the fastidious pathogens in VAP cases.

VAP prolongs the duration of mechanical ventilation, increases the length of stay in ICU and extends hospital stay. Treatment of suspected and confirmed VAP cases is estimated to account for approximately 50% of antibiotics used in ICU[4]. These factors make VAP a potent driver of morbidity, cost and the cultivation of antibiotic resistant bacteria. With the knowledge of morbidity and mortality associated with VAP, clinicians & policy makers have targeted VAP for elimination. Hospitals galvanized *to address* VAP, however are confronted by an increasing set of options to prevent VAP ranging from probiotics to hand hygiene. Many organizations promote the adoption of 'ventilator bundles' which include an array of measures that target VAP. The most famous band is that of Institute for Healthcare Improvements includes elevation of head end of the bed, thromboembolism prophylaxis, stress ulcer prophylaxis, daily sedative interruption and daily assessment of patient's readiness to wean from mechanical ventilation, continuous aspiration of subglottic secretions or silver coated endotracheal tubes.[5]

A definition should be decided for particular institution, which is to be followed consistently for the diagnosis of VAP. The ICU should work in a close collaboration with hospital infection control committee to track cases. Suveillance programme decrease the nosocomial infection rate[6]. The local antibiotic resistance patterns are to be known and the information should be applied when choosing empirical therapy awaiting culture reports. The data needs to be reviewed periodically. As the duration of mechanical ventilation is an important determinant of VAP, it is necessary to decide about exact time of extubation.[7] A structural approach is to be adopted for early extubation that will reduce nosocomial infection.[8] A standardized practical protocol is to be practised for weaning of the patient. Endotracheal intubation may be avoided as far as possible and wherever possible, noninvasive ventilation may replace endotracheal intubation. Recently the division of Healthcare Quality Promotion, National Center for Infectious diseases USA has updated, expanded and replaced the previous published CDC 'Guidelines for prevention of nosocomial pneumonia'. Among the change in recommendation to prevent VAP are preferential use of orotracheal rather than nasotracheal tubes, use of non invasive ventilation, changing the breathing circuits when they are malfunctioning or are visibly contaminated, use of endotracheal tube with a dorsal lumen (when feasible) to allow drainage of respiratory secretions. No recommendations were made about the use of sucralfate, H2 receptor antagonists or antacids for stress bleeding prophylaxis.[9]

Along with this protocol continuous medical education of healthcare workers should be encouraged to minimize the incidence of VAP and also morbidity, mortality associated with VAP in critically ill patients.

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Original Article

ANTITHROMBOTIC THERAPY FOR VALVULAR HEART DISEASE: A FIVE YEAR FOLLOW UP STUDY

S. Mohapatra*, A. Mohapatra**

ABSTRACT

Background: *Cerebrovascular catastrophes in the form of embolic infarction and its consequences are devastating in patients with valvular heart disease;particularly with patients having prosthetic heart valves. So despite the risk of bleeding with antithrombotic agent it is appropriate to start and maintain antithrombotic therapy to reduce the risk of stroke and its debilitating consequences in patients with prosthetic valves as well as in patients with native valve in the presence of associated co-morbid conditions.[1,2]* ***Methods:*** *We followed up cases with valvular heart disease with effect from January 2006 to December 2010 and categorized them into a) Patients with native valve and associated co-morbid conditions like atrial fibrillation, hypertension stage 2, diabetes, old age(>70yrs) and history of stroke. b) Patients with metallic prosthetic valves c) Patients with biological valves We followed up these cases for thrombotic infarction, embolic infarction, bleeding(both trivial and fatal) and in case of pregnancy for teratogenecity ,maternal or foetal death.* ***Result:*** *We picked up 128 cases (36 males,72 females) in the beginning of our study with effect from 1st January 2006 to 31st March 2006. We tried to follow up these cases for 5 years and at the end of 5 years only 62 cases(28 males,34 females) were left for completion of our study. Out of the 66 cases who could not complete the five year study course, 6 males and 18 females did not turn up for follow up after being discharged from the hospital;2 males and 8 females died due to congestive cardiac failure and 2 females died due to intracerebral haemorrhage; the rest 30 came for follow up after discharge only for a short while but did not complete the 5 year follow up study and hence were excluded.Out of 62 cases who completed the study, 7 cases(2 males,5 females) had bleeding from gum, transient thrombocytopenia with increased clotting time.Cerebral stroke was observed in 4 cases but all of them survived and were without any significant disability.* ***Conclusion:*** *Although the addition of antithrombotic therapy is not without the risk of bleeding episodes which are minimal and in the event of stroke due to antithrombotic agent, death and permanent disability are rare.Out of 62 followed up cases, 7 cases had complications. 2females who died due to intracerebral haemorrhage were not taking their medication regularly and had co-morbid conditions like stage 2 hypertension and chronic renal failure. Hence antithrombotic agents cannot be pinpointed to be the cause of intracerebral haemorrhage.* ***Keywords :*** *Antithrombotic therapy, valvular heart disease, prosthetic heart valves.*

INTRODUCTION:

Cerebrovascular strokes in the form of thrombotic infarction, embolic infarction and haemorrhagic infarction are very devastating, debilitating in patients who have valvular heart disease with prosthetic valves.Prosthetic valves whether metallic or biological are always supplemented by antithrombotic agents to prevent risk of thrombotic strokes.Similarly patients who have native diseased valves and who have co-morbid conditions like atrial fibrillation, left ventricular dysfunction, hypercoagulable state, previous episodes of thromboembolic strokes, uncontrolled diabetes, renal

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failure, uncontrolled hypertension and extreme old age are also prone for frequent thomboembolic stroke.[3,4,5,6,7]

Bleeding is a risk factor while the patients are undergoing antithrombotic therapy but the risk of thromboembolic phenomena calls for the initiation of antithrombotic agent.[1.2] Patients with native valve disease with the aforementioned risk factors also need anti thrombotic agents. Although there is no need for continuation of antithrombotic agents in patients with biological prosthetic valves it is mandatory for patients with metallic prosthetic valves to undergo antithrobotic therapy for lifelong with frequent monitoring of prothrombin time and estimation of platelets , bleeding time and clotting time as the need arises.

AIM AND OBJECTIVE:

To make a prospective study of antithrombotic therapy in adult patients having valvular heart disease.

Study design:

All patients would be categorized into 3 groups:

A) patients with native valve disease and associated with co-morbid conditions like atrial fibrillation ,severe hypertension(stage 2), diabetes, old age(>70 yrs) and with previous history of stroke

B) patients with metallic prosthetic valves

C) patients with biological valves

METHODS:

All the patients receiving antithrombotic therapy were followed up for 5 years and episodes of thrombotic infarction, embolic infarction, bleeding episodes, thrombocytopenia and in case of pregnant females, teratogenecity ,maternal and fetal deaths were also looked for. Study period was from 1st January 2006 to 31st December 2010.

All the patients in this study were adult males and females with valvular heart disease undergoing treatment with anticoagulants (oral and injectable as the situation warranted).

All patients who were taken up for this study had given their voluntary consent after they were made to understand the details of the study.Permission was granted by the local ethical committee for conducting the study.

The patients were subjected to thorough clinical examination with particular reference to past history of rheumatic fever, valvular heart disease, surgery, and type of prosthetic valve implanted. History of hypertension, diabetes, stroke and bleeding episodes were also noted. Patient's name, age, sex, ethnicity, family history of diabetes,ischaemic heart disease and hypertension were also noted.

All patients underwent tests like haemoglobin estimation, platelet count, bleeding and clotting time,prothrombin time , accelerated prothrombin time, blood sugar estimation,liver and renal function tests and as the need arose echocardiographic evaluation was done. Catastrophic events like embolic stroke ,bleeding episodes(both trivial and severe) were noted.Patients having adverse episodes were treated appropriately .CT scan was done in all cases of stroke ,severe thrombocytopenia with altered sensorium. Doppler study of arteries was done when suspicion of embolic ischaemia was there. Fundus examination was done in patients having blurred vision,petechiae and thrombocytopenia.

RESULT:

Total number of 128 patients(36 males,72 females) were picked up for study.we tried to follow up these cases for 5 years but at the end of 5 years only 62 patients(28 males,32 females) were left for completion of our study.Out of 66 cases who were left out from the study,6 males and 28 females did not complete even 1 year of follow up. 2 males and 8 females died due to congestive heart failure during first 3 years of study.2 females who had chronic renal failure and stage 2 hypertension died due to intracerebral haemorrhage. Their INR was less than 3 and hence they were not included in the study as chances of haemorrhage due to antithrombotic therapy was less likely. 30 females were not included in our study as they were lost during follow up.

2 females who became pregnant during our study, we had to discontinue oral anticoagulant agent and instituted injectable unfractionated heparin.We could not stop anticoagulation as these cases were high risk cases for embolic episode. In one case of pregnancy elective caesarean section had to be performed at 38th week of pregnancy as it was a precious child.There was no maternal death and no evidence of teratogenecity in the foetus.

We encountered 4 cases of bacterial endocarditis suspected due to prolonged fever and all these cases were proved to be so by microbiological analysis.They were treated with appropriate antibiotic therapy for 2 to 3 weeks. 4 more cases who were culture negative but since there was strong echocardiographic evidence of valvular vegetation we instituted injection ceftriaxone and amikacin for 2 weeks.

2 patients had to undergo surgery for obstructive hernia and we discontinued oral anticoagulation three days prior to surgery.1 patient had peptic perforation and oral anticoagulation was stopped immediately as the patient had to undergo emergency surgery.We had to transfuse 6 units of whole blood during and within 24hours of surgery.6 patients had stroke during this 5 year follow up study which is quite high and is attributable to non adherence of the drug schedule.During this acute episode of stroke we had CT examination of brain on day 0 and day 3.since there was no evidence of intracerebral haemorrhage we started injection low molecular weight heparin(enoxaparin 0.6 ml BD) for 5 days along with anticoagulation. 4 patients made total functional recovery within three months and 2 made recovery with grade IV power in all 4 limbs.During injectable anticoagulation INR was maintained between 2 to 4 and there was no intracerebral haemorrhage on CT scan taken between 7 to 10 days.

All patients were tried to be maintained at INR 2 to 3 and whenever INR exceeded 5 we stopped anticoagulation.Between INR 3 to 5 we adjusted the dose of anticoagulation by reducing the dose.

6 patients had major bleeding episodes requiring blood transfusion and we stopped oral anticoagulation for 2 weeks. Before starting anticoagulation we started with 75mg aspirin in 3 of these patients as they showed significant LV dysfunction i.e. LVEF <35%.

Biological valve was implanted in 7cases and oral anticoagulation was discontinued after 3 months as none of these cases had co-morbid conditions like diabetes, severe hypertension(stage 2) or atrial fibrillation.None of these cases had shown any thromboembolic phenomenon during the entire period of follow up.

In 1 patient there was need for implantation of a permanent pacemaker for which we had to discontinue oral anticoagulation for three days prior to the implantation and we restarted with oral anticoagulation 4 days after the implantation. 3 patients had acute myocardial infarction for which we instituted full 7 days of injection low molecular weight heparin(Enoxaparin) after which we sent those cases for angioplasty. 3 days prior to angioplasty all oral anticoagulants and clopidogrel was stopped.As all 3 were put on drug eluting stents, we continued with oral anticoagulants plus clopidogrel for one year and thereafter we continued with oral anticoagulant but stopped clopidogrel.

Patients who had facility from the public sector undertaking hospital (18 males , 20 females) had only 4 episodes of minor bleeding ,2 episodes of stroke whereas 24 patients (10 males ,14 females) had 4 episodes of stroke and 7 episodes of major bleeding.This shows that regular monitoring and frequent adjustment of the anticoagulant agent would result in statistically significant reduction in stroke and major bleeding disorders

			Males	Females
Total no. of patients		62	28	34
Total no.of PSU patients		38	18	20
Total no.of non PSU patients		24	10	14
Total no. of episodes of stroke	In PSU pts	2	0	2
	In non PSU pts	4	1	3
Total no. of episodes of major bleeding	In PSU pts	0	0	0
	In non PSU pts	7	3	4

DISCUSSION:

This study was carried out in a public sector undertaking hospital and various other hospitals from which patients were referred to the first author.The patients were mostly from the city of Rourkela and adjacent places of Jharkhand and Chhatisgarh states.Patients who were entitled to get free treatment from the public sector undertaking hospital and had referral facility for advanced treatment at higher centres comprised of the lucky few and could be followed up along with full treatment during the 5 year study period.But patients who could not afford diagnostic or treatment facilities like angiography ,angioplasty ,frequent echocardiographic examinations, frequent check-ups for prothrombin time,clotting time,bleeding time, platelet count etc had maximum number of bleeding episodes as well as thromboembolic phenomena.

Till recently only aspirin, warfarin, unfractionated heparin and thrombolytic agents were recommended for prophylaxis of thromboembolic phenomenon in valvular heart diseases.But now low molecular weight heparin, glycoprotein IIBIIIA inhibitors ,clopidogrel, prasugrel and direct thrombin inhibitors are also being used to prevent thromboembolic episodes.Use of all these agents may theoretically increase the incidence of bleeding episodes but in practice we have tried to address this unfounded fear and have clearly depicted that use of anticoagulants does not cause any additional harm.

Biological prosthetic valves rarely cause thromboembolism.[18]Similar observation was made in our series as we did not encounter a single episode of thromboembolic episode in our patients who had implanted biological valves.

In patients not taking oral anticoagulants, episodes of stroke exceeded 10%.[6]In our case, episodes were more than 6% even on oral anticoagulation; this could be due to noncompliance of the patients.In our case, mitral valve was involved in more than 75% of all cases of valvular heart disease.

We encountered cases of ischaemic heart disease requiring angiography and angioplasty.we also encountered cases requiring emergency surgery for which we had to discontinue anticoagulation.

In 7 cases who showed evidence of thromboembolic phenomenon inspite of use of oral anticoagulation agents we had to add low dose (75-150mg) aspirin to prevent further embolic episodes.This is in agreement with other authors.[9,10,11,12]In another study[13] addition of aspirin to patients who had mitral prosthetic metallic valve, episodes of minor thromboembolic phenomenon was significantly less in patients taking both aspirin and oral anticoagulants than in patients taking only oral anticoagulants;but as far as major haemorrhagic events were concerned there was no significant difference.

Risk factors for thromboembolism

Patients with valvular heart disease Reference (43)Hurst	
1. Atrial fibrillation	
2. Previous thromboembolism	
3. LVEF < 35 %	
4. Mitral valve disease > aortic valve disease	
5. Hypercoagulable state	
Patients without valvular heart disease	
With atrial fibrillation	Relative risk
1. TIA/stroke	2.5%
2. Diabetes	1.7%
3. Hypertension	1.6%
4. CAD	1.5%
5. CCF	1.4%
6. Advanced age	1.4%

Risk of thromboembolism

High risk (>2% per year)
1. Atrial fibrillation
2. LV dysfunction
3. Previous thromboembolism
4. Hypercoagulable state
5. Mechanical prosthesis
Low risk (<1% per year)
1. Normal sinus rhythm
2. Normal LV function
3. No previous thromboembolism
4. Biological prosthesis

Antithrombotic therapy at the time of surgery:

1. We stopped oral anticoagulation 72 hours prior to elective surgery
2. We stopped aspirin prior to elective surgery

In high risk of thromboembolism we stopped oral anticoagulants 72 hours prior to surgery.We started heparin 48 hours before procedure and stopped it 6 hrs

Data of the study group (1st January 2006 to 31st December 2010)

Age		16 to 30yrs	31 to 60yrs	61 to 70yrs	> 70 yrs
No. of patients		10	40	10	2
Sex		M4 , F6	M18 , F22	M4 , F6	M2 , F0
Diabetes		M0 , F0	M12 , F6	M2 , F1	M2 , F0
Hypertension		M0 , F0	M8 , F2	M2 , F1	M2 , F0
Prosthetic valve	Mitral	M4 , F6	M6 , F8	M0 , F1	M1 , F0
	Aortic	M0 , F0	M2 , F4	M2 , F0	M0 , F0
Biological valve	Mitral	M0 , F0	M1 , F1	M1 , F0	M0 , F0
	Aortic	M0 , F0	M0 , F1	M1 , F2	M0 , F0
Renal failure		M0 , F0	M1 , F0	M0 , F0	M0 , F0
Thrombocytopenia		M0 , F2	M2 , F8	M3 , F8	M0 , F0
Stroke		M0 , F1	M0 , F2	M1 , F2	M0 , F0
Major bleeding		M0 , F0	M1 , F2	M1 . F2	M0 , F0
Trivial bleeding		M0 , F1	M0 , F4	M2 , F1	M0 , F0
LVEF <35%		M0 , F0	M1 , F3	M1 , F1	M0 , F0
Hypercoagulable state		M0 , F0	M0 , F0	M0 , F1	M0 , F0
Atrial fibrillation		M2 , F3	M7 , F9	M2 , F2	M1 , F0
Bacterial endocarditis	Microbiologically Proved	M1 , F0	M0 , F3	M0 , F0	M0 , F0
	Echocardiographically Suspected	M1 , F0	M0 , F3	M0 , F0	M0 , F0
Acute myocardial infarction		M0 , F0	M0 , F0	M2 , F0	M0 , F0
Pregnancy		F2	F0	F0	F0

prior to the surgery.we restarted heparin 24 hours after surgery and restarted oral anticoagulants and continued both for at least 48 hours prior to stopping heparin. APTT was maintained at 60 to 80 seconds and INR at 2 to 3.[14,15,16]

Along with antithrombotic therapy antibiotics were also used in patients with endocarditis. Cases with CNS involvement were given injection heparin/ LMWH.[17]

CONCLUSION:

Use of antithrombotic agents is not without complications like bleeding, trivial or severe.In spite of risks involved the benefits are huge.With the use of antithrombotic agents thromboembolic phenomenon can be reduced by 12%.The consequence of cerebral ischaemia is devastating.The consequent disability that remains can ruin the life of the patient as well as his family members both financially and socially.Many a

times thromboembolic event can lead to amputation of a limb which is far more debilitating .Hence it is worthy to take the risks involved and to use antithrombotic agents in all cases of valvular heart disease with metallic prosthesis and in high risk cases.It is important to note that there is no rule of thumb for all patients while choosing an antithrombotic agent.There is no fixed dose of anticoagulants.There is no fixed duration of unfractionated heparin or LMWH.Each patient must be looked into separately and treatment schedule should be altered accordingly.Of paramount importance is the regular estimation of prothrombin time and INR , and to fix the dose accordingly.Most ideally INR should be between 2.5 to 3.If in spite of ideal INR there is evidence of thromboembolism the dose of the agent used is to be increased and if required aspirin should be added with an aim to increase INR to 3.5 to 4.5.Similarly at the time of acute attack of CNS thromboembolism there is need for unfractionated heparin/LMWH which should be started preferably after 72 hours i.e. if the second CT scan taken 72 hours after the first does not show intracerebral haemorrhage.There is a risk of converting non-haemorrhagic stroke to a haemorrhagic one if heparin is started within 72 hours.[40] Finally it can be stressed upon that antithrombotic therapy , despite the risks involved, should be instituted in all cases of valvular heart disease with metallic prosthesis for life long, in native valve disease with high risk involvement and in biological prosthetic valve for a limited period.

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Original Article

MANIFESTATIONS AND OUTCOME OF MIXED SPECIES (P.VIVAX AND P.FALCIPARUM) MALARIA IN ADULTS.

M.K. Mohapatra*, L.K. Dash, P.K. Bariha***, P.C.Karua****, A. Mohapatra#, S. Chugh*****

ABSTRACT

Objective: *Studies on malaria due to co-existent P.falciparum and P.vivax infections are negligible in India. Therefore, this study was undertaken to find out the clinical profile, prognostic factors, and outcome of mixed species malaria.* ***Methods:*** *This prospective, observational study has been conducted in a tertiary health care institution with high prevalence of malaria. A cohort of 118 patients of mixed malaria was enrolled in this study. The diagnosis of malaria was made by Giemsa stained peripheral blood smear with detection of both P.vivax and P.falciparum in the same smear. The clinical presentation, biochemical and haematological findings, occurrence of severe malaria, and outcome were recorded, and analyzed. All the patients were treated according to WHO guidelines.* ***Results:*** *Out of 118 patients of mixed malaria, severe malaria was found in 21(17.8%) cases of which 14 (66.6%) had single complication and 7 (33.3%) cases had multiple complication. There were 3 independent risk factors for a patient of developing complicated malaria. They were: presenting without fever, high parasite count, and prolonged fever to treatment interval. The outcome of patients with mixed malaria was good with only 1 (0.8%) death.* ***Conclusion:*** *In conclusion mixed species infection is not uncommon in the locality where both species coexists. Mixed species infection can complicate with severe malaria. In mixed infection, P.vivax malaria has a protective effect against the severity of falciparum malaria.* ***Keywords :*** *Malaria, Falciparum malaria, vivax malaria, manifestations, outcome.*

INTRODUCTION

Human malaria is caused primarily by 4 different species of Plasmodium namely; P.falciparum (Pf), P.vivax (Pv), P. malariae (Pm), and P. ovale (Po). Clinical pictures, outcome, prognostic factors, and changing clinical pattern of malaria due to individual species infection have been studied [1]. In a geographical area when more than one species coexist, sympatric combination of these infections in an individual cannot be ruled out[2]. But profile of malaria due to multiple species infection is considerably underestimated due to lack of studies[3].

In South-east Asia region, India alone contributes 80% of malaria cases and in India malaria is contributed the most by Orissa state[4,5]. Both Pf and Pv malaria are common in this part of India. However, research on malaria due to co-existent infection of both Pf and Pv is uncommon. Out of few available clinical studies on coincident infection, some studies showed that Pv has a protective effect against severe disease of Pf[6]. On the contrary some studies showed that dual Pf and Pv infection in children increases the disease severity[7,8]. Experimental dual infection of Pf and Pv as a part of malariotherapy in patients with neurosyphilis and mathematical model of parasitic dynamics of Pf and Pv co-infection showed that Pv infection suppresses the severity of Pf[9,10]. In this context, the knowledge about mixed species infection is important not only for control measures but also for therapeutic options and futuristic vaccine programme. Therefore, we have undertaken this research to study the clinical pattern and outcome of mixed species malaria in adults in a tertiary care hospital.

METHODS

This prospective observational study has been undertaken in the Department of Medicine of V.S.S.

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Medical College, Burla, Orissa, as a part of our ongoing non-funded study on malaria. The results from the mixed species malaria stratum are the subject of this study. All the patients of malaria who were admitted to the indoor during March 2007 to February 2009 had been screened for species diagnosis and patients of mixed species malaria were included in this study. All the participants stayed in the hospital till recovery and subsequently followed up for one month. The diagnosis was made with detection of asexual forms of Pf and Pv from Giemsa stained peripheral blood smear at the time of admission. The parasitic count had been made from the peripheral blood smear and was expressed as numbers of asexual parasites per micro liter of blood and was calculated from the numbers of parasitized cells per 200 leukocytes in a thick film i.e. No. of parasites X total leukocyte count / 200. Gametocyte counts are made from thick films.

On admission, we did the clinical work up in accordance with the proforma designed for this study. The laboratory investigations done were: complete blood count (CBC), blood glucose, blood urea, serum creatinine, serum bilirubin, alanine-amino transferase (ALT), aspartate-amino transferase (AST), alkaline phosphatase and glucose-6-phosphate dehydrogenase (G-6-PD), serum sodium, and potassium. Severe malaria was diagnosed according to the guidelines of World Health Organization[11].

To identify prognostic variables and assess the severity of disease we analyzed the clinical, parasitological, and biochemical variables. Temperature was recorded and PBS was examined 12 hourly to determine fever resolution and parasitic clearance time. Lumbar puncture was done to study cerebrospinal fluid (CSF) in unconscious patient.

All patients were treated with artesunate as per WHO guidelines[12]. Patients of uncomplicated mixed malaria were treated with artesunate and mefloquine combination and radical treatment was given with primaquin for 14 days. Patients were examined and assessed twice daily until full recovery. All patients were followed up for 1 month after discharge either at the out door or by correspondence.

Analyses were performed with the use of SPSS software, version 10. Continuous data are presented as mean ± SD if data were normally distributed. Univariate analysis was done for risk analysis.

RESULTS:

During the study period 888 diagnosed patients of malaria were admitted in the hospital. Of them mixed malaria was present in 118 (13.2%) patients. Among the patients of mixed malaria, there were 83 (70.3%) males and 35(29.6%) females with a ratio of 2.4:1. Majority of patients belonged to 21 to 40 years of age group (Table-1).

Fever was the most common (93.2%) clinical presentation. Intermittent fever was present in 100 (84.7%) cases whereas continuous fever was present in 10 (8.5%) cases (Table-3). The intermittent fever was tertian and quotidian in 80 (67.8%) and 11 (9.3%) cases. Nine (7.6%) patients had 2 peaks of typical paroxysm within 24 hours. In addition to fever complaints like head ache, vomiting, abdominal pain was found in 45 (38.1%) cases. Splenomegaly was found in 93.2% cases. Hepatosplenomegaly was present in 45 (38.1%) cases. Severe malaria was found in 21(17.8%) patients. Of them, 14 (66.6%) had single complication and 7 (33.3%) had multiple complications. Out of single complication, cerebral malaria, Jaundice, and severe anaemia was present in 4(19.1%), 2(9.5%), and 8(38.1%) patients respectively. Out of 7 patients with multiple complications cerebral malaria with severe anaemia, cerebral malaria with jaundice, and cerebral malaria with jaundice as well as renal failure was present in 4, 1, and 2 patients respectively. Cerebral malaria alone or in combination with other complications was present in 11(9.3%) cases. Convulsion was present in 5 (4.2%) cases.

Severe anaemia was found in 12 (10.2%) cases of which 8 had severe anaemia without any other complications and 4 had severe anaemia with cerebral malaria. The mean Hb was 4.2 ± 1.4 g/dl. Moderately severe anaemia (Hb. 6-9 g/dl, mean=8.1±2.4 g/dl.) was present in 60 (50.8%) cases and rest 46 (38.9%) patients had mean Hb. of 10.2 ± 3.4 g/dl. Thrombocytopenia (platelet count < 80.000) was detected in 4 patients, with a mean count of 72000.8 ± 1200.8/cmm. One patient had peripheral pancytopenia with normal bone marrow picture. G-6-PD deficiency was found in 5 (4.2%) patients.

Jaundice was present in 5 (4.2%) cases. S. bilirubin, AST, ALT, and alkaline phosphatise was 6.25±2.2mg/dl, 86.8±8.6IU/L, 92.8 ±10.4IU/L, and 84.8±11.2IU/L respectively. S. bilirubin returned to

TABLE-1 : AGE AND SEX DISTRIBUTION

Age	Male	Female	Total (Per centage)
18-20	12	4	16 (13.5%)
21-30	15	6	21 (17.8%)
31-40	22	10	32 (27.1%)
41-50	15	5	20 (16.9%)
51-60	13	8	21(17.8%)
>61	6	2	8 (6.8%)
Total	**83 (70.3%)**	**35 (29.7%)**	**118**

TABLE-2 : TYPES OF SEVERE MALARIA

Severe malaria	Number	(%)
A. Single Complication:	14	(66.7%)
1. Cerebral malaria (CM)	4	(19.1%)
2. Jaundice (J)	2	(9.5%)
3. Anemia (A)	8	(38.1%)
B. Multiple Complications:	7	(33.3%)
1. CM+A	4	(19.1%)
2. CM+J	1	(4.8%)
3. CM+J+Renal failure(R)	2	(9.5%)
Total number	**21**	

TABLE-3 : CLINICAL PRESENTATIONS

Symptoms and Sign	Number (%)
I.General Symptoms	
A. Fever	110 (93.2%)
1. Intermittent	100 (84.7%)
a. Tertian	80(67.8%)
b. Quotidian	11(9.3%)
c. Twice a day	9(7.6%)
2. Continuos	10(8.5%)
3. Absence of fever	8 (6.8%)
B. Non-febrile Symptoms	
1. Head ache	45(38.1%)
2. Vomiting/Nausea	35(29.6%)
3. Abd. Pain	10(8.4%)
4. Myalgia	38(32.2%)
5. Prostration	15(12.7%)
6. Fainting attack	1(0.8%)
7. Sleep disturbance	2(1.7%)
8. Sub conjuctival haemo.	1(0.8%)
9. Diarrhoea	1 (0.8%)
II. Organ Specific	
A. CNS	
1. Unconsciousness	11(9.3%)
2. Convulsion	5(4.2%)
3. Extensor plantar	8(6.8%)
B. Renal	
1. Oliguria	2(1.68%)
C. Gastro intestinal	
1. Jaundice	5(4.2%)
2. Abd.pain	1(0.8%)
3. Splenomegaly	110(93.2%)
4. Hepatosplenomegaly	45 (38.5%)
D. Haematological	
1. Anaemia	12(10.2%)
2. Thrombocytopenia	4 (3.4%)
3. Leukopenia	4(3.4%)
4. Pancytopenia	1(0.8%)

TABLE-4 : BASE LINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	Mean ± SD
Admission Interval (Days)	2.8±1.1
Parasitic Count (no./ ìL)	4300.7±180.5
Gametocyte Count (no./ ìL)	55.5 ± 15.5
Temp. (°F)	104.6±2.8
Pulse rate (no/mt.)	110.2±10.5
Mean BP (mm Hg.)	107.8±3.5
Resp.rate (no./mt)	25.3±5.2
GCS	10.9±5.2
Hb.(gm/dl)	7.8±3.5
TLC(10^9/L)	8.6±1.2
Platelet (10^9/L)	180.7±50.9
B.glucose (gm/dl)	90.5±12.5
S. Sodium (mEq/L)	122.6±4.5
S.potassium (mEq/L)	4.1±1.2
S.bilirubin (mg/dl)	1.9±1.1
SGOT (IU/L)	35.8±10.2
SGPT (IU/L)	45.8±9.8
Alk.Phosphatase (IU/L)	125.9 ±19.2
Urine output (ml/24 hrs.)	1200.8±89.7
B.urea (mg/dl)	25.2±12.8
S.creatinine(mg/dl)	1.8±0.3

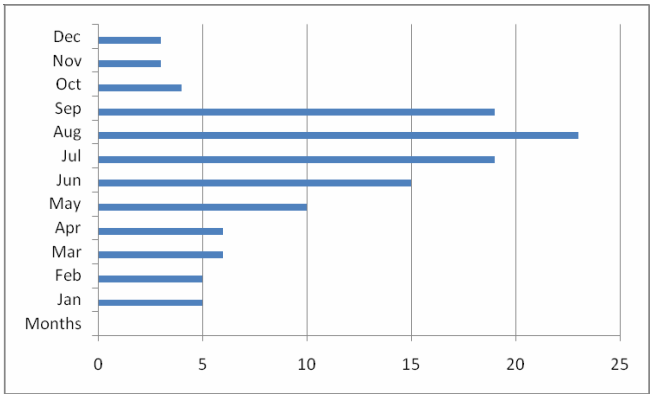

Fig.1 Month wise distribution of Mixed malaria Cases.

normal within 5 to 10 days (6.5±3.2 days) after initiation of treatment. Renal failure was found in 2 cases and both of them needed dialysis.

The diagnosis of malaria was made from peripheral blood smear and the mean parasitic count was 4300.7 ± 180.5/ìL . Gametocyte was detected in 8 (6.7%) cases of mixed malaria and the mean gametocyte count was 55.5 ± 15.5/ìL. The mean interval of onset of fever to hospitalization is 2.8 ± 1.1 days.

There were 3 independent risk factors for a patient of developing complicated mixed species malaria. They were 1) presenting without fever (OR=1.9[95%CI 1.2-3.1], p=0.002), 2) high parasite count >3000/uL (OR=1.6 [95%CI=1.1-2.2],p=0.01, and 3) prolonged fever to treatment interval (>4days) OR=2.8 [95%CI=2.2-5.3],p=0.001).

The outcome of patients of mixed malaria was good. Only 1 (0.8%) patient with multiple complications died. The number of mixed malaria was found more in rainy season i.e. from June to September (Fig.1).

DISCUSSION

Since little information is available on profile of mixed species malaria in India, the present hospital based study is of interest. The present research revealed that mixed species malaria can cause severe malaria and the outcome is good.

Out of 4 species that cause human malaria, P. falciparum malaria is notorious for development of various complications that lead to severe malaria[11,13]. Therefore, severe malaria is almost synonymous with falciparum malaria. However, earlier through a prospective study we have reported that P. vivax monoinfection can cause severe malaria and in hospitalised patients severe vivax malaria was about 11.2%[14]. Subsequently severe vivax malaria has been reported from other parts of India and world[15,16]. Severe mixed species malaria has not been studied extensively. It was believed that mixed infection reduces the severity of falciparum malaria[2,3]. However, severe mixed species malaria could be detected among hospitalized patient with mixed species infection[7]. Earlier hospital based study showed that severe anaemia was the common form of severe malaria in mixed infection.[7]The most common form is anaemia whereas cerebral malaria may be encountered[17]. In a study from Papua New Guinea, among the children below 5 years, the frequency of severe malaria in dual Pf and Pv infection is 17% which was more than Pf (12%), and Pv (9%) monoinfection. Of them neurological manifestation, anaemia, respiratory distress was found in 8.0%, 5.3%, and 10.3% respectively[16]. The present study showed that all forms of severe malaria like cerebral malaria, anaemia, renal failure, jaundice, multi organ failure can occur in adult patients with mixed malaria. The increased risk of severe malaria in children has been attributed to higher overall parasite burden. In our study we found 3 independent risk factors for the development of severe mixed species malaria. They were high parasitic count, increased fever to treatment interval, and absence of fever at the time of presentation. High parasitic count always contributes to the severity of the disease irrespective of species[11]. Increased fever to treatment interval is another important risk factor because the pyrogenic threshold of P. vivax is less than P. falciparum. As a result the patients seek medical attention early and prompt treatment has been administered. Delay in treatment increases the parasite burden casing severe disease. Absence of fever at presentation is another important risk factor. As intermittent fever is one of the characteristics of malaria fever, very often the patient is afebrile at the time of presentation. Such patients when presented with complication may cause difficulty in diagnosis hence delay in treatment.

The present study showed that mixed species malaria was found in 13.2% cases of total hospitalized patients of malaria and of them 17.8% cases had severe malaria. The incidence of mixed malaria has been influenced by geographical heterogeneity, seasonal variation, type of study, and diagnostic methods used. Therefore, the incidence is variable in different studies. Population survey reported that mixed infection constituted less than 2% of total malaria infection[6]. However, therapeutic studies in Thailand demonstrated that without further exposure 30% of patients with Pf malaria had suffered from symptomatic Pv malaria[18]. Similarly, 8% of patients treated for Pv malaria had cryptic coincident Pf infection that had been diagnosed by PfHRP-2 antigen[19]. It is notable that a high incidence of cryptic mixed infection has been detected by sensitive PCR technique. In a population study where all the 4 species were present, the prevalence of double species infection with PCR was as high as 36.4% and triple

infection was 23.7%[20]. Since PCR method is costly and not yet accepted as a routine investigation for diagnosis and treatment of malaria, we used slide test for the diagnosis of mixed malaria like other available studies.[17,18]. The present study had 13.2% cases of mixed malaria which is in agreement with other hospital based study (12.7%)[7,16,17]. Due to use of slide test for the diagnosis of mixed malaria there is a possibility of under reporting compared to PCR and rapid diagnostic test. However, it represented definite cases of mixed malaria. Underreporting may play a part in mixed malaria, but probably this may be a real phenomenon due to partial cross immunity to heterologous species or biological interference.[3,9] Geographic heterogeneity and seasonal variation also influence the prevalence of **mixed malaria in a locality.**[2,3]The present study showed that mixed malaria infections occurred more in wet season than dry season. This seasonal variation may be due to relative abundance of the species in a geographical area. This could result from variations in the presence of mosquito species, which may have species-specific transmission. Seasonal variation of Pf infection with Po and Pv had been reported from Malawi and Papua New Guiena[8,19]. It has been observed that same anopheles mosquito can harbor both Pf and Pv infection and bite of that particular mosquito can inoculate both the species simultaneously[9]. Malaria patients attending during the wet season were more likely to develop severe malaria than dry season.

Studies on mixed malaria showed that the coincident infection of Pf and Pv reduces the risk of severe malaria due to Pf by 4 fold[2,6,9]. The protective potential of Pv against Pf is so much that Pv has been considered as the best available falciparum malaria vaccine. It has also been postulated that á thalasaemia are positively selected in a population predisposed to Pv infection and thereby protects against Pf [6,9]. It is notable that in mixed P.malariae and P.falciparum malaria infection also P. malariae protects the severity of falciparum malaria[20].

Experimental studies in humans and rodents as well as mathematical models revealed a complex parasitic dynamics of MS infection that has clinical consequences affecting the mortality and morbidity[9,10]. One may get severe malaria in mixed species infection depending on whether it is Pf or Pv superinfection. Pv superinfection over an existing Pf infection leads to rise of Pf parasitaemia. It is important since Pv can reappear in the blood following either a new inoculation or a relapse from liver hypnozoites. In this situation, Pv may trigger high Pf parasitaemia that may cause severe malaria. In contrast to the deleterious effect of Pv superinfection, Pf superinfection over an existing Pv infection reduces Pf parasitaemia significantly (by 28%) thus preventing the development of severe malaria. It is notable that simultaneous inoculation by a single mosquito behaves as a Pv superinfection. Simultaneous inoculation will delay the appearance of Pv in the blood by 0.75 days because the pre-erythrocytic stage of Pf lasts for 5.5 to 7.5 days and of Pv for 6 to 8 days[9]. Hence, Pf will appear first and simultaneous inoculation behaves as Pv superinfection causing a rise in Pf parasitaemia[21].

The following explanations may be put forward for less severe malaria in mixed infection. Firstly, patients with mixed infection developed fever earlier than Pf mono infection. It resulted in early medical attention and treatment reducing the chance of development of severe disease. Clinically the mean duration of seeking treatment in mixed infection was 3.2±1.3 days that is earlier than Pf monoinfection 5.8±2.8 days ($p<0.05$). It is due to low pyrogenic threshold of Pv. The pyrogenic threshold of Pv is 150-200 parasites / µL which is much lower than that of Pf (1500-2000 / µL)[21,22]. Even under conditions of Pv super infection in which Pf grows more rapidly than Pv, the later usually reached its pyrogenic density first seeking the medical attention quickly[9]. Secondly, the presence of interspecies cross immunity prevents from severe malaria[21]. Thirdly, non-immune mechanism probably causes mutual suppression of other species. There may be competition for nutrients in the blood stream[22].

In conclusion mixed species infection is not uncommon in the locality where both species coexists. Mixed infection can complicate with severe malaria but its incidence is significantly less suggesting a protective effect of Pv infection. It is important because, if previous Pv infection does protect against severe Pf infection, then control of vivax malaria may reduce the vivax-associated protection against severe falciparum infection enhancing increased incidence of severe falciparum malaria.

CONCLUSION:

In conclusion mixed species infection is not uncommon in the locality where both species coexists. Mixed species infection can complicate with severe malaria. In mixed infection, P.vivax malaria has a protective effect against the severity of falciparum malaria.

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Original Article

VENTILATOR ASSOCIATED PNEUMONIA: EPIDEMIOLOGICAL PROFILE, MICROBIOLOGY AND OUTCOME IN A SEMI-URBAN MEDICAL COLLEGE & HOSPITAL OF EASTERN ORISSA

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ABSTRACT

Objectives: *Ventilator-associated pneumonia is a common nosocomial complication in the intensive care units (ICUs). This study was carried out to analyze the epidemiological profile, microbiological isolates and outcomes for ventilator-associated pneumonia (VAP) in our ICU.* ***Methods :*** *Observational prospective matched cohort study of patients admitted in ICU from September 2010 to August 2011. The epidemiological profile, microbiological characteristics and the outcome, in a cohort of critically ill patients with confirmed diagnosis of VAP were analyzed. Patients on mechanical ventilation (MV) for more than 48 hours were included; tracheal aspirates were collected before starting antibiotics or within 24 hours of changing antibiotics.* ***Results:*** *200 patients on MV were studied of which 24 had VAP (12%), at a rate of 11.71 episodes per 1,000 days of mechanical ventilation. Mean age of the patients was 58 years; male patients were more prevalent (male: female ratio 2.9: 1). The mortality rates in the intensive care unit (ICU) and during the hospital stay were 37% and 42%, respectively. MV duration in patients with VAP was 15.7 (range 5-43) days and among patients who had not developed VAP was 6.6 (range 2-30) days ($p < 0.0001$) 90.8% of the samples were positive, with a high prevalence of Pseudomonas, Acinetobacter and Staphylococcus aureus. Risk factors for death included advanced age and longer duration of MV. Conclusions: This study demonstrates that VAP is a common nosocomial infection that is associated with poor clinical outcomes. The VAP incidence in this study is slightly higher than in the Western and other affluent countries though similar to that in other parts of our country. The percentage of various bacterial pathogens isolated are typically institution specific but showed a similar pattern of isolates to that found in other studies. The mortality rate of 37% in our study is comparable to that of others. In our study patients with VAP had a significantly longer duration of mechanical ventilation (16.7 ± 8.5 days vs 6.4 ± 2.5 days, $p < 0.001$), ICU stay (20 ± 10.0 days vs 6.6 ± 5.1 days, $p < 0.001$), and hospital stay (32.3 ± 14.7 days vs 10.0 ± 5.6 days, $p < 0.001$). VAP increases hospital recourses utilization and incseases cost of therapy. Preventive strategies may help reduce VAP occurrence and improve outcomes.* ***Key-Words****: Ventilator-associated pneumonia, epidemiological profile, microbiology.*

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation (MV). Diagnosing VAP requires a high clinical suspicion combined with bedside examination, radiographic examination, and microbiologic analysis of respiratory secretions [1]. The study was aimed for evaluation of the incidence, microbiological isolates and outcome of VAP. Ventilator-associated pneumonia is usually suspected when the individual develops a new or progressive infiltrate on chest radiograph, leukocytosis, and purulent tracheobronchial secretions. Unfortunately, and unlike for community-acquired pneumonia, accepted

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clinical criteria for pneumonia are of limited diagnostic value in definitively establishing the presence of VAP. In a postmortem study by Fabregas et al., when findings on histologic analysis and cultures of lung samples obtained immediately after death were used as references, a new and persistent (>48-h) infiltrate on chest radiograph plus two or more of the three criteria (i) fever of >38.3°C, (ii) leukocytosis of >12 x 10^9/ml, and/or (iii) purulent tracheobronchial secretions had a sensitivity of 69% and a specificity of 75% for establishing the diagnosis of VAP[2] . Ventilator associated pneumonia is the most common nosocomial infection in intensive care units (ICUs) occurring in upto 60% of patients. The mean incidence rate of VAP is 7 cases per 1,000 days of mechanical ventilation, ranging from 1 to over 20 cases per 1,000 days of mechanical ventilation, in American ICUs [1]. Its incidence varies from 23% to 28% in patients submitted to orotracheal intubation and mechanical ventilation, when we examine patients who do not have acute respiratory distress syndrome (ARDS) and 37% to 60% in patients with ARDS. Prevalence of Ventilator associated pneumonia (VAP) varies between 6 and 52 cases per 100 patients, depending on the population studied. Mortality rates associated with this condition are high, from 25% to 50%, and may reach 70% if the pulmonary infection is caused by multiresistant microorganisms. Some predisposing factors are age, trauma, burns, and the severity of the underlying disease is associated with a high risk for developing VAP; previous use of antibiotics and mechanical ventilation duration are the main factors involved. The highest hazard ratio for developing VAP is in the first 5 days of mechanical ventilation and a plateau in additional cases (1% per day) after ~2 weeks [3]. Though bronchoscopy with quantitative cultures of broncho alveolar lavage fluid helps optimize antibiotic therapy, it is not universally accepted routine procedure due to lack of benefit shown in objective studies. Overall non-bronchoscopic techniques are comparable to bronchoscopic sampling methods [4]. We sought to determine the epidemiological profile and microbiological characteristics of endotracheal aspirates and the outcome of critically ill patients submitted to mechanical ventilation for 48 hours or more and who have clinical diagnosis of VAP.

METHODS

Ours is an observational, prospective study of a consecutive cohort of patients in the ICU of a semi-urban teaching hospital, over a period of 12 months (September 2010 to August 2011). Study was approved by the ethics committee. All patients in our hospital submitted to mechanical ventilation for more than 48 hours were included in the study. Clinical diagnosis of VAP was defined as the presence of a new and/or progressive lung infiltrate in a chest X-ray, associated with at least two of the following criteria: (1) purulent tracheal secretion; (2) white blood cell count > 12,000 or <4,000/mm^3 or bands count > 10%; (3) axillary temperature >38°C or <36°C; and (4) worsening of PaO2/FiO2 ratio (PF Index) > 15% in the previous 48 hours. A Clinical Pulmonary Infection Score (CPIS) of more than 6 was considered consistent with the diagnosis of VAP (Table. 1). An Exclusion criteria (1) low-survival expectancy in 30 days, (2) diagnosed cases of acquired-immunodeficiency syndrome, (3) patients receiving chemotherapy, and (4) neutropenic patients were excluded from the study. All patients included in the study were submitted to the collection of demographic data and other variables useful to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores [5], considering the worst scores in the previous 24 hours before inclusion in the study. Sepsis consensus conference criteria [6] were used to define organic dysfunction, and the worst results obtained 24 hours before inclusion in the study, as well as results from the microbiological examination were used to calculate the Clinical Pulmonary Infection Score (CPIS) [7]. All patients were followed up until discharge from the hospital. All patients were submitted to material collection for culture (tracheal aspirate and blood culture), within the first 24 hours after the beginning of antibiotic treatment or after changing antibiotics. Respiratory fluid material was collected through endotracheal aspirate. This technique is the simplest non-invasive means of obtaining respiratory secretions from mechanically ventilated patients; it is readily performed at the bedside and requires minimal training of health-care providers. These tracheal aspirates were sent to microbiology department for quantitative cultures. The cut-off point established was more than 1000000 ($>10^6$) colony forming units (cfu) to define infection[8].

The patients included in the study were given empirical antibiotics as per the ICU protocol for empiric antibiotic use in ventilator associated pneumonia (Figure. 1 and Tables. 2) elaborated by the ICU staff, together with the antibiotics policy team. Risk factors for multidrug-resistant pathogens causing ventilator-associated pneumonia are as follows:

1. Antimicrobial therapy in preceding 90 d 2. Current hospitalization of 5 d or more 3.High frequency of antibiotic resistance in the community or in the specific hospital unit. 4. Presence of risk factors for HCAP: Hospitalization for 2 d or more in the preceding 90 d, Residence in a nursing home or extended care facility, Home infusion therapy (including antibiotics), Chronic dialysis within 30 d, Home wound care. Family member with multidrug-resistant pathogen 5.Immunosuppressive disease and/or therapy.

Initial empiric antibiotic therapy for ventilator associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity are as follows: The potential pathogens are S. pneumoniae, H. influenzae, Methicillin-sensitive S. aureus, Antibiotic-sensitive enteric gram-negative bacilli, E. coli, K. pneumoniae, Enterobacter species, Proteus species, S. marcescens. The preferred antibiotics are : Ceftriaxone (2gm IV/24 hr) or Levofloxacin (750mg IV/day), Moxifloxacin (400mg IV/day), or Ciprofloxacin (400mg IV/8 hrly) or Ertapnem (1gm IV24 hrs). The frequency of penicillin-resistant S. pneumoniae and multidrug-resistant S. pneumoniae is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

Initial intravenous, adult doses of antibiotics for empiric therapy of hospital-acquired pneumonia, including ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens are as follows: *Antipseudomonal cephalosporin* Cefepime (1–2 g every 8–12 h) Ceftazidime (2 g every 8 h) *Carbepenems,* Imipenem (500 mg every 6 h or 1 g every 8 h) Meropenem (1 g every 8 h), *ß-Lactam/ß-lactamase inhibitor* Piperacillin–tazobactam (4.5 g every 6 h) *Aminoglycosides* Gentamicin (7 mg/kg per d), Tobramycin (7 mg/kg per d), Amikacin (20 mg/kg per day), *Antipseudomonal quinolones,* Levofloxacin (750 mg every day), Ciprofloxacin (400 mg every 8 hrs), Vancomycin (15 mg/kg every 12 h), Linezolid (600 mg every 12 hr).

Antibiotic therapy was considered adequate when the isolated microorganism was found susceptible to the prescribed antibiotic based on examination of the tracheal-secretion aspiration. De-escalation of broad spectrum antibiotics was done based on sensitivity reports. The following routine-care procedures were maintained for all patients submitted to mechanical ventilation: proper hand hygene, nurse and physiotherapist assistance, use of a Heat Moisture Exchanger (HME) filter, closed tracheal aspiration system, oral hygiene with chlorexidine, supraglotic aspiration and semirecumbent position.. Patients included in the study were compared to patients without diagnosis of lung infection in relation to mechanic al ventilation duration; the similarity among groups was analyzed through APACHE II and SOFA scores.

vs. survivors).

Statistical Analysis

Univariate analysis was used to compare the variables for the outcome group of interest (patient with VAP vs. those without VAP and non-survivors vs survivors. Comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were compared using student's t test for normally distributed variables and Wilcoxon's rank-sum test for non-normally distributed variables. The chi-square statistic or Fisher's Exact Test was used to compare categorical variables. The primary data analysis compared mortality rates between patients with and without VAP. The results of these tests were confirmed with multiple logistic regression analysis. All values were expressed as the mean +/- SD (continuous variables) or as percentage of the group they were derived from (categorized variables). All p values were 2-tailed and p values of < 0.05 were considered statistically significant.

RESULTS

During the study period, 212 patients were submitted to mechanical ventilation for more than 48

hours. Out of the subgroup of patients receiving mechanical ventilation for more than 48 hours, 12 were excluded as per the exclusion criteria. Two hundred of these patients were included and were submitted to mechanical ventilation for at least 48 hours, for a total of 1538 days of mechanical ventilation.

There were 24 VAP cases diagnosed of the 200 patients studied (12%), at a rate of 11.71 episodes per 1,000 days of mechanical ventilation. Median age of the patients was 58 years; male patients were more prevalent (Male: Female ratio was 2.42 :1). MV duration in patients with VAP was 15.7 (range 5-43) days and among patients who had not developed VAP was 6.6 (range 2-30) days ($p < 0.001$). At diagnosis of VAP, 16.65% (n=4) had received mechanical ventilation (MV) for less than 5 days and 69.45% (n=20) had received mechanical ventilation for more than 5 days with a mean of 7.2+5 days (mean + standard deviation) of MV at onset of VAP. The mortality rates in the intensive care unit (ICU) and during the hospital stay were 37% and 42%, respectively. Moreover, patients with VAP had a significantly longer duration of mechanical ventilation (16.7 ± 8.5 days vs 6.4 ± 2.5 days, $p < 0.001$), ICU stay (20 ± 10.0 days vs 6.6 ± 5.1 days, $p < 0.001$), and hospital stay (32.3 ± 14.7 days vs 10.0 ± 5.6 days, $p < 0.001$ (Table 3). Microbial Patterns: (Table 4). Pseudomonas spp. (37.5%), Acinetobacter spp. (20.8%) and Staph aureus (20.8%)

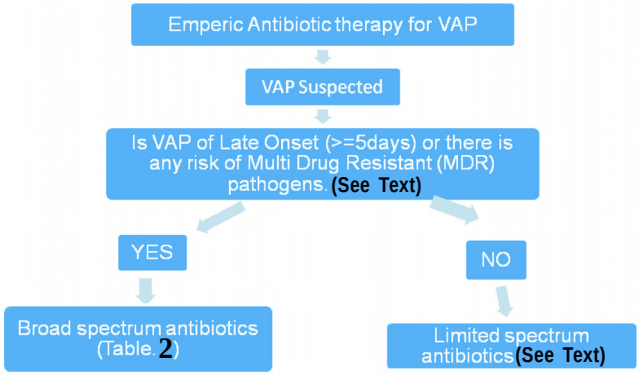

FIGURE 1. Flowchart for initiating empiric antibiotic therapy for ventilator-associated pneumonia (VAP).

TABLE 1.
Clinical Pulmonary Infection Score (CPIS) Scoring system for VAP diagnosis

Day	Parameter	Value for score of:	
		1 point	2 points
1	Temp (°C)	38.5 to 38.9	?39 or ?36
2	White blood cells/mm^3	<4,000 or >11,000	<4,000 or >11,000 and ?50% bands
3	Secretions	Nonpurulent	Purulent
4	PaO_2/FiO_2	>300	?240 and no ARDS
5	Chest X-ray infiltrates	Diffuse or patchy	Localized
6	Temp (°C)	38.5 to 38.9	?39 or ?36
7	Secretions	Nonpurulent	Purulent
8	Progression of chest X-ray infiltrates	No	Yes (no ARDS or congestive heart failure)
9	Sputum	Culture >1+	Culture >1+ and same organism on Gram staining

A total CPIS Score more than 6 is consistent with the diagnosis of ventilator associated pneumonia. ARDS, adult respiratory distress syndrome;CHF, congestive heart failure PaO2/FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen.

TABLE-2.
Initial empiric therapy for ventilator-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity

Potential Pathogens	Combination Antibiotic Therapy*
Pathogens listed in Table 2 and MDR pathogens Pseudomonas aeruginosa Klebsiella pneumoniae ($ESBL^+$)† Acinetobacter species†	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbepenem (imipenem or meropenem) or ß-Lactam/ß-lactamase inhibitor (piperacillin–tazobactam) plus Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin) or Aminoglycoside(amikacin, gentamicin, tobramycin) plus
Methicillin-resistant Staphylococcus aureus (MRSA) Legionella pneumophila†	Linezolid or vancomycin‡

Initial antibiotic therapy should be adjusted or on the basis of microbiologic data and clinical response to therapy. If an $ESBL^+$ strain, such as K. pneumoniae, or an Acinetobacter species is suspected, a carbepenem is a reliable choice. If L. pneumophila is suspected, the combination antibiotic regimen should include a macolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside. If MRSA risk factors are present or there is a high incidence locally.

were the most common pathogens causing VAP. Staphylococcus aureus associated with VAP were all methicillin resistant. Klebsiella pneumoniae was isolated in 12.3% of cases. E.coli and Citrobacter were found in 4.1% cases each.

DISCUSSION

The present study shows that VAP incidence in our ICU is 12% among ventilated patients at 11.71 per 1,000 ventilator days. In a study from Pondicherry, India, the incidence of VAP was 30.67 and 15.87 per 1,000 ventilator days in the two different ICUs [39]. Whereas in a study by Pawar (2003),[8] from New Delhi, India, only 2.6% of ventilated patients had VAP. Trivedi (2000), [9] reported an incidence of 9.38% of nosocomial pneumonia and 38% had ventilator associated pneumonia. In the United States, another study with VAP patients found a 9.3% incidence rate [10] . There is a high variability of VAP incidence in our country. Its incidence in our study is slightly higher than in the United States which could be a consequence of various factors, such as the severity of the underlying disease of patients included in the study (APACHE II score above 16), advanced age and prolonged mechanical ventilation duration. These factors, associated with the need for nasogastric tube feeding and prolonged sedation [11] are associated with a higher risk of developing VAP.

VAP is associated with crude mortality rate of 20 -70%. Mortality as a result of VAP is especially high when it is caused by multi-drug resistant organisms like pseudomonas or Acinetobacter species [10]. Kollef

* Dosages are based on normal renal and hepatic function.
Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.
Trough levels for vancomycin should be 15–20 μg/ml.

TABLE-3. Demographic charateristics of ventilator-associated pneumonia patients in the intensive care unit.

Charateristics	VAP (n= 24)	No VAP (n=176)	P value
Age (years) Mean	58 (median) Range: 12 – 76)	51 (median) Range : 14 – 67)	NS
Gender			
Male (%)	70.83% (n=17)	67.05%(n=118)	NS
Female(%)	29.17% (n=07)	32.95%(n=58)	NS
Type of admission			
Medical	79.17% (n=19)	47.15%(n=83)	P<0.001
Surgical (non-trauma)	12.50% (n=3)	34.65%(n=61)	P<0.001
Trauma	08.33% (n=2)	18.20%(n=32)	P<0.001
Source of admission			
Casualty	37.5%(n=9)	40.34% (n=71)	P<0.05
Hospital Ward	41.65% (n=10)	57.57% (n=102)	P<0.05
Operating room	-	0.56% (n=1)	P<0.05
Another Hospital	20.83% (n=5)	1.14% (n=2)	P<0.001
APACHE II Score	24.7+/-7.0 (mean +/- SD)	15+/-3(mean +/- SD)	P<0.001
SOFA score	8.7+/-3.3 (mean +/- SD)	6.6+/-2.3(mean +/- SD)	P<0.001
CPIS score	9.3 +/-1.8 (mean +/- SD)	2+/-1 (mean +/- SD)	P<0.001
Hospitalized before VAP	12.7 +/- 16.1	Not applicable	
ICU stay before VAP	8.2 +/- 5.1	Not Applicable	
Duration of MV before VAP	7.2 +/-5.0	Not applicable	
Mechanical ventilation days	16.7 +/- 8.5(mean +/- SD)	6.4+/-2.5(mean +/- SD)	P<0.001
Total ICU stay (days)	20 +/- 10.0 (mean +/- SD)	6.6+/-5.1 (mean +/- SD)	P<0.001
Total Hospital stay (days)	32.3 +/- 14(mean +/- SD)	10.0+/-5.6(mean +/- SD)	P<0.001

TABLE-4
Bacteriological isolates from tracheal aspirates of ventilator-associated pneumonia patients in the intensive care unit

Bacterial isolate	Percentage of VAP cases
Pseudomonas spp	37.5% (n=09)
Staphylococcus aureus	20.8% (n=05)
Acinetobacter spp.	20.8% (n=5)
Klebsiella spp.	12.3% (n=3)
E.coli	4.1%(n=1)
Citrobacter	4.1% (n=1)

MH reported that overall mortalities in patients with VAP were 37.5% as compared with 8.5% in patients without VAP [11]. P.Rakshit (2005) reported a mortality rate of 37% among VAP patients in Mumbai [12] .The mortality rate of 37% in our study is comparable to that of others. In our study patients with VAP had a significantly longer duration of mechanical ventilation (16.7 ± 8.5 days vs 6.4 ± 2.5 days, $p < 0.001$), ICU stay (20 ± 10.0 days vs 6.6 ± 5.1 days, $p < 0.001$), and hospital stay (32.3 ± 14.7 days vs 10.0 ± 5.6 days, $p < 0.001$. In the United States patients with VAP also had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 days vs 4.7 ± 7.0 days, $p < 0.001$), ICU stay (11.7 ± 11.0 days vs 5.6 ± 6.1 days, $p < 0.001$), and hospital stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days, $p < 0.001$(18). This is comparable to our study. VAP is not only associated with poor clinical outcome but also increases the economic burden [10].

Trivedi (2000), [9] reported that commonest isolates were pseudomonas (55%), Acinetobacter (20%), Staph. aureus (14.5%) and Klebsiella (15%). Donald (2000) reported that VAP occurring > 4 days after admission is more commonly caused by *Pseudomonas aeruginosa*, Acinetobacter or Enterobacter spp, or methicillin-resistant *Staphylococcus aureus* (MRSA) [13]. In our study most of VAP developed after > 4 days of mechanical ventilation (MV) (7.2 +/-5.0). *Pseudomonas spp. (37.5%), Acinetobacter spp. (20.8%) and Staph aureus (20.8%)* were the most common pathogens causing VAP in our study. We found a slightly higher isolates of Staphylococcus aureus and lower incidence of pseudomonas. This could be due to the longer duration of mechanical ventilation. As noted by Meduri (1994), Staphylococcus aureus can become an important causative agent of VAP, especially in patients who have risk factors for VAP and are on mechanical ventilation for extended periods [14].

CONCLUSION

This study demonstrates that VAP is a common nosocomial infection that is associated with poor clinical outcomes. The VAP incidence in this study is slightly higher than in the Western and other affluent countries though similar to that in other parts of our country. The percentage of various bacterial pathogens isolated are typically institution specific but showed a similar pattern of isolates to that found in other studies. The mortality rate of 37% in our study is comparable to that of others. In our study patients with VAP had a significantly longer duration of mechanical ventilation (16.7 ± 8.5 days vs 6.4 ± 2.5 days, $p < 0.001$), ICU stay (20 ± 10.0 days vs 6.6 ± 5.1 days, $p < 0.001$), and hospital stay (32.3 ± 14.7 days vs 10.0 ± 5.6 days, $p < 0.001$ which is similar to that of others. Prevention and control programs based on continuing medical education of health care workers should be encouraged in order to minimize the morbidity and mortality rates of VAP in critically-ill patients.

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Original Article

STUDY OF CLINICAL PROFILE AND OUT COME OF DENGUE FEVER CASES DURING AUG-SEP 2011 OUTBREAK IN ORISSA

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ABSTRACT

Objectives: *To study the various clinical presentations, changes in laboratory parameters, outcome and correlation of clinical/ laboratory Parameters with outcome in dengue fever cases.* ***Methods:*** *Total of 360 confirmed cases of dengue fever were included in the study. Cases were classified into 3 groups- Dengue fever(DF), Dengue haemorrhagic fever(DHF) and Dengue shock syndrome(DSS). Clinical features of each case were noted using a questionnaire and daily clinical examination. Everyday investigation reports were documented. At the end all the data were analysed.* ***Results:*** *Out of 360 cases 259 were male and 101 were female. Most cases were in the age group of 20-40 yrs. Number of DF, DHF and DSS cases were 312(86.6%), 42(11.6%) and 6(1.8%) respectively. Fever was the most common symptom(97.2%) followed by headache(92.7%), Myalgia(60.5%), abdominal pain(43.6%), skin rash(17.2%), loose motion (15.5%), pruritus(11.6%) and retro-orbital pain(11.1%).Bleeding from various sites was seen in 14.4% cases, GI Tract being the most common site. Significant laboratory parameter changes were TLC of <4000/cmm in 81.9% cases, TPC of <100,000/cmm in 91.1%, total billirubin >2 mg/dl in 15.6% , AST>45U/L in 22.7%, ALT >45U/L in13.8% and ALP>60U/L in 16.6% cases. Overall mortality in this study was 1.1%.All patients, who died had MODS. 50% of patients who died, had ARDS and 50% had severe UGI bleeding. All 4 patients who died had TPC<50,000/cmm and Hematocrit >45%.* ***Conclusion:*** *Fever, headache, myalgia, arthralgia, abdominal pain are common presenting symptoms of dengue fever. Leucopenia and thrombocytopenia are most common haematological changes. An increased liver enzyme is fairly common and is a marker of poor prognosis. Mucosal bleeding, particularly upper GI bleeding is the most common complication. Development of MODS carries a very poor prognosis.* ***KEY WORDS:*** *Dengue fever, Dengue haemorrhagic fever, Dengue shock syndrome, Thrombocytopenia, Leucopenia.*

INTRODUCTION

Dengue infection, an arthropod-borne viral haemorrhagic fever, continues to be a major challenge to public health especially in south East-Asia region[1]. It has the potential of causing large scale outbreaks. Dengue has shown an increase in trend in recent years due to rapid urbanisation, life style change, deficient water management, improper water storage practices in urban, peri-urban and rural areas leading to proliferation of mosquito breeding sites.[2] With advent of methods of viral isolation and serological techniques, all 4 serotypes (DENG 1 to DENG 4) of dengue virus complex has been extensively reported from various parts of India since its first report in 1956 from vellore.[3] Presently it is endemic to most States and Union Territories of India(Fig.1) including Orissa, with an upsurge in incidence during Jul-Nov every year. [2] In Orissa, baring few sporadic cases no major outbreak

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was reported till 2011. In Aug 2011, first case was reported in Orissa from Angul district. As per the information collected from Dengue control centre, Directorate of Health Services, Govt of Orissa, Bhubaneswar, by 21st September 1594 cases reported from 24 different districts of Orissa with 26 deaths .In Hitech medical college & hospital , a 500 beded tertiary care hospital with an well equipped laboratory, Blood component separation facility and 16 bedded ICU, situated in Bhubaneswar, the state capital , we admitted a large no of cases of Dengue fever during this outbreak. This study was undertaken in order to document the present clinical profile and outcome of Dengue fever.

METHODS:

The study was undertaken as a hospital based descriptive study with prospective data collection over a period of 1 month extending from 8th Aug to 6th Sept. The provisional clinical diagnosis of Dengue fever was made on the basis of history of fever of short duration (< 15 days), constitutional symptoms suggestive of Dengue fever with or without haemorrhagic manifestations and investigation showing leucopenia or thrombocytopenia. All patients with provisional diagnosis of dengue fever were screened for Dengue NS1 Ag, IgM and IgG Ab by *Advantage dengue NS1 Ag and Ab combi card test*(J Mitra & co pvt Ltd).This is a rapid solid phase immunochromatographic test for the qualitative detection of Dengue NS1 antigen and differential detection of IgM and IgG antibody to dengue virus. It has 93% sensitivity and 99% specificity for NS1 Ag and 91% sensitivity and 98% specificity for IgM/IgG Ab(as evaluated by Haffkins Institute, Mumbai).Though Haemaglutination –Inhibition (HI) test or IgM capture ELISA are standard tests used in many studies, Immunochromatographic tests also have high sensitivity(upto 98%) and specificity(>90%).[4,5,6,7] Those showing NS1 Ag or IgM Ab. reactivity were included in the study. The clinical data were collected by using a questionnaire developed and symptoms and signs observed during hospital stay. Investigation reports were collected on day-to-day basis .Patients were classified into three groups (a) classical dengue fever (DF), (b) dengue haemorrhagic fever(DHF)and (c) dengue shock syndrome(DSS) according to guidelines of Directorate of NVBDCP/Govt of India.[8] All the clinical data and investigation reports were analysed and Chi Square analysis was used to detect the trends.

RESULTS:

Of the 360 cases of confirmed Dengue fever, 259 cases (71.95%) were male and 101 cases (28.05%) were female with male: female ratio of 2.56:1. Patients were mostly in the age group of 20 to 40 years (186/360, 51.6%) followed by 41 to 60 years(123/360,34.1%). As per case definition , 312cases (86.6%) were dengue fever(DF) 42 cases (11.6%) were DHF and 6 cases (1.8%) were DSS.(Fig.1) Mean duration of illness was 8 days.

Fig. 2 presents the clinical manifestations observed in the study. Fever was the most common symptom, documented in 350 cases (97.2%). 10 cases in whom fever was not documented during hospitalisation had history of fever prior to admission. Headache was the next common symptom complained by 334 cases (92.7%) which was holo cranial and observed during first half of fever. Retro orbital pain was complained by only 40 cases (11.1%).Sever myalgia was present in 218(60.5%) cases. Mild to moderate joint pain was complained in 74 cases (20.5%). Diarrhoea was present in 56 patients (15.5%) while pain abdomen of varying intensity was complained by 157cases (43.6%). 62 cases (17.2%) had skin rash mostly over trunk and proximal limbs. Rash was seen in first phase of fever in majority of cases. A few cases (7/62) had rash observed in convalescent phase of fever which was more in palms and sole. Majority of patients with rash were in DHF/DSS category. Significant pruritus was complained by 42 cases (11.6%).

Tourniquet test was positive in 59.5% cases of DHF/DSS (25/42 cases). Bradycardia was noted in 52 patients (14.4%) and in all cases it was sinus bradycardia. Clinicaly hepatomegaly was observed in 38 case (10.5%) and splenomegaly in 11 cases (3.05%)out of which 9 cases had coinfection with

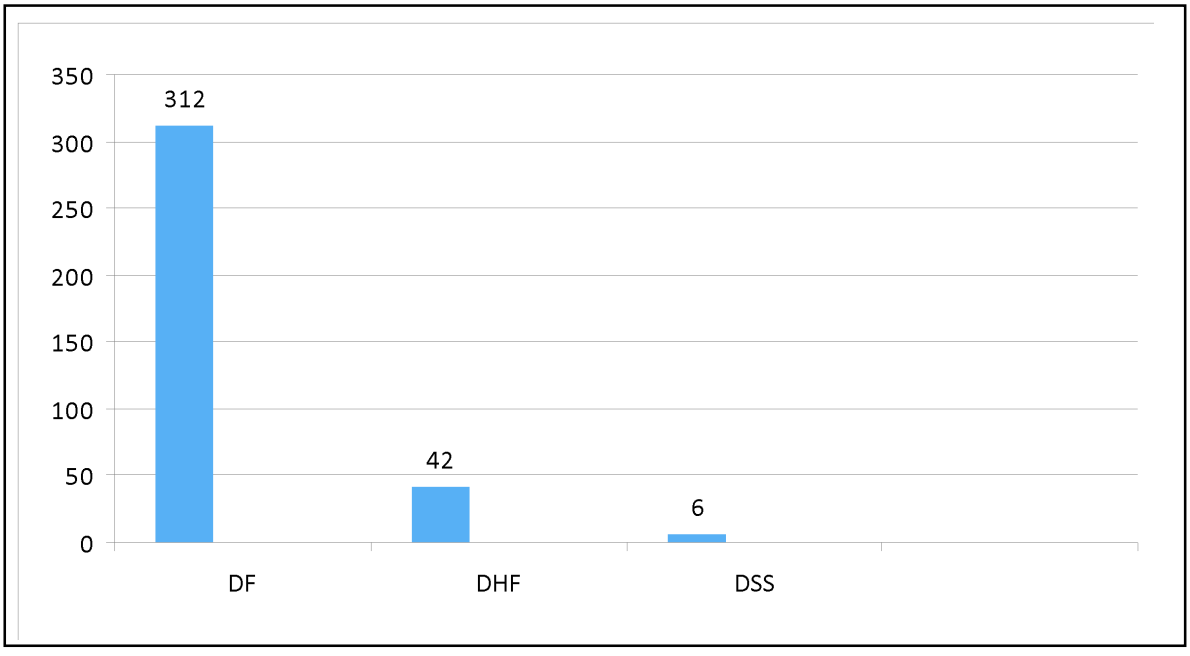

Figure-1 Distribution of clinical categories of dengue fever cases.
DF - Dengue Fever, DHF - Dengue Haemorrhagic Fever, DSS - Dengue Shock Syndrome

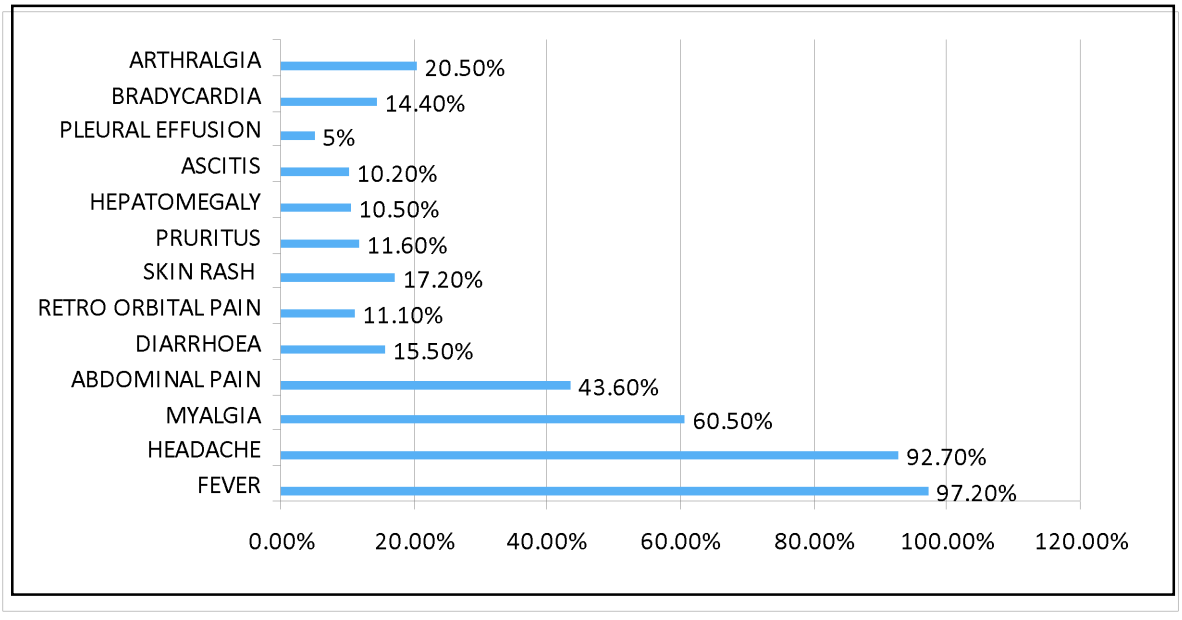

Figure-2. CLINICAL MANIFESTATION OF DENGUE FEVER

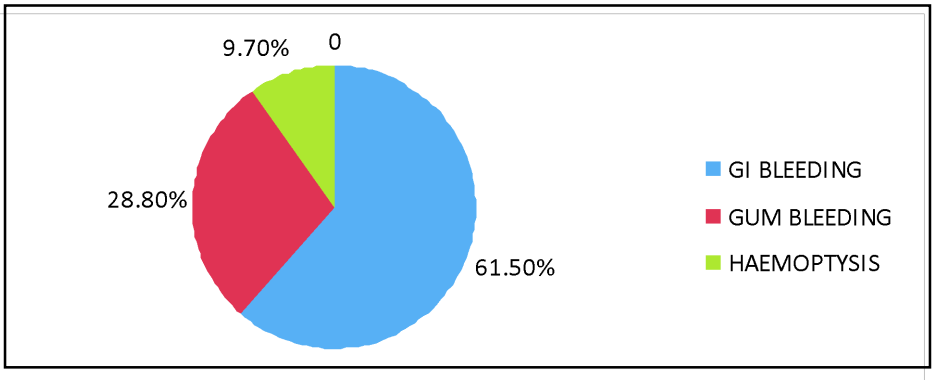

Figure-3. Bleeding Manifestation of Dengue Fever

PARAMETERS	Percentage (%)
HB > 16 gm %	10.5
PCV > 45 %	11.1
PCV<35%	3.3
TLC < 4000	81.9
PLATELET COUNT < 100000	91.1
PLATELET COUNT < 20000	14.1
BILIRUBIN > 2 mg %	15.6
AST > 45	22.7
ALT>45	13.8
ALP>60	16.6

TABLE 1: LABORATORY PARAMETERS

malaria(MP ICT positive).Ascitis was observed by ultrasonography in 37(10.2%) cases and pleural effusion in 18 cases(5%) by X-Ray or Ultrasonography. Neither ascitis nor pleural effusion was clinically detectable and both were seen in DHF/DSS patients.

Spontaneous bleeding in the form of melena, hematemesis , gum bleeding and /or haemoptysis was noted in 52 cases(14.4%).Fig 3 shows the details of bleeding manifestations with GI bleeding being the most common form. Petechie was noted in 21 cases (5.8%).

Among laboratory parameters (Table-1) most notable was leucopenia and thrombocytopenia with differential count showing normal neutrophil count. Total leukocyte count (TLC) of <4000/cmm was noted in 295 cases (81.9%). Total platelet count (TPC) of<100,000/cmm was present in 328cases (91.1%). Among them 128 Cases (35.5%) had TLC<50,000/cmm and 51 cases (14.1%) had TPC <20,000/cmm. Haemoglobin (Hb) of >16 gm% was found in 38 patients (10.5%). Hematocrit(Hct) was measured in all cases of whom Hct >45% was noted in 40 cases (11.1%). All the patients with Hct>45% had TPC <20,000/cmm and Hct of <35% found in 12 cases(3.3%).Liver Function Test(LFT) was done in 160 patients and Total Bilirubin was >2mg% in 25 cases(15.6%).AST of >45U/L was observed in 22.7% cases , ALT>45U/L in 13.8 % cases and ALP > 60 U/L in 16.6 % cases.

Out of 360 cases 4 cases (1.1%) died. 3 patients out of four were in the age group of 40 -60 yrs. All patients above 60 yrs survived. No death reported in age group below 20 yrs. No sex difference was observed in mortality (M:F=1:1). All 4 patients died were in DSS category, had MODS and were treated in ICU. 2 out of 4 cases died had ARDS requiring ventilator support. Renal and hepatic dysfunction was present in all 4 cases. Massive UGI bleeding was present in 2 cases.All 4 patients who died had TPC<50,000 and Hct >45%.

DISCUSSION:

This study describes the clinical profile, laboratory features and outcome of DF/DHF/DSS in adult patients. In this study 312 cases (86.6%) were DF, 42 cases (11.6%) were DHF and 6 cases(1.8%) were DSS. This is in accordance with the study result from Delhi by Sharma et al[8] and Makroo R N et al[9]. However few studies in India have reported a higher percentage of DHF in their study.[10, 11] Incidence of gastrointestinal symptoms noted in this outbreak was similar to the observation of Sharma et al[8]. Pain abdomen was noted in 43.6% cases in our study as of 38% reported by Sharma et al. In contrast, Daniel et al[10] from Kollam, kerala had reported a higher incidence of pain abdomen (62.4%) in their study. Hepatomegaly was observed in 13.4% cases which was similar to the observation by R S Chhina et al[17] (12.1%) and Sharma et al (13.5%) from India and Nimmanitya S et al[14] (13.5%) from Thailand. but lower than other Indian studies.[10] Hepatomegaly was more common in DHF/DSS than DF cases. Bleeding from various sites was seen much less in the present study (10.8%) similar to the observation by Daniel et al(15.2%) .In contrast Horvath et al[12] from Australia and Sharma et al[8] from Delhi reported a higher incidence of bleeding episodes(63% and 69% respectively).The GI tract was the predominant site of bleeding observed like most other studies.(Daniel et al, Sharma et al,)

Though thrombocytopenia was found in most of the patients (91.1%) , it poorly correlates to the bleeding tendencies(10.8%), an observation similar to the one made by Sharma et al. and Daniel et al. Rapid fluctuation in platelet count was observed in some of our patients.

Biochemical liver dysfunction in the form of increased transaminase was found in most of the cases (60.8%-70.4%), which was similar to the observation of RS Chhina et al[17]. AST value were higher than ALT values, which was in accordance with many other studies.[11,15, 16] The exact cause of this change is uncertain but as suggested may be due to excess release of AST from monocytes. Deranged liver function was more common in DHF/DSS patients than DF cases as observed by Wahid et al.[13]

In our study mortality was significantly associated with increased hematocrit (>45% in 4/4 cases). Severe thrombocytopenia noted in all 4 cases of death. Though thrombocytopenia of <20,000/cmm was present in 14.1% case, mortality was only 1.1%, which shows poor correlation of thrombocytopenia and mortality.

Overall mortality in our study was 1.1%(4/360) similar to that of Daniel et al(3.2%). Mortality in DSS was 66.6 %(4/6).None of the patients died from DF category.

CONCLUSION:

In summary Dengue fever is a self limiting disease with DSS being the most serious component having high mortality but the overall death rate in dengue is low. Fever, headache, muscle pain, joint pain, abdominal discomfort, loose motion are common clinical presentations. Leucopenia, thrombocytopenia, raised liver enzymes are common. Deranged liver function correlates with severity and prognosis unlike platelet count which does not correlate with bleeding manifestations. Preferentially high AST may serve as an early indicator of dengue infection in a relevant clinical situation. Increased billirubin, ALT and ALP may act as poor prognostic markers. Multiorgan dysfunction with hepatic failure, renal failure and ARDS occurs in a few patients with a very high mortality.

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Original Article

CLINICO-AETIOLOGICAL PROFILE OF ACUTE RENAL FAILURE IN A TERTIARY CARE HOSPITAL OF ODISHA

N. Mohapatra*, S. Ratha, B.L. Parija***, S. Mahata****, S. Kansurkar#, J. Narayan#, P. Panda#, M. Mandal#**

ABSTRACT

The study was undertaken with the aim of determining the clinico-aetilogical profile and outcome in acute renal failure (ARF) patients in a tertiary care hospital. All patients with serum creatinine >3 times normal or decrease in GFR>75% (RIFLE criteria) were included while all cases of chronic renal failure, obstructive uropathy and those with history of diabetes were excluded from the study. All cases were subjected to detailed history taking, thorough clinical examination and investigations including serum urea, creatinine, serum electrolytes, and coagulation profile. Creatinine clearance & GFR was calculated in all cases & kidney biopsy done in some. The treatment modalities and outcome were noted. Out of 140 patients, 86(61.42%) were male and 54(38.47%) were female. Common clinical presentations were anaemia (71.42%), fever (42.85%) and hypertension (42.85%). The aetiologies were malaria (42.85%), acute gastroenteritis (21.42%), vasculotoxic snake bite (18.57%), septicaemia (2.85%) and unknown (14.28%). Oliguric ARF was seen in 56.42% while 43.57% were non-oliguric. Coagulation profile abnormality was seen in 31.42%. Mean glomerular filtration rate (GFR) at admission was 19.542±4.007, and at discharge was 34.52±5.410. 60(42.85%) patients needed dialysis during treatment and 8 patients (5.71%) died during hospital stay. Kidney biopsy done in 20 cases with unknown aetiology revealed primary glomerular disease in 10 cases while biopsy was normal and aetiology remained unknown in 10 cases. Irrespective of the aetiology, prompt management of the patients including conservative measures and dialysis minimised the mortality. ***Key Words:*** *Acute renal failure, Aetiology, Malaria, Vasculotoxic snake bite, Gastroenteritis.*

INTRODUCTION

Acute renal failure (ARF) is characterized by a rapid decline in Glomerular filtration rate (GFR) over hours to days, and contributes significantly to the morbidity and mortality of critically ill patients. ARF may complicate up to 5% of hospital admissions and up to 30% of admissions to intensive care unit (ICU). Mortality remains as high as 80%in the ICU.[1] New approaches continue to emerge and clinicians must understand the aetiology of ARF to prevent its occurrence and start treatment early to minimize mortality.

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AIMS OF STUDY

To study the aetiology, clinical presentation, treatment and outcome in patients with ARF, in a tertiary care hospital.

METHOD

All cases of ARF diagnosed by RIFLE criteria [2] with a Serum Creatinine >3times normal or a decrease in GFR >75% normal who were admitted to the department of Medicine S.C.B. Medical College, Cuttack, during the period of August 2009 to December 2010 were taken up for the study.

Patients of chronic renal failure, obstructive uropathy and diabetes were excluded from the study.

All cases were subjected to detailed history taking, thorough clinical examination and basic investigations including complete haemogram, ICT for malaria, serum urea, serum creatinine, serum electrolytes and coagulation profile. GFR was calculated on the

day of admission and on the day of discharge. Ultrasonography of abdomen to know the kidney size was done in all cases but renal biopsy was done in only those cases in which the cause of ARF was not found out. All the patients were treated adequately including haemodialysis when required and the outcome noted.

RESULTS AND DISCUSSION

140 adult patients of ARF were studied, out of which majority were in the age group of 30-40 years. 86(61.42%) were males and 54(38.57%) were females. Similar findings were observed in studies conducted by Panda etal, Mehta et al, and Prakash et al which showed that the majority of the cases were in the age group of 30-40 years with a male preponderance. [3, 4, 5]

The clinical presentation of the patients are summarised in Table1. Majority of the patients presented with anaemia (71.42%), fever (42.85%) and hypertension (42.85%). Jaundice was present in 22.85%, diarrhoea in 21.42% and cerebral symptoms in 17.14% of patients.

Table-1
Clinical presentation of cases of ARF (n=140)

Clinical features	Number of patients	Percentage
Anaemia	100	71.42%
Hypertension	60	42.85%
Fever	60	42.85%
Hypotension	40	28.57%
Jaundice	32	22.85%
Acute gastroenteritis	30	21.42%
History of snakebite	26	18.57%
Cerebral symptoms	24	17.14%
Oedema	20	14.28%
Haematuria	10	7.14%
ARDS	4	2.85%

The different aetiologies of ARF in our study are shown in Table2. Out of the 140 cases, 60 (42.85%) cases were malaria, 30(21.42%) cases were acute gastroenteritis and 26(18.57%) cases were vasculotoxic snake bite. Renal biopsy done on the 20 cases of unknown aetiology revealed primary glomerular disease in 10 patients whereas biopsy was normal and aetiology remained unknown in 10 cases. In the study done by Prakash etal, the most common cause of ARF was found to be acute gastroenteritis(35.2%) followed by acute glomerulonephritis (10.3%), post abortal septicaemia(10.5%) and Falciparum malaria(4.2%).[6] As Orissa is an endemic state for malaria our study showed malaria as the most common cause of ARF. The second common cause of ARF was acute gastroenteritis as Orissa is an economically backward state with people living in unhygienic conditions and without adequate health awareness. Vasculotoxic snake bite was also a common cause of ARF due to the vast majority of people residing in rural and forest areas, engaged in farming and agricultural activities.

Table-2
Aetiology of ARF

Disease	Number of cases	Percentage
Malaria	60	42.85%
Acute gastroenteritis	30	21.42%
Vasculotoxic snake bite	26	18.57%
Septicaemia	4	2.85%
Unknown aetiology	20	14.28%
Total	140	

In our study 79(56.42%) patients had oliguric ARF and 61(43.57%) had non oliguric ARF. Malaria (65.57%) was found to be the most common cause of non oliguric ARF, while acute gastroenteritis (35.64%) was the most common cause of oliguric ARF as shown in Table 3. Similar findings were seen in the study conducted by Panda S K et al. Which showed that oliguric ARF was more common than non oliguric ARF. In our study the most common cause of oliguric ARF was acute gastroenteritis due to the resulting hypovolumia and dehydration leading to ARF.

Table-3
Aetiology of oliguric and non-oliguric ARF

Aetiology	Oliguric ARF	Non-oliguric ARF
Malaria	20(25.31%)	40(65.57%)
Vasculotoxic snake bite	20(25.31%)	6(09.83%)
Acute gastroenteritis	25(31.64%)	5(08.19%)
Septicaemia	4(5.06%)	0(0%)
Unknown aetiology	10(12.65%)	10(16.39%)
Total	79	61

Coagulation profile was done in all 140 cases. Abnormal results, in the form of increased serum Fibrin Degradation Products and decreased platelet count were seen in 44 patients (31.4%). As shown in Table 4, majority of the patients with coagulation profile abnormality were vasculotoxic snake bite, 25 cases

(56.85%), followed by malaria, 15(34.09%) and septicaemia, 4(9.09%). The study done by G Ali et al showed that 34% of patients of snake bite with ARF had coagulation profile abnormality.

Table-4
Correlation of abnormal coagulation profile with aetiology of ARF

Aetiology	Number of cases	Percentage
Malaria	15	34.09%
Vasculotoxic snake bite	25	56.81%
Septicaemia	4	9.09%
Total	44	

Mean GFR at the time of admission was 19.542±4.007, while the mean GFR at the time of discharge was 34.52±5.41, Table 5. Majority of the patients of vasculotoxic snake bite and acute gastroenteritis had decreased GFR at admission, but improved after management.

Table-5
GFR of ARF patients at admission and discharge

GFR(ml/min)	Number of cases at admission	Number of cases at discharge
10-20	68	0
20-30	52	44
30-40	18	66
40-50	2	14
50-60	0	8
	Mean GFR 19.542±4.007	Mean GFR 34.52±5.410

Mortality was very low in our study (Table 6). Out of 140 cases 8 died (5.71%), while 132 (94.28%) were discharged from the hospital. Highest mortality was seen in patients of septicaemia with ARF and lowest in acute gastroenteritis. In Malaria with ARF, mortality was 3.33% while higher mortality rates were seen in studies conducted by Panda et al (20%), Mehta et al (29%), Prakash et al (30.8%) and Shah P R (21%).[3, 4, 5, 8] The reason for decreased mortality in malaria in our study may be due to improved health awareness among patients, increased communication facilities to our tertiary care hospital, adequate supportive measures, prompt treatment of complications and earlier institution of dialysis wherever required.

Table-6
Correlation of outcome with aetiology of ARF

Aetiology	Total cases	Discharge	Death
Malaria	60	58	2
Vasculotoxic snake bite	26	24	2
Acute gastroenteritis	30	30	0
septicaemia	4	0	4
Unknown aetiology	20	20	0
Total	140	132(94.28%)	8(5.71%)

60 patients (42.85%) needed dialysis while 80 patients (57.14%) improved with conservative treatment as shown in table 7. A higher percentage of patients required dialysis in earlier studies conducted by Panda et al (75%), Mehta et al (92%) and Shah PR (78%). Our study showed less requirement of dialysis as majority of the patients presented to us earlier and were treated with adequate supportive measures.

Table-7
Correlation of aetiology of ARF with treatment

aetiology	Conservative treatment	Dialysis	Number of cases
Malaria	40	20	60
Vasculotoxic snake bite	9	17	26
Acute gastroenteritis	20	10	30
Septicaemia	0	4	4
Unknown aetiology	11	9	20
Total	80(57.14%)	60(42.85%)	140

CONCLUSION

Among the 140 cases of ARF, malaria was the most common aetiology, followed by acute gastroenteritis and vasculotoxic snake bite. With the available investigations including renal biopsy, we were unable to find out the aetiology in 10 patients. Here the electron microscopy to study the renal tissue might have clinched the diagnosis. Irrespective of the aetiology of ARF, prompt and adequate management including haemodialysis as and when required, saves the lives of patients and minimises mortality.

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BEST PAPERS OF 2011

The following original article and case reports are selected as best papers of 2011 by the following refrees and are to be awarded on 12th November, 31st APICON Odisha Branch, 2011.

Refrees : Prof. J.P. Das (Cuttack), Prof. M. Kar (Burla), Dr. S.K. Kar (Bhubaneswar)

Original Article

Title : Prediabetes (IFG/IGT) with special reference to carotid & femoral intima media thickness.

Authors : Dr. S.K. Jena, Dr. R.K. Dalai, Dr. M.R. Behera, Dr. S.C. Singh

(Dept. of Medicine, SCB Medical College, Cuttack)

Case Report : (Jointly declared best Case Reports)

** Title : Intravascular Haemolysis in Black Phenyl Poisoning : 2 case reports.*

Authors : Prof. L.K. Dash, Dr. P.K. Mohanty, Dr. C.R. Khatua, Dr. G.P. Nayak.

(Dept. of Medicine, VSS Medical College, Burla)

** Title : An unusual case of Recurrent Hemoptysis.*

Authors : Dr. K.P. Tripathy, Dr. P.K. Behera, Dr. R. Panigrahi, Prof. A. Devi.

(Dept. of Medicine, Hi-Tech Medical College, Bhubaneswar)

Original Article

COMPARATIVE STUDY OF ISCHEMIC STROKE VERSUS HEMORRHAGIC STROKE IN RELATION TO RISK FACTORS IN SOUTHERN ORISSA

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ABSTRACT

*Two hundred and forty cases of CT-scan stroke patients admitted in Department of Medicine in MKCG Medical College and Hospital, Berhampur during the period from October, 2008 to October, 2010 were the subjects of the present study. 62.5% of patients were male and 37.5% female, with male to female ratio 1.6:1. Maximum numbers of cases were observed between age group 51-60 years in males and 61-70 years in females. Mean age of presentation for males was 58 years and for female, 55 years. Young stroke «40 years constituted 7.1 % cases. Cerebral infarctions constituted 60% of cases, 38% cases were intracerebral hemorrhage and 2% cases were SAH. Maximum number of infarction had lesion in MCA territory (77.7%) followed by PCA (14%) and ACA (8.3%). Among hemorrhage cases most had lesion in MCA territory (88.5%) followed by PCA (7.3%) and ACA (4.2%). The common risk factors for stroke were hypertension (48.3%), hyperlipidemia (38.33%), smoking (26.3%), IHD (25%), obesity (22.9%), DM (14.6%), peripheral vascular diseases (10%) and valvular heart diseases (3.8%). The other risk factors observed were sickle cell disease, leukemia, SLE, and pregnancy/puerperium. In male the commonest risk factors were hypertension (50%), hyperlipidemia (39.6%), smoking (42%), alcohol intake (27.3%), IHD (25.3%), obesity (21.3%) and DM (148%). In female it was hypertension (45.1 %), hyperlipidemia (36.3%), obesity (25.3%), IHO (24.2%) and DM (14.3%). Most common risk factors in young stroke was valvular heart diseases (33.3%). Others included sickle cell disease (11.1%), leukemia (11.1%), family history (11.1%), SLE (5.6%), and pregnancy/puerperium (5.6%). It was found that morbidity were more with uncontrolled hypertension and DM. The study "Comparative Study of Ischemic Stroke Versus Hemorrhagic Stroke in Relation to Risk Factors in Southern Orissa" was carried out in the Department of Medicine of MKCG Medical College and Hospital, Berhampur during the period from October, 2008 to October, 2010. 240 CT proved cases of stroke was studied.****Keywords :*** *Ischemic Stroke, Hemorrhagic Stroke, Risk Factors.*

INTRODUCTION

Stroke is a medical emergency and can cause permanent neurological damage, complications and death. It is the leading cause of adult disability in the United States and Europe. It is the number two cause of death worldwide and may soon become the leading cause of death worldwide (Feigin VL (2005).

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METHODS

The study was done with following aims:

1. To assess the incidence, prevalence, morbidity and mortality of stroke in Southern Orissa in relation to Ischemic vrs. Hemorrhagic Stroke. 2.To study the role of risk factors life, age, sex, blood pressure, smoking, blood lipids, diabetes mellitus, family history of stroke, existing vascular disease etc in relation to Ischemic vrs. Hemorrhagic Stroke. Study Group: 240 cases of CT-Scan proven stroke patients after exclusion by the following exclusion criteria, were selected as the study group.

Exclusion Criteria: i) Age > 80 years and <15 years. ii) Patients with history of past major stroke. iii) History of head injury within 3 months. iv) Fever and meningial signs. v) Patients with tumor, brain abscess and other space occupying lesion. Study Protocol: Clinical history was taking from either the patient or his/her relative or attendants. Particular importance was given regarding presence or absence of vomiting, headache, and convulsion within 2 hours post ictus. Past history of TIA, hypertension, diabetes, CAD, RHD, collagen diseases, meningitis, endocrine disorders, and congenital disorders were taken. Personal history with particular regards for dietary habits, smoking, alcohol intake, and socio-economic status were noted. Detailed general examination with particular importance to height, weight, BMI, waist/ Hip ratio, markers of atherosclerosis, blood pressure was noted. Detailed neurological examination based on proforma was done within 2 hours of admission. Other systems like cardiovascular system, GIT, respiratory system were examined in detail. In all cases routine hematological investigations FBS, lipid profile, serum electrolytes, serum urea and creatinine, urine routine and microscopy, electrocardiogram were done. CT Scan after 24 hours onset of symptom was taken with the patient being stabilized. All relevant data were recorded in a proforma.

Patients were given complete bed rest. Oxygen supplementation, nasogastric tube and catheterisation of the bladder were given for required patients. Measures were taken to prevent aspiration pneumonia and bedsores. Cerebral edema was managed with intravenous mannitol. Patients with infractions were put on aspirin 350 mg. or clopidogrel 75mg. once daily. Patients were classified as hypertensives if they had previous history of hypertension or persistent BP of > 140/90 mm. of Hg. even after one week of stabilization. Hypertension, diabetes mellitus and hyperlipidimia were adequate managed.

With adequate recovery, he or she was discharged with the advice of continuing the treatment, lifestyle modification, physical and social rehabilitation. They were asked to follow up on regular interval.

The socio-economic status was assessed based on Kuppuswamy criteria. BMI was calculated based

Table Showing Overall Risk Factors (N=240)

Risk Factors	No. of cases			%
	<41 yrs.	41-60 yrs.	>60 yrs.	
1. Cardio Vascular diseases				
i) Hypertension	3	45	68	48.3
ii) IHD	0	15	45	25.00
iii) Valvular heart diseases	6	3	0	3.8
iv) Peripheral				
2. Diabetes Mellitus	0	7	17	10.00
3. Hyperlipidemia		16	19	14.6
3. Hyperlipidemia	0	50	42	38.33
4. Obesity	0	30	25	22.9
5. Smoking	2	40	21	26.3
6. Alcohol	0	30	11	17.1
7. Family History	2	16	12	12.50
8. Others				
i) Sickle cell disease	2	0	0	0.83
ii) Leukemia	2	0	0	0.83
iii) Pregnancy/Peripartum	1	0	0	0.42
iv) SLE	1	0	0	0.42

on the formula weight in Kg /Height in Square Meter.CT Scanning was done 24 hrs post ictus. Schimadzu CT *3000T* CT scanner was used which belongs to third generation of CT scan machine. In all cases only plain CT was done. The patients are kept in supine portion and 15° tilt upwards is given along the orbito-meateal line to prevent radiation to face. 8mm. sections were taken infratentorial and 10mm. section supratentorial.

RESULTS

Overall risk factors

Among over all risk factors 48.3% had hypertension, 25% had IHD, 3,8% had Valvular heart diseases, 10% had peripheral vascular diseases, 14.6% had Diabetes Mellitus, *38.3'1'0* had hyperlipidemia, 22.9% had obesity, 12.50% had family history. 26.3% had history of smoking and 17.1 % had history of alcohol intake. Other risk factors constitute.

Age distribution of stroke

The youngest patient was a female of 19 years; the oldest was an 80 year old male. Maximum numbers of cases were observed between age group 51-60 years in males and 61-70 years in females. This is comparable with the study by Abraham et al. Vellore 1970; Razdon et al. 1994. Mean age of presentation for males was 58 years and for females, 55 years. Increasing age as an important risk factor has been recognized by Bamford et al. 1990. Young stroke (age <40 years) constituted 17 cases. In various Indian studies which also includes patients < 15 years, (which cannot be included in the present study) shows percentage ranging from 7 to 32% for young stroke (Bansal Be et al. 1973; Prabakar S. et al. 1999).

Sex distribution of stroke

In the study 62.5% of the patients were males while 37.5% female with male to female ratio 1.6: 1. Male preponderance of stroke was reported earlier by Halberman, Rose et al. 1987; Framingham study. Similar pattern has been shown by many Indian authors, 1.6: 1 by Gupta et al. 1965; 1.43:1 by Venkataraman et al. 1997. Table-3 shows that out of 150 males 56 cases (37.3%) had hemorrhagic stroke and 94 cases (62.7%) had infarction. Out of 90 females 40 (44.4%) had hemorrhagic stroke and 50 (55.6%) had infarction. Thus incidence of hemorrhagic stroke is high in females in the study.

CT evaluation of types of stroke

The present study shows 144 cases (60%) of ischemic stroke and. 96 cases (40'%) of hemorrhagic stroke. Out of which 5 cases (2.0%) were SAH. The higher percentage of hemorrhagic stroke is comparable with that of other studies conducted in India. Khan et al. 2001 Stroke in Kashmir Valley has demonstrated higher percentage of hemorrhagic stroke in Kashmir. Cerebral hemorrhage constituted 10-15% cases in Europe and America (Kurtz JF, 1985), but in developing countries hemorrhagic lesion is far commoner partly because of poorly controlled hypertension. At Siriraj Hospital cerebral hemorrhage accounted for 40-50% of stroke (Poungvarin et al. 1991). Denise Nassisi et al 2010, study has shown 40.9% hemorrhagic stroke. Jamary Oliveria-filho, Walter J Koroshetz et-al, 2010 study has shown 61% incidence of ischemic stroke.

Socio-economic class of stroke patients

Most of stroke patients 132 cases (55%)) belonged to the middle class. Various studies (J. Assos physicians of India, 1998, Apr.: 46) has shown lower prevalence of stroke in rural community compared to that of urban area. Ethnic, socio-economic, and dietary factors may be responsible for this variance. This may be also due to the bias in the admission rate as less people of low income, avail of hospital facilities.

Localisation of the lesion according to arterial territory

In maximum cases, MCA territory was involved, 112 (77.7%) cases of infarction and 85 cases (88.5%) of hemorrhage. This is in consistent with other studies, which has shown that most frequently involved vessel is MCA. This may be related to the frequent involvement of internal carotid artery branches by atheromatous process and the high percentage of blood (80%) carried by MCA to the cerebral hemispheres. (Bogousslavsky J, Caplan LR, Stroke syndromes,

Clinical syndromes based on arterial territory involved

Most of the cases (103 (43%)) belonged to PACS. This is followed by TAGS (92 (38.3%)), POCS (31 (12.9%)) and lacunar syndrome (14 (5.8%)). Predominance of TAGS has been shown in various studies, 35% in Dennis et al. 1991; Bamford et al. 1991; Mead et al. 2000.

Types of Lacunar Syndrome

Study showed that majority of lacunar syndromes belonged to pure motor type (9 cases out of 14(64.3%)). This is followed by 3 cases (21.4%) of ataxia and 2 cases (14.3%) of dysarthria clumsy hand syndrome. Predominance of motor type has been shown in various studies (Fisher CM, Neurology 1982; Chamorro A et al. 1991].

Risk Factors

The common risk factors for stroke in the present study were hypertension (48.3%), hyperlipidemia (38.33%), smoking (26.3%) and lHD (25%). Valvular heart diseases were observed in 3.8% cases. Obesity (22.9%), DM (14.6%) and PVD (10%) was also observed. The risk factors observed in this study were alike the previous study in India (WHO task force 1989). 24 patients had both DM and hypertension as shown in table 15.

In males, the commonest risk factor were hypertension (50%), Hyperlipidemia (39.6%), smoking (42%) Alcohol intake (27.3%), lHD (25.3%), obesity (21.3%) and DM (14.8%). The risk factors commonly observed in females were hypertension (45.1%), hyperlipidemia (36.3%), Obesity (25.3%), IHD (24.2%) and DM (14.3%). ICMR prospective case control study of strokes has shown that hypertension, high blood sugar and smoking are most important risk factors involved.

High blood pressure is a major risk factor in both sexes at all ages (Dalai PM, Dalai KP. et al 1980-89; Whelton 1994; Thrift et al. 1998). The percentage difference in stroke risk associated with blood pressure is similar in male 50%, present study (48.3%) at all levels of blood pressure. Table 14 clearly shows that morbidity and mortality due to hypertension is more in patients in whom, BP is not treated or inadequately treated. This has been clearly demonstrated by Framingham study, 1991.

Diabetes mellitus is listed as one of the risk factors contributing to stroke morbidity and mortality (Abbot RD et al. 1987; Dalai P.M, 1989, ICMR study). Table 15 shows that more death in inadequately controlled DM. This suggests that a better glycaemic control in diabetes probably improves the prognosis in acute stroke (Northern Manhattan stroke study).

Smoking as risk factor has been confirmed by ICMR risk factor study for cerebral disease and Dalai PM 1989 .. Smoking has been related to the extent of carotid disease in-patient selected for angiography by ultra sound (Homer et al. 1991).

In the study mean value for serum cholesterol and triglyceride for ischemic (195. 7±68.4 and 145.0±68.4) is more than that in hemorrhagic stroke (195±35.6 and 115.3 ± 26) LDL value in hemorrhagic stroke (145 ± 20.1) is higher than that for ischaemic stroke (135.3±42.2). HDL value in ischemic stroke (37.1 ± 5.3) is lower than in hemorrhagic stroke (45.6±9.7). In the literature no constant relationship has been observed between cholesterol levels and risk of stroke (Dalai et aJ. 1989; Bansal BG et aJ.] 979; (Prospective studies collaboration 1995).

The association of risk factors obesity (22.9%), lHD (25%) and PVD (10%) may be mediated by associated hypertension and diabetes (Welin et a1. 1987; Shi ton et al. 1995; and Rexvode et a1. 1997).

Other risk factors in the present study were sickle cell disease (0.83%), Leukemia (0.83%), Pregnancy puerperium (0.42%) and SLE (0.42%). This is consistent with ICMR study 1994 where hematological diseases like sickle cell disease, leukemia and pregnancy related coagulopathy together constituted around 4.6% of stroke.

In the present study most important risk factor for young stroke was valvular heart diseases (35.3%). Cardiac embolisation from RHD has been reported to

be responsible for 10-15% young stroke in India. Other risk factors in the study include hematological disorders like sickle cell diseases and leukemia, pregnancy puerperium for young stroke. Strokes in relation to pregnancy and puerperium is common in India (Bansal BC et al. 1973; Chopra JS et a1. 1979).

Clinical picture in stroke

In hemorrhagic stroke, mode of onset was sudden in 80.2% and gradual in 19.8%. There was history of vomiting and headache in 75% of patients . On admission 50% patients were stuporous or confused and 35.4% were comatose.

In ischemic stroke mode of onset was sudden in 68.1% and gradually in 31.9%. There was history of vomiting and headache only in 22.2% of cases. On admission 46.5% were stuporous or confused and 43.1% patients were alert. Only 10.4% patients were comatose. The most important risk factors for cerebral hemorrhage were hypertension (45.8%), smoking (4].7%), hyperlipedemia (32.3%), obesity (27.1%), alcohol intake (25%), IHD (22.9%) and DM (11.5%). The most important risk factors for cerebral infarction were hypertension (50%), hyperlipedemia (42.3%), IHD (26.4%) obesity (20.1%), DM (16.7%), alcohol intake (11.8%) and smoking (15.9%). Similar clinical features and risk factors are documented by Virikejakul et al. 1982 and Poungavarin et al. 1991.

CONCLUSION

Two hundred and forty cases of CT-proved stroke patients were studied. 62.5% were male and 37.5% female with male to female ratio] .6: 1. Maximum male patients were in 5th decade and female in 6th decade. Young stroke constituted 7.1% cases. Cerebral infarction constituted (60'1"0), intracerebral hemorrhage (38%) and SAH (2%,) of patients. Maximum lesion was in MCA territory. Commonest risk factors were hypertension, hyperlipidemia and smoking. Stroke is one of the leading causes of death and disability in our country. Its toll is likely to increase unless definite steps are taken for primary and secondary prevention of risk factors, especially hypertension. In the study only patients admitted in the hospital was taken into account, which under estimates the true incidence and prevalence of the morbidity and mortality of stroke. Essentially, studies to measure the incidence and define the risk factors are urgently required so that sound preventive strategies could be planned .

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Original Article

CLINICO EPIDEMIOLOGICAL PROFILE AND OUTCOME IN POSTERIOR CIRCULATION STROKE

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ABSTRACT

Introduction*: The incidences of posterior circulation stroke (PCS) are on rise accounting 10 to 15% of all strokes, with up to 20-60% having an unfavorable outcome.* ***Aims and objectives:*** *The purpose of this study was to analyse the clinical presentations, epidemiology and outcomes associated with posterior circulation stroke.* ***Methods:*** *The patients admitted to the Dept. of General Medicine, VSS Medical College, Burla from the period of August 2009 to July 2011were included. CT scan or MRI was done for diagnosis of PCS. Clinical manifestations, epidemiological evaluation, risk factors involved and outcome were studied.* ***Result:*** *Of 1407 patients with stroke, 148(10.52%) patients had PCS, with a male to female ratio of 3:1. PCS occurred in age range of 20-90 years with more than 75% over 50 years. 72.3% had ischemic and 27.7% had hemorrhagic PCS. Infratentorial PCS (60.8%) was more common than supratentorial (28.4%). Cerebellum was the commonest site for both ischemic (68.4%) and hemorrhagic (60.0%) infratentorial PCS. Occipital lobe was most often the site in case of supratentorial ischemic (77.1%) and hemorrhagic (71.4%) PCS. Hypertension (41.9%) and tobacco abuse (23.6%) were the commonest risk factors. The most frequent manifestation was motor weakness in ischemic (59.8%) and altered sensorium in hemorrhagic (97.6%) PCS. Other findings in PCS were headache, vomiting, dysarthria, vertigo, dizziness, ataxia, blurring of vision, double vision, cranial nerve involvement, cerebellar signs and respiratory distress. Only 24.5% patients were suspected clinically to be PCS. 75.5% patients thought to have stroke involving anterior circulation clinically were found to be PCS by CT/MRI. The arterial distribution of infarction was undetermined in 51.5% and where delineation possible posterior cerebral artery (PCA) was most commonly affected (25.3%). In our study 56.8% survived, 33.6% died and 9.6% cases lost to follow up.* ***Conclusion:*** *A significant (10.52%) proportion of strokes are due to PCS. CT scan/MRI is useful for diagnosis. Many patients of PCS with vertigo, dizziness or vomiting may be misdiagnosed. Mortality rate was 33.6% in this study. However, early diagnosis and management improved outcome.* ***Key words:*** *Posterior Circulation Stroke, Ischemic PCS, Hemorrhagic PCS*

INTRODUCTION

Stroke involving anterior circulation are commoner than posterior circulation but presently the incidence of posterior circulation stroke (PCS) are on rise and accounts for approximately 10 to 15 percent of all stroke, with up to 20-60 percent having an unfavorable outcome [1, 2,3]. Published data from the Tufts New England Medical Center posterior circulation stroke registry document that 58% of patients are male and 42% are female, with the mean age of stroke being 61.5 years.[4]

The posterior circulation consist of the vertebral artery, the basilar artery, the posterior cerebral arteries and their branches and supply brain stem (medulla, pons and mid brain), thalamus, cerebellum, occipital lobes and parts of the temporal lobe [5]. Unlike the intracranial portion of the anterior circulation, these arteries are prone to atherosclerosis much as are other systemic arteries.

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Death from posterior circulation ischemic stroke is uncommon, but concomitant basilar artery occlusion carries mortality of over 90% [1]. Mortality is higher in hemorrhagic PCS [8].

Patients with PCS may present with wide variety of syndromes ranging from fluctuating brainstem symptoms caused by intermittent insufficiency to many syndromes like lateral medullary, medial medullary, locked in syndrome and top of basilar syndrome [6]. Some times initial clinical presentations suggestive of anterior circulation stroke are found to result from a posterior circulation stroke, a fact that may generate erroneous decision in clinical management.

There are only few studies for the stroke involving posterior circulation [7]. In Indian population no registry is available to reflect the true incidence of cerebrovascular disease. There are very few studies available for posterior circulation ischemic strokes in India and to the best of our knowledge there were no studies available in posterior circulation hemorrhagic strokes in India in literature except the recent publication in 2011 by Kora SA et al [8].

Considering PCS as not uncommon problem in our day to day experience with high morbidity and mortality we studied the clinical and epidemiological profile, associated risk factors and outcome in PCS.

METHODS

The study was conducted on the patients admitted to the Dept. of General Medicine, VSS Medical College, Burla from the period of August 2009 to July 2011.

All clinically suspected stroke patients were evaluated by CT scan for detection of posterior circulation stroke. MRI was done in cases where CT scan was normal. CT scans showing recent infarction or hemorrhage in the anterior circulation and other non-vascular lesions were excluded from the study.

A detailed history was obtained from the patient or a close relative regarding the onset and progression of stroke, risk factors, past illness, family history, personal history and treatment history. A detailed physical examination and systemic examination was done.

All the patients were investigated with CT scan of head, hematological and biochemical parameters like CBC, ESR, urine analysis, plasma glucose, blood urea, serum creatinine, serum electrolytes, lipid profile, serum homocystine , sickling test and others like ECG , chest radiography, USG abdomen and pelvis, Echocardiography, Doppler study of carotid artery, MRI, etc were done wherever necessary.

RESULT

During the two year study period the total number of strokes and posterior circulation stroke (PCS) were 1407 and 148 respectively and the percentage of PCS was 10.52% of all strokes. Out of 148 PCS, 111 patients were male and 37 were female with male to female ratio 3:1. PCS occurred in a wide range of age groups (20-90 years). Age wise incidence of PCS is as follows: <20 years : 0.7%, 21-40 years: 6.8%, 41-50 years: 17.6%, 51-60 yrs: 30.5%, 61-70 years: 22.2%, >70 years: 22.2%.

The various types and sites involved in PCS are mentioned in Table-1

Table-1: Types and sites of PCS (N=148)

Types of PCS	Infratentorial		Supratentorial		Infra & Supratentorial		Total	%
	No.	%	No.	%	No.	%		
Ischemic	60	56.1	35	32.7	12	11.2	107	**72.3**
Hemorrhagic	30	73.2	7	17.1	4	9.7	41	**27.7**
Total	90	60.8	42	28.4	16	15.8	148	**100**

Hypertension (33.6%) and smoking (29%) were the most common risk factors in ischemic PCS whereas hypertension (963.4%) singled out as the commonest and most important risk factor in hemorrhagic PCS. (Table-2)

Table-2: Risk factors for PCS

Risk factors	Ischemics PCS	Hemorrhagic PCS
Hypertension	33.6%	63.4%
Smoking history	29%	9.8%
Diabetes	14%	12.2%
Hyperlipidemia	6.5%	4.9%
RHD	6.5%	0%
Ischemic heart...	4.7%	0%
Alcohol	1.9%	7.3%
Cardiomyopathy	1.9%	0%
Sickle Cell disease	1.9%	0%
Past h/o TIA	0.9%	0%
Pregnancy/peripartum.	0.9%	0%
Past h/o stroke	0%	2.4%

The most frequent manifestation was motor weakness (59.8%) in ischemic PCS and altered sensorium (97.6%) in hemorrhagic PCS. Other clinical presentations in PCS are described in Table-3.

Table-3: Clinical Manifestations in PCS.

MANIFESTATIONS	ISCHEMIC PCS		HEMORRHAGIC PCS		Total (N=148)	%
	No. (N=107)	%	No. (N=41)	%		
Altered sensorium / LOC	60	56.1	40	**97.6**	100	**67.6**
Dizziness	36	33.6	-	-	36	24.3
Lightheadedness	36	33.6	-	-	36	24.3
Headache	59	55.1	27	65.6	86	**58.1**
Vertigo	42	39.3	8	19.5	50	33.8
Vomiting	44	41.4	28	68.3	72	**48.6**
Dysarthria	46	43.0	10	24.4	56	**37.8**
Blurring of vision	20	18.6	4	9.8	24	16.2
Double vision	3	2.8	-	-	3	2.0
Motor weakness	64	**59.8**	10	24.4	74	**50.0**
Ataxia	40	37.4	10	24.4	50	33.8
Dysphagia	16	14.9	2	4.9	18	12.2
Convulsion	5	4.7	5	12.2	10	6.8
Sensory disturbances	8	7.5	-	-	8	5.4

Serum Homocystine was estimated in 20 patients (12 ischemic and 8 hemorrhagic). Elevated level (>13.9µmol/L) were found in 9 cases of ischemic and 4 cases of hemorrhagic PCS. The mean serum homocystine level in ischemic and hemorrhagic PCS were 15.08µmol/L and 12.75µmol/L respectively. However, this was not statistically significant (p>0.10) (Table-4).

Table-4: Serum Homocystine level in PCS (N=20)

	No. of cases	Range(µmol/L)	Mean	SD	'P' Value
ISCHEMIC PCS	12	7-24	15.08	5.583	<0.10
HEMORRHAGIC PCS	8	5-23	12.75	5.898	<0.10

Clinical symptoms and signs were suggestive of PCS in 36(24.5%) of cases which are confirmed later on by CT/MRI whereas in 112 (75.5%) cases the diagnosis of PCS was not suspected clinically and detected only after CT scan/MRI. 134 cases of PCS were detected by C.T. scan on first instance, 10 cases by repeat C.T. scan after 72 hours and 4 cases by MRI..

The various arterial territories involved in PCS and their associated mortality reflected in Table-5. In a major proportion (51.5%) the exact arterial territories involved could not be determined. Incidence of mortality in ischemic PCS was 31.7% and it was higher in stoke involving basilar artery (66.6%).

Table-5: Arterial Territory Involved & their association with mortality in Ischemic PCS (N=107)

Arterial territory	No. of cases	%	No. of death (%)
Posterior cerebral artery (PCA)	27	25.3	9(33.3%)
Posterior inferior cerebellar artery (PICA)	10	9.3	4(40%)
Anterior inferior cerebellar artery (AICA)	7	6.6	2(28.5%)
Superior cerebellar artery (SCA)	4	3.6	1(25%)
Vertebral	1	0.9	0(0%)
Basilar	3	2.8	2(66.6%)
In determined	55	51.5	16(29%)
Total	**107**	100	**34(31.7%)**

Discussion

During the two year study period the total number of patients admitted to medical ward were 23725, out of which 1407 patients had stroke accounting 5.9% of total admission. Among all strokes, 10.52% had PCS which is comparable with other studies conducted by Kora SA et al[8] (12.3%), Jones.et al[13] (17%) and Richard et al[14] (14.8%)

The occurrence of PCS in present study is commoner in male (M: F=3:1). Male preponderance of PCS is also reported from India by Kora SA et al[8] (3.1:1).

PCS occurred in a wide range of age groups the youngest being 20 years old and the oldest 90 years in our study and more than 75% of cases were found above the age of 50 years. 11 patients were

Various findings in CT scan & their correlation with mortality in hemorrhagic PCS is depicted in table-6.

Table-6

Various CT Finding and their association with mortality in hemorrhagic PCS (N=41)

C.T. findings	No.of cases	%	No. of Death (%)
Intra ventricular communication	8	19.5	2(25%)
Midline shift	6	14.6	3(50%)
Hematoma size >3cm	8	19.5	6(75%)
Hydrocephalus	6	14.6	3(50%)
With Sub Arachnoid Hemorrhage (S.A.H.)	3	7.4	1(33.3%)
Not associated with above C.T. findings	10	24.4	1(10%)
Total	**41**	100	**16(39%)**

Outcome : In our study 56.8% survived, 33.6% died and 9.6% cases lost to follow up.

under the age of forty years i.e. young stroke (7.5%). PCS are more common in the age group 51-60 years (30.5%) both in male and female. Ischemic PCS was more common in age group 51- 60 years and hemorrhagic stroke in age group 71-80 years. Kora SA et al [8] reported 41 to 50 and 71 to 80 age groups are more common for ischemic and hemorrhagic PCS respectively.

Out of the 148 cases of PCS, 107 (72.3%) cases are ischemic and 41 (27.7%) cases are hemorrhagic PCS which is similar to observation made Kora SA et al [8] (76% ischemic strokes vs 24% hemorrhagic strokes) and Uma Sundar et al[15] (77% ischemic strokes).

The commonest site of PCS was infratentorial in location (60.8%) for both ischemic (56.1%) and hemorrhagic (73.2%) PCS (Table-1). Infratentorial location of ischemic stroke reported by Kora SA et al [8] and Bogousslavsky et al study[16] were 63% and 70% respectively. The slightly higher incidence in case of Bogousslavsky et al study[16] could be due to greater use of MRI in his study. Incidence of Infratentorial hemorrhagic strokes was high (73.2%) compared to other sites in the present study which was close to as observed by Kora.et al[8] (63%).

Of the infratentorial stroke, Cerebellum was the most common site for both ischemic (68.4%) and hemorrhagic (60.0%) PCS. Occipital lobe was the most common supratentorial site for both ischemic (77.1%) and hemorrhagic (71.4%) PCS. The second most common site for hemorrhagic PCS was Pons (23.3 %%) and for ischemic it was combined Cerebellum & Brainstem (14.1%) (Figure-1).

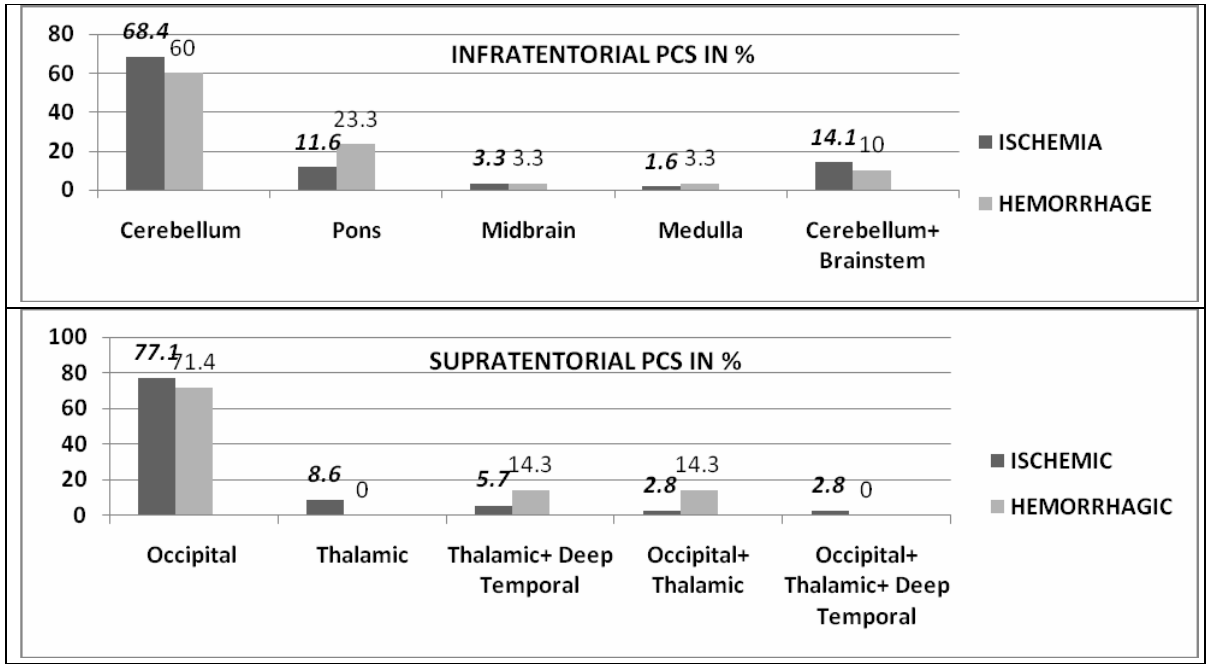
Of the various risk factors associated with PCS hypertension (41.9%) was the commonest (Table-2). In ischemic PCS hypertension was associated in 33.6% cases and in hemorrhagic PCS it was found in 63.4% cases. Hypertension was also the most common risk factor in studies of PCS done by Kora SA et al [8] , E.Ratnavalli et al [18], Capalan et al [19], and Uma et al [15] and Dalal et al[18].

In our study, smoking was a risk factor in 23.6% cases (29% of ischemic and 9.8% of hemorrhagic PCS) and diabetes in 13.5%(14% of ischemic and 12.2% of hemorrhagic PCS) cases of PCS. Incidence of tobacco abuse and diabetes were comparable with the studies by E.Ratnavalli et al [20] (20%) and Uma et al [17] (21%) respectively. Other risk factors associated with PCS are alcohol consumption, hyperlipidemia, sickle cell disease, rheumatic heart disease, ischemic heart disease, cardiomyopathy, pregnancy related hyper coagulopathy, past history of TIA and past history of stroke. (Table-2).

In our study many patients had more than one associated risk factors and in 16.2% of cases definite risk factors could not be found out.

Out of 148 cases, 100 (67.6%) presented with impaired consciousness, of 35 patients were comatose and rest were in confused or stuperous state. Seventy four (50%) patients presented with motor weakness (hemiparesis / hemiplegia). This findings are close to

Figure-1: Distribution of PCS as per CT scan



the Patrick et al [17] , Kora SA et al [8] and Gonzalez et al [21].

Sixty five (43.9%) patients presented only with following symptoms, without significant impairment of consciousness and hemiparesis which include (in descending order of incidence) – Headache (58.1%), Vomiting (48.6%), Speech disturbance (37.8%),Vertigo (33.8%), Ataxic gait (33.8%), Dizziness (24.3%), Lightheadedness (24.3%), Blurring of vision (16.2%), Dysphagia (12.2%), Convulsion(6.8%), Sensory disturbances (5.4%), Double vision (2.0%). This is similar to the study of P.J. Kelly et al [22].

The most common neurological signs in ischemic PCS were motor weakness (59.8%) and altered sensorium (56.1%). Others were cranial nerve involvement (5^{th}, 6^{th}, 7^{th} or 8^{th}) in 46.7% and cerebellar signs in 40.2% of cases. In hemorrhagic PCS 97.6% and 39.0% patients had altered sensorium & respiratory distress respectively. Hypertensive retinopathic changes were seen in 41.9% patients of PCS and were more common in hemorrhagic variety. Other neurological findings like nystagmus and neck rigidity were found in 31.1% & 10.1% of cases respectively. Majority of neurological findings of present study are comparable with Kora SA et al[8] and Patrick et al[17] in Table-7.

Table-7: Comparision of Neurological findings

Neurological Findings	Patrick et al [17] (%)	Kora SA et al [8] (%)	Present study (%)
Premonitory symptom	-	-	43.9
Altered level of consciousness +/- other	47	63	67.6
Respiratory distress	-	-	18.9
Cranial Nerve involvement	64	53	39.2
Motor weakness +/- other Symptoms	43	63	50.0
Cerebellar sign	29	37	33.1
Nystagmus	29	32	31.1
Neck rigidity	-	05	10.1
Hypertensive retinopathic changes	-	37	41.9

Clinical diagnosis of PCS is difficult and is usually missed as compared to anterior circulation stroke.

Only one fourth (24.5%) PCS were suspected clinically and confirmed later by CT/MRI. In rest of the patients (75.5%) initially thought to be stroke of anterior circulation was found to be PCS by CT/MRI. Thus imaging studies like CT/MRI are very important tools in suspected cases. These are also useful to distinguish PCS from labyrinthitis, SAH, space occupying lesions, meningitis, migraine etc.

Because of lack of MRI facility in our institution and also cost factor arterial distribution could not be evaluated in all PCS. It was possible to know only in 52 cases (48.5%) of ischemic PCS. Posterior cerebral artery (PCA) was most commonly affected (25.3). In all, 34 ischemic PCS cases died (31.7%) of which the mortality was highest in that involving basilar artery (66.6%). (Table-5).

Out of 41 hemorrhagic PCS cases, 8 had intra ventricular communication, 6 were having midline shift, 8 had large hematoma > 3cm in maximum diameter (Cerrebellar-6 cases, Occipital-2 cases), 6 cases had hydrocephalus and 3 with SAH . Mortality was 39% in hemorrhagic PCS and it was higher in patients with large cerebellar hematoma of size >3cm (75%). (Table-6).

Out of 148 patients 56.8% survived, 33.6% died and 9.6% were lost to follow up. Incidence of mortality was slightly higher as compared to other studies like Patrick et al [17]study (25.6%) and Jones et al [13] study (27.5%). Survival rate was lower in studies by Kora SA et al [8] (47%) and Jones et al [15] (35%). In our study mortality was higher in hemorrhagic strokes than ischemic strokes (39% vs. 31.7%) [* Internal error: Invalid file format. | In-line.WMF *] where as Kora SA et al [8] reported higher mortality of 50% in hemorrhagic PCS that is almost double that of mortality in ischemic PCS (26.3%).

CONCLUSION

A significant (10.52%) proportion of strokes are due to PCS. PCS mostly occurs after 50yrs age and is more common in men. Ischemic type and Infratentorial site (cerebellum) are more common. Hypertension and tobacco use are commonest risk factors. Clinical diagnosis of PCS is difficult and may be missed. Risk factors are similar in strokes involving both posterior circulation and anterior circulation strokes. However, they differ in clinical in clinical presentation, as different anatomical structures are involved. This may also be explained by a more frequent arterial branch disease in the territory of the basilar artery that gives classical lacunar syndromes. Many patients without significant focal neurological deficit were found out as cases of cerebellar stroke. CT and MRI helped in early diagnosis of PCS. Many patients of PCS with vertigo, dizziness or vomiting may be misdiagnosed as labyrinthine or vestibular disorders. Incidence of mortality was higher in hemorrhagic PCS[* Internal error: Invalid file format. | In-line.WMF *]. Early recognition and prompt management is required for better outcome.

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Original Article

IMPACT OF CIRCADIAN VARIATION ON INFARCT SIZE IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

The circadian clock influences a number of cardio-vascular events including the incidence of acute myocardial infarction. Recent scientific literature has shown a circadian variation in infarct size in rodents. However this path-breaking discovery has not been tested in clinical settings. We sought to find out whether such a pattern exists in humans. This is an observational study based on case records at referral hospitals. ***Keywords :*** *Acute myocardial infarction, Infarct size, Circadian variation.*

INTRODUCTION

It is well known that changes in circadian rhythm influences cardiovascular events such as diurnal variations in blood pressure, heart rate, cardiac output and endothelial function.[1] These changes in cardiovascular physiology influence events such as myocardial infarction (MI), sudden cardiac death, accelerated hypertension and cardiac arrhythmias with higher incidence in the early morning hours especially the transition between night to day hours.[2] Such circadian variations in cardiovascular events could be due to alterations in epinephrine and cortisol levels, prothrombin factors, platelet aggregation and coronary arterial flow.[3]

Epidemiological studies have shown that the incidence of acute myocardial infarction (AMI) varies significantly throughout the day with a peak incidence in the transition period from night to day.[4,5] The question is does this circadian variation in incidence of AMI have any effect on the extent of myocardial damage? The survival of cardiac myocytes (cardioprotection) depends to some extent on the degree of salvage pathways.[6] Preclinical studies have shown that the expression of some proteins involved in this salvage pathway may show a circadian variation.[7] It is therefore possible that this fluctuation could influence infarct size.

The aim of this study therefore was to determine the impact of time-of-day of AMI onset on infarct size in patients with ST elevated myocardial infarction (STEMI).

METHOD

Patients admitted with STEMI to Cardiology ICCD of VSS Medical College; Burla and Department of, Medicine, SCB Medical College, Cuttack formed the study population. STEMI was defined by the following criteria:

(a) Typical chest pain of $\geq$ 30 min.

(b) Significant ST elevation ($\geq$ 0.1 mv or $\geq$ 0.2mv in $\geq$ 2 adjacent limb or precordial leads respectively) (c) New onset left bundle branch block, and confirmed by rise in biomarkers. The time of onset of AMI was carefully collected from the respective units admitting these patients. The primary endpoint was myocardial infarct size which was defined according to peak Creatine Kinase (CK) and Troponin I (Tnl) levels. Cardiac enzymes were measured at admission and every 12 hours until a fall of enzymes occurred.

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Time of day of onset was divided into four-6 hours-periods [period 1: midnight-6.00 hrs ; period 2: 6.00hrs- noon(dark to light transition period) ; period 3: noon-18.00 hrs ; period 4: 18.00hrs-midnight]. The shape of relationship between peak enzyme concentrations and time of day was analyzed. The study period consisted of AMI patients over a period of two years.

RESULTS

A total of 256 patients (nonconsecutive) with STEMI were analyzed prospectively after excluding patients with a previous history of AMI or those who had undergone a revascularization procedure. Clinical variable of the four groups of patients are shown in Table-I.

Patients from different time periods were well matched in all the classical risk factors. The incidence of AMI was significantly higher in the dark to light transition than in the other three groups. Anterior wall AMI was significantly more frequent in the 12 hour time period from midnight to noon. The estimated maximum for CK and TnI peaks showed parallel projections with a maximum between 6.00 hr and noon and a minimum between noon and 18.00hr. Left Ventricular Ejection Fraction (LVEF) was significantly lower in patients in the dark to light transition group than in the other groups (50.2±1 vs 53.6±1, p=0.04). Consequently, the rate of heart failure was higher in patients with AMI onset in the 6.00hr-noon period (36.6% vs 27%. p=0.03).

Infarct size was significantly larger in the dark -to-light transition group than in patients with AMI in any other period [CK 134.6 IU vs 102.4IU (p=0.026); TnI 6.65ng/ml vs 4.36 ng/ml (p=0.032)].

DISCUSSION

Cardiovascular physiology is significantly modulated by the circadian rhythm with circadian· oscillations in blood pressure, heart rate, cardiac output, myogenic tone, endothelial function and circulating levels of humoral factors. Previous reports have found an increased incidence of AMI, sudden cardiac death, ventricular malignant arrhythmias, cardiogenic shock, stroke, acute aortic dissection and rupture of aneurysms of aorta, in the early morning hours.[8,9] In addition to AMI the effectiveness of thrombolytic therapy also depends on time of day. Despite strong evidence for the time of day dependence of the incidence of AMI it is not known if there is a circadian oscillation in the infarct size and thereby human tolerance to ischaemia.

TABLE 1 : CLINICAL VARIABLES AND ISCHAEMIA

	Total	Period-1 MN-6.00h	Period-2 6.00-noon	Period-3 noon-18.00	Period-4 18.00-MN
No. of patients (%) of total)	256(100%)	38(15%)	90(35%)	72(28%)	56(22%)
Male (%)	72	80	76	74	80
Hypertension(%	45	38	54	44	40
Dyslipidaemia(%)	40.2	40.4	42	42.2	38.5
Current smoking(%)	51	51.5	50.2	50	56
Diabetes Mellitus(%)	22	19.2	23.3	16.8	16.6
Prior B blockers(%)	7.4	6.2	5.4	6.0	7.8
Prior statins (%)	5.2	4.8	5.0	4.6	6.0

This is an observational study where we analysed the effect of time of day at onset of AMI on infarct size at two referral hospitals. The main findings of the study are :

(1) there is a significant circadian oscillation in infarct size in patients according to time of day of STEMI onset; and

(2) onset of AMI in the dark to light transition period (6am-noon) is associated with significantly larger MIs as evaluated by peak rise in enzyme concentrations.

Numerous studies have evaluated the impact of time of day on the incidence of AMI, using the same time intervals as we have done. Cohen et. al performed a metaarralysis of more than 60,000 patients and explored the time of day distribution of AMI onset.[10] They found a consistently increased incidence of AMI in the dark to light transition period (6.00-.noon) representing 32% of the entire meta analysis population. Our data are in agreement with these results with 35% of the patients in our cohort had AMI onset in the early morning hours (6.00-noon).

We found no difference between groups in the percentage of patients on β blockers prior to the index event. It has been shown the treatment with β blocker abolishes the dark to light transition peak incidence of both AMI and sudden death.[11,12] Though the ultimate mechanism is unknown it has been speculated that this protective effect of β receptor antagonist therapy could be secondary to the blockade of the morning surge in sympathetic activity. The lack of any such effect of β blocker in our study was probably due to the small sample size and also the study had no objective to see the effect of beta blocker on infarct size.

In addition we found a trend towards a higher incidence of AMI in diabetes mellitus in the transition period between light and day. The impact of diabetes on the circadian nature of morning peak of AMI has been debated, with conflicting reports of high as well as low incidence of AMI in early morning hours.[13]

It is interesting to note that we found significant differences in AMI location according to time of day. Patients in the sleeping and sleep to wake hour had higher incidence of anterior wall MI. The mechanism however is still unclear.

The first examination on the effect of time of day on infarct size was undertaken by Durgan et.al.[14] We found a second peak in infarct size in the 18.00-MN period. This was observed by increases in both CK and Tnl. The appearance of the second increase (small) in the infarct size suggest that the oscillations in infarct size are influenced to some extent by the circadian clock. If confirmed by prospective randomized studies these results might have significant clinical implications in the analysis of clinical trials of cardio protection.

Limitation :

The study was observational and therefore subject to bias., More over a 12 hour interval between estimations of cardiac enzymes could very easily miss an earlier peak level of cardiac enzyme. Estimation of infarct size was done by a surrogate marker -'namely cardiac enzymes. Even though this is said to correlate fairly accurately with the state of myocardial ischaemia, a direct evaluation of MI' , size (MRI or scintigraphy) would have evaluated MI size more precisely.

CONCLUSION

In this study we evaluated the impact of time of day of AMI on infarct size. We found that patients with AMI in the light to dark transition period, in addition to having higher incidence of AMI also had larger infarct size. In addition we found a higher incidence of anterior MI in the dark to light transition period. These results advocate the inclusion of 'time of AMI' onset as an important variable in strategies of cardio protection.

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PICTORIAL CME

TOPHACEOUS GOUT

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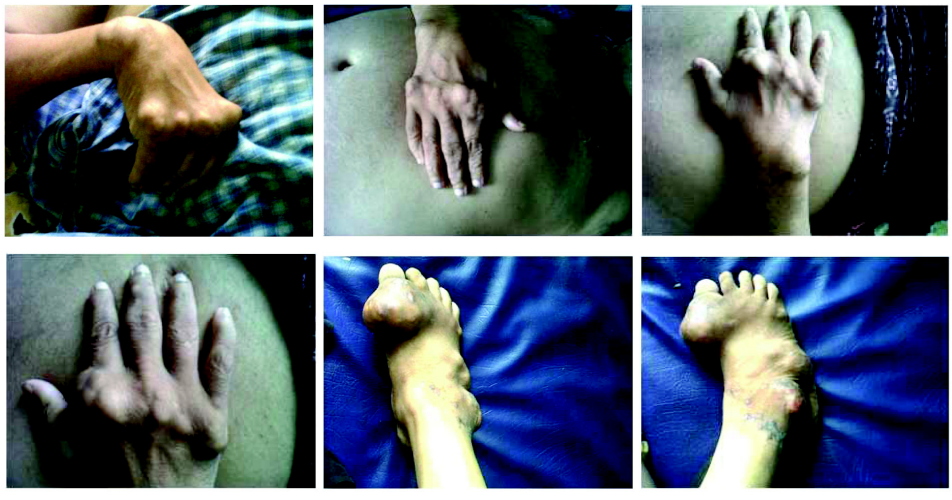

(Multiple tophi over hands & feet)

A 50 yrs old man, chronic alcoholic, presented with multiple joint swellings and pain with past history of arthritis for last 10-12 yrs on ayurvedic medication. On examination there was arthritis of bilateral 1st metatarso phalangeal joints, ankles, metacarpophalangeal and wrist joints. Some of them were ulcerated with oozing of chalky white material. Multiple tophi were present over the hands and feet, Serum uric acid was 10 mg/dl, 24hr urinary uric acid excretion was 114 mg/dl (low excretor). Patient was discharged with short term tablet colchicine and regular treatment with febuxostat (80mg) daily. Patient improved in follow up.

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Review Article

BIOLOGICAL AGENTS IN EARLY RHEUMATOID ARTHRITIS

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ABSTRACT

There is a potential scope for biologics as disease modifying therapy in early rheumatoid arthritis (RA). Biological agents can achieve rapid control of synovial inflammation and decrease in cumulative inflammatory burden. Studies showed that a window period for potential therapy exists in RA as early as 12 weeks. Most of the conventional DMARDs are slow acting. So there is a strong scope for the biological agents as early DMARDs therapy. The other potential advantage is possible efficacy of these agents to induce drug free remission in early RA, rather than need for prolonged biologic agents in DMARDs refractory RA. However there is a risk of possible overtreatment when it could be achieved with much cheaper methotrexate monotherapy or combination DMARDs. Thus there is an intense need to identify those patients who can be DMARDs refractory and possible efficacy of biological agents in those selected patients in early phase of the disease process. With better predictors, biological markers and genetic markers it is possible to select choice of therapy in early RA. ***Keywords :*** *Biological agents, Rheumatoid Arthritis, DMARD.*

INTRODUCTION

The 1987 ACR criteria describes the symptoms of late stage RA and has been criticised for their lack of sensitivity, especially in early disease.. New and highly effective DMARDs have continued to emerge and treatment strategies have changed during this period, and stressed the importance of early referral and early DMARD therapy. The points that are very clear in the management of RA includes that early treatment is beneficial in long term and this window of opportunity exists as early as 12 weeks. In this regard identification of early RA using ACR criteria for 1987 is very difficult. A joint working group from the ACR and the European League Against Rheumatism developed, in three phases, a new approach to classifying RA[1]. They re-evaluated patient data of nine early arthritis cohorts and investigated among those patients newly presenting with undifferentiated inflammatory synovitis, factors that best discriminated between those who were and those who were not at high risk for persistent or erosive disease. The relative weight of each of these factors was also determined. This resulted in a new criteria set, confirming definite RA in a group of patients that present with symptoms of synovitis in at least one joint, with the synovitis not better explained by an alternative diagnosis (Table 1).This new classification system not only emphasize the features of earlier manifestations of this disease but also stressed the predictors of poor long term outcome.

Thus, researchers have placed most efforts in identifying patients with 'preclinical disease' by virtue of the presence of specic anticitrullinated antibodies or nonspecic early symptoms,and devising strategies to secondarily prevent clinical RA in this population [2,3,4,5,6,7,]. Secondary prevention of RA in patients with preclinical disease may be the most feasible and cost-effective strategy for arresting the full expression of the RA phenotype.

OVERVIEW OF THERAPY IN RHEUMATOID ARTHRITIS

Several studies have demonstrated that regardless of which antirheumatic agents are selected, goal-

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oriented management strategies with frequent assessments and, if necessary, adjustments in therapies achieve superior outcomes. With an ever expanding armamentarium of pharmacologic options for effectively treating the clinical symptoms of RA and halting radiographic progression, it is incumbent to consider the relative efcacy, cost and toxicities associated with each therapy.

The four general strategies in the management of RA includes sequential monotherapy, targeted therapy utilising biological agents, step-up combination therapy and initial combination (induction) therapy. The later two therapies gained wide acceptance as more evidence based data poured in to the literature. The potential disadvantage of induction combination therapy is unnecessary toxicity, when it could be achieved with montherapy or gradual step up therapy. When it comes to the selection of DMARDs, MTX remains the sheet anchor drug in most of the combination therapies. Several trials demonstrated the efficacy of combinational therapies in MTX repsonders. However the addition of SSZ to LFN is more associated with GI toxicity with out much treatment efficacy. The land mark study for induction therapy (COBRA trial), where patients with early RA are randomized to SSZ alone or SSZ+MTX+high dose prednisolone with taper to low dose by 6 weeks and taper to SSZ alone by 6 months, showed the rate of radiographic damage was significantly lower in induction /step down therapy. The BeST trial that compared all four treatment strategies in patients with early, active RA showed a modest benet to escalation to triple therapy (MTX, SSZ, and HCQ). which was consistent with previous studies[8,9]. In the Swefot trial, early RA patients (<1 year active disease) were treated with MTX monotherapy (up to 20mg perweek) and those with an incomplete response (DAS 28 >3.2) were then randomized either to infliximab or HCQ and SSZ in combination with their MTX. Although the infliximab arm had better clinical responses at 1 year compared with the triple therapy arm, a signicant percentage of patients receiving the conventional DMARDs achieved ACR benchmarks (ACR20/50/70 of 45, 34, and 15%, respectively), demonstrating that triple DMARDtherapy is an effective therapy in certain patients[10].

The TEAR trial, a double-blind, placebo-controlled trial comparing early combination therapies (either etanercept and MTX or triple DMARD therapy) with each other and with step-up from MTX monotherapy to either combination regimen at 6months if DAS28 of less than 3.2was not achieved in early RA patients. This study demonstrated no signicant difference in DAS28 at 2 years with mean DAS28s at 2 years ranging between 2.9 and 3.1[11]. All these trials emphasize the importance of treating to a goal of low- disease activity, regardless of which agents are selected, and demonstrate the efcacy of conventional DMARDs when used with this strategy. Although 'step-up' therapy has become common, there is limited data that 'step-down' therapy may be more effective in early RA. A signicant percentage of patients in the BeST trial who were treated early with combination regimens achieved remission and were able to discontinue biologic agents, without are of disease activity[12].

FIRST-LINE MONOTHERAPY: Biologic DMARDs

Three TNF inhibitors (etanercept, infliximab, and adalimumab) and one interleukin-1 (IL-1) inhibitor (anakinra) are U.S. Food and Drug Administration (FDA) approved for the treatment of RA. Each has been demonstrated to be efficacious as monotherapy for the treatment of RA, although anakinra is a relatively weak agent compared with the TNF inhibitors and infliximab is recommended only in conjunction with methotrexate (in order to suppress antichimeric antibodies). Compared with aggressively dosed methotrexate, neither etanercept monotherapy nor adalimumab monotherapy shows superiority in reducing clinical signs and symptoms of disease, although each does exhibit modest superiority in reducing radiographic progression[13,14,15]. Nonetheless, this modest advantage is offset by the high costs of these agents such that methotrexate remains the preferred first-line DMARD. There are patients, however, in whom first-line monotherapy with etanercept or adalimumab is preferred, such as those with multiple contraindications to non-biologic DMARDs. Evolving clinical experience suggests that TNF inhibitors may be relatively safe during conception and pregnancy[16]. Although more

Table 1: 2010 ACR/EULAR classification criteria for rheumatoid arthritis

Target population (Who should be tested?): 1. Patients who have at least 1 joint with definitive clinical synovitis (swelling) 2. with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ?6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
>6weeks	1

Table 2: Benefits of Biological agents

1. Efficacy, safety, and approval for use in numerous inflammatory states: rheumatoid arthritis (RA), juvenile arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, and ulcerative colitis
2. Increased odds of remission in both randomized controlled trials and clinical practice (in both early and established RA)
3. Significant disease modification as assessed by radiographic studies
4. Dramatic normalization of acute phase reactants
5. Reduced levels of serum rheumatoid factor and cyclic citrullinated peptide antibodies
6. Decreased frequency of cardiovascular events in RA patients

study is required before their use under these circumstances can be recommended. Insofar as the most common use of TNF inhibitors is in combination with MTX[17], these drugs are addressed in greater detail later in the discussion on "step-up" therapy.

First-line monotherapy with anakinra or either of the newer approved biologic DMARDs, abatacept and rituximab, has not been studied. First-line therapy with abatacept in combination with methotrexate has been recently evaluated (see later).

BIOLOGIC DMARDs: TNF Inhibitors

For patients with an inadequate response to several months of aggressively dosed methotrexate, the addition of a TNF inhibitor is a highly effective and generally safe strategy for further reducing synovitis. That the combination of a TNF inhibitor plus methotrexate is superior to monotherapy with methotrexate in reducing signs, symptoms, and radiographic progression of disease in patients with early and/or advanced RA has been demonstrated for etanercept in the TEMPO trial[15], for infliximab in the ASPIRE and ATTRACT trials[18,19], and for adalimumab in the PREMIER and ARMADA trials[14,20]. Their ability to effect robust, rapid, and sustainable clinical responses in many patients has overshadowed, but not eclipsed, concerns about short- and long-term toxicities. These toxicities include enhanced risk of serious and opportunistic infections, induction of autoantibodies, and risk of inducing or exacerbating symptoms of congestive heart failure and of demyelinating diseases. Fortunately, the incidence of these potential side effects is uncommon. The superior efficacy of adding a TNF inhibitor (infliximab) to methotrexate over the addition of sulfasalazine/hydroxychloroquine in early RA patients was recently confirmed in the SWEFOT trial[21]. The increasing prescription of TNF inhibitors over the years since FDA approval has proven that self-injection and intravenous infusion are acceptable routes of administration for treatment of patients with RA. In patients at high risk for joint damage, the high cost of anti-TNF therapy is expected to be balanced or offset in the long term by a reduction in joint surgeries, disability, and unemployment. Thus their position as the ideal choice for second-line therapy for patients with moderate to severe residual disease activity on background MTX is now relatively commonplace.

No evidence suggests that one TNF inhibitor is superior to another. Furthermore, potential adverse effects are generally comparable among the three, although infliximab treatment has been associated with a higher incidence of opportunistic infection[22]. Therefore the selection of TNF inhibitor is often based on patient preference. Etanercept and adalimumab are self-administered via subcutaneous injection (50 mg once per week or 25 mg twice per week for etanercept; 40 mg every 1 to 2 weeks for adalimumab). Higher doses of etanercept were not shown to increase response[23]. Infliximab is administered as an intravenous infusion every 8 weeks (after an initial loading regimen). The standard dose of infliximab, 3 mg per kilogram body weight, can be titrated up to 10 mg per kilogram if needed and/or the dosing interval can be decreased (to every 6 or every 4 weeks). It is recommended that infliximab be administered concurrently with methotrexate (at least 7.5 mg per week) to prevent the development of neutralizing antibodies, although other mechanisms might be relevant with respect to the enhanced efficacy of infliximab in combinations with MTX because the efficacy of other TNF inhibitors is also increased by combination with MTX, and infliximab is effective as monotherapy in psoriatic arthritis and ankylosing spondylitis. Limited data suggest that the combination of a TNF inhibitor with non-biologic DMARDs other than methotrexate (e.g., leflunomide and/or sulfasalazine) is safe and perhaps efficacious as well[24,25]. Formal drug interaction studies, however, have not been done with these drugs and the anti-TNF therapies. However, combining TNF inhibitors or combinations of TNF inhibitors with other biologic DMARDs is not recommended[26] because of the risk of enhanced infection and other toxicities.

In general, the onset of action of TNF inhibitors is more rapid than non-biologic DMARDs, with many patients achieving a clinical response after only 8 to 12 weeks of therapy. However, some patients may be slower to respond and, similar to methotrexate,

approximately 50% of patients fail to have a robust response to anti-TNF therapy at all[13,19,20,27]. The factors responsible for this variability are not known, although pharmacogenetic studies are under way to investigate the issue.

BIOLOGIC DMARDs: T-cell costimulatory modulators

The T-cell costimulatory modulator abatacept has been shown to have clinical efficacy as monotherapy in moderate to severe RA patients with an inadequate response to methotrexate[28], and in combination with methotrexate in patients who have failed methotrexate monotherapy[29], other non-biologic DMARDs[30], and/or TNF inhibitors[31]. Reduction in radiographic progression compared with placebo has also been observed uniformly across these studies. A recent study showed that early, very active, DMARD-naïve RA patients treated with the combination of abatacept + methotrexate were significantly more likely to achieve clinical remission at 1 year compared with those treated with methotrexate alone[32]. However, an abatacept monotherapy arm was not included in this study. In the only head-to-head trial assessing efficacy of abatacept against a TNF inhibitor, clinical response outcomes were similar over 1 year for active RA patients randomized to receive abatacept versus inlfiximab[33], although infliximab was only allowed at the minimum (3 mg/kg) dose.

Overall, the safety profile of abatacept from clinical trial data is modestly superior to TNF inhibitors. Infusion reactions were lower in abatacept-treated patients compared with infliximab-treated patients[33] and no cases of tuberculosis or other opportunistic infections have been associated with abatacept. However, compared with the TNF inhibitors, long-term and safety registry data on the incidence of serious infections and malignancies with abatacept are limited. In particular, a potential signal for lung cancer and pulmonary exacerbations in patients with COPD noted in a large safety trial (ASSURE)[30] has not been replicated in subsequent studies but warrants additional confirmation and investigation into mechanism.

Abatacept is administered according to weight and a loading regimen is recommended. Thereafter, infusions are administered every 4 weeks. Because the onset of clinical effect can be delayed, a recent consensus statement recommends continuing abatacept for at least 16 weeks before evaluating efficacy[34].

Optimal placement of abatacept in the sequence of RA therapeutics has not been firmly established. Although clinical trials data indicate efficacy at most stages of disease, the lack of long-term efficacy and safety data generally relegate abatacept to a position behind the TNF inhibitors as second-line agents. However, it is an appealing option in patients who have failed TNF inhibitors or those with contraindication to TNF inhibitors. Abatacept should not be combined with TNF inhibitors because the combination was associated with higher infection rates without improved efficacy[35].

BIOLOGIC DMARDs: B-cell depletion

Rituximab, a chimeric monoclonal antibody directed against CD20, has been shown to be efficacious in combination with methotrexate in reducing the signs and symptoms of active RA and in slowing radiographic progression of disease in patients with inadequate responses to methotrexate and/or TNF inhibitors[36,37,38]. Rituximab is currently FDA approved in the United States only for use in RA patients who have had an inadequate response to TNF inhibitors. It has not been specifically studied in early RA, in combination with other biologic DMARDs, or with other non-biologic DMARDs except methotrexate and cyclophosphamide. The best evidence for its efficacy is in populations selected on RF seropositivity[36,37]; however, it has been applied with success in seronegative patients[38], suggesting that the mechanism of action of the drug is not dependent on reduction in autoantibodies.

The safety profile for the first treatment course (paired infusions 2 weeks apart) of rituximab is generally favorable, with few serious infections and no opportunistic infections noted in clinical trials. Infusion reactions are more frequent with rituximab than the other infused biologic DMARDs, necessitating the recommendation for pretreatment corticosteroids. Infusion reactions tend to diminish with repeated infusions. Reductions in immunoglobulin levels have been noted over two to three courses of treatment; however,

these decreases have not been associated with an increased risk for infection to date. Open label studies will provide information as to whether longer-term treatment will result in progressive and clinically important depletion of immunoglobulins that might limit length of treatment. Sporadic cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving rituximab for non-Hodgkin lymphoma, systemic lupus erythematosus, and RA[39], although additional concomitant immunosuppressing agents have generally been present in these cases.

Rituximab administered as two doses of 1000 mg separated by 2 weeks is the current FDA licensed dosage, although one study showed nearly equivalent efficacy with two 500-mg doses[37]. The duration of effect is variable but is typically greater than 6 months[40]. Durable responses of 18 and greater months have been reported[41]. In some cases, subsequent infusions result in longer duration of response. Although peripheral B cells are rapidly diminished after treatment in most cases, reemergence of B cells does not predict loss of response and continued depletion does not guarantee maintenance of response. Importantly, patients who do not achieve a response with the first treatment course do not benefit from repeated treatments[42].

Related to its licensing in the United States, rituximab is usually reserved as third-line therapy in patients who have failed other biologics, although it may be a good option for patients with specific contraindications to other therapies. Some concern has been raised about the safety of initiating therapy with other biologics in patients with depleted B cells but an inadequate clinical response to rituximab. However, preliminary evidence suggests that starting a TNF inhibitor in this scenario may be safe[43].

BIOLOGIC DMARDs: IL-1 inhibitors

There is only one FDA-approved inhibitor of IL-1 (anakinra) on the market for the treatment of RA. Anakinra is administered as a once-daily subcutaneous injection. It has been shown, both as monotherapy and in combination with methotrexate, to be superior to placebo in reducing signs, symptoms, and radiographic progression in patients with advanced RA. Although generally safe when used in combination with non-biologic DMARDs other than methotrexate in patients with comorbid illnesses, there was a modest increase in incidence of serious infections in anakinra-treated, compared with placebo-treated, patients in a large clinical trial[44]. The combination of anakinra with etanercept (or presumably other TNF inhibitors) is not recommended, however, because it was associated with a significantly higher rate of serious infections (compared with etanercept monotherapy) without enhancing efficacy[45]. Although anakinra has not been compared directly with any of the TNF inhibitors, its efficacy in clinical trials is consistently and substantially lower than that of the TNF inhibitors. This, coupled with the inconvenient dosing schedule, has placed anakinra as a distant choice for step-up therapy in clinical practice. However, it is a reasonable alternative in patients with inadequate responses to the available biologic DMARDs or in patients with contraindications to TNF inhibitors such as moderate to severe congestive heart failure or multiple sclerosis.

FUTURE

A subset of RA patients with very destructive disease will not respond adequately to aggressive management with multiple DMARDs, low-dose steroids, and NSAIDs. Data from clinical trials have shown that 30% to 50% of patients do not achieve clinically meaningful response, for example, to the combination of a TNF inhibitor and methotrexate. Fortunately, a number of new drugs have novel mechanisms of action that hopefully will provide alternatives for these patients. Additional TNF inhibitors, second-generation B-cell depleting therapies, and novel biologic inhibitors of IL-6, BLyS, TACI, and small molecule inhibitors of enzymes in inflammatory pathways (e.g., kinases) are all in various phases of clinical investigation. In the coming years, clinical research will establish where these agents fit in the evolving treatment algorithms for RA.

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Review Article

LATE - ONSET HYPOGONADISM (LOH) IN MALES

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Synonyms : Age Related Hypogonadism (ARH), Partial Androgen Deficiency in Aging Men (PADAM), Andropause.

The concept of sexuality and aging is controversial. A steady reduction in men sexuality from early and middle years (35 to 65) has been observed.[1] A study in Danish male has observed progressive decline in sexual interest and ereCtion between 41 to 65 and further a faster decline from 66 to 95.[2] The traditional view held by some that sexuality in the elderly is irrelevant, unnecessary, or even obscene. The fact is however, that sexual drive is not exhausted with aging, and as life expectancy increases it is necessary to recognize that continued sexual activity is an important requirement of old age to promote satisfactory relationships, personal wellbeing, and quality of life.[3] Sexuality in primitive cultures has been studied and there is evidence of continued activity in males and females, but elsewhere there are negative attitudes.[4] Many older people today have problems because they grew up in sexually restricted times so that ignorance was and still is widespread. Also society has an obsession with youth and its sexuality while largely ignoring this subject in old age.[5] In addition, as is generally the case with disabled people, the organization of institutions for the elderly does not recognize their sexuality, so their needs, for example opportunities for privacy, are ignored.[6]

At the World Congress on the Aging Male in Prague, 2004, an expert group of 12 international key opinion leaders convened for a consensus meeting on the diagnosis and treatment of late onset hypogonadism.[7] LOH is defined as "A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels." The terms late onset hypogonadism and andropause are now mostly being used to describe the cluster of symptoms related to testosterone deficiency that may occur in men as they age. Almost all studies relevant to late onset hypogonadism have focused on testosterone, with other androgen as a secondary concern. Thus in the following sections, studies of the decline in testosterone with age and the effects of testosterone therapy in aging men will be taken as relevant to late onset variety of endocrine hypogonadism, although many studies were carried out before the term was coined.[8]

Declining plasma testosterone with increasing age:

The normal aging of otherwise healthy men is accompanied by adverse changes in a variety of endocrine organs, including the adrenals, the pancreas and the testes. Also blood flow to the testes has been shown to decline with age. Decline of testicular function is associated in elderly men with a high prevalence of low levels of total and bioavailable testosterone, which manifests itself in a variety of ways, including reduction of bone mass, muscle mass and strength, and sexual vigor. Concentrations of testosterone and its metabolite DHT in a variety of tissues have also been shown to decline with aging. Almost all studies of testosterone physiology have been performed in Caucasian men, although an increasing data is becoming available for other ethnic groups.[9]

One of the largest studies that have investigated the reduction of testosterone levels with increasing age is the Massachusetts Male Aging Study. This study in US Caucasian men included 415 healthy subjects and

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1294 subjects with one or more ailments, aged 39-70 years. In a cross-sectional analysis, free testosterone levels fell by a mean of 1.2% per year and albumin bound testosterone by 1.0% per year, which SHBG increased by 1.2% per year, resulting in a rate of decline of total testosterone of 0.4% per year. Although testosterone levels were 10-15% higher in the healthy group than in the men with illness, trends in the two groups did not differ significantly. Similar results from cross sectional studies have also been obtained in other population such as US African Americans, European Caucasians and Asian men. Overall, these studies indicate an annual decrease of total testosterone of 1-2% per year, whereas the annual decrease of bioavailable testosterone is 2-3%. Follow-up data of 1156 men of the Massachusetts Male Aging Study indicated that poor health defined as presence of chronic illness, prolonged medication, obesity or excessive drinking, might accelerate the age related decline in androgen levels. A Dutch study performed in 400 men aged 40-80 years showed similar results. Their study also suggested that the age related decline in androgens might be affected by general health status including BMI, waist circumference, smoking and physical activity.[10]

The decrease of plasma testosterone levels, as initially observed in cross sectional studies, was confirmed in a longitudinal study in aging males. The decrease of plasma testosterone with increasing age was accompanined by increases of SHBG, FSH and LH. At the start of the study, all subjects had normal testosterone levels, whereas after 15 years of follow-up, about one third had plasma testosterone levels which were below the normal range for young adult men. The largest longitudinal study on the subject to date in 890 healthy men reported that total testosterone decreases progressively from age 30 years onward, whereas SHBG increases with age. The latter was also found in the Dutch study cited above. Moreover, the prevalence of hypogonadism increased from 12% in men in their 50s to 19%, 28% and 49% in men in their 60s, 70s and 80s, respectively. Using the free testosterone index, these percentages were even higher.[11]

In contrast to the reduction of plasma testosterone levels with aging plasma levels of SHBG increase with age. It has been postulated that this SHBG increase is associated with a relatively estrogenic dominance in plasma with increasing age.

The net effect of this increase in SHBG is to lock up even more testosterone and to accentuate even further the rate of decline of bioavailable testosterone in comparison with that of total testosterone. This has been confirmed in a large scale study of time trends of bioavailable testosterone involving 810 men aged 24-90 years.

The plasma concerntration of total testosterone has been reported to decline by about 3.5 nmol/L per decade. Consequently, mean total plasma testosterone levels at 80 years of age are only 50% of those at age 30 years. In addition, bioavailable testosterone levels at 80 years are only 50% of those of 20 years. It has been reported that half of healthy men aged 50-70 years have bioavailable testosterone levels lower than those in healthy men aged 20-24 years. Eighty five percent of healthy elderly men have total testosterone levels in the lower normal range (12-16 nmol/L) and might, therefore be described as borderline hypogonadal. Other studies have shown that bioavailable testosterone levels start to decline before levels of total testosterone. Further support for the decline of testosterone with age comes from a meta-analysis of 44 separate studies published in 1991. Finally it should be mentioned that there is a seasonable variation in plasma testosterone levels, with a peak during late winter and a nadir at the end of the summer.[12]

Using the lower normal level of total testosterone for the young adult male (<12 nmol/L) to define testosterone deficiency in aging men, prevalence of late onset hypogonadism of 11-35% has been reported. However, estimates of the prevalence of late-onset hypogonadism based on bioavailable testosterone level range from 25% to 50%. Bioavailable testosterone appears to correlate better with age than total testosterone appears to correlate better with age than total testosterone. Moreover, in most studies bioavailable testosterone correlates better than total testosterone

with age-related cognitive and physical parameters and may therefore be a more sensitive marker of late onset hypogonadism than total testosterone.[13]

Reasons for a decline in plasma testosterone with increasing age :

Changes at all levels of the HPG axis probably account for the decline of testosterone levels with age in healthy men. Major causes are the reduction of Leydig cells and impaired testicular perfusion. Testicular response to gonadotropins is also reduced in older men, whilst the effects of androgen suppression on gonadotropin release are attenuated and the pulsatility of the GnRHs is altered. Concomitant illness and medications also reduce testosterone levels, as was shown in the Massachusetts Male Aging Study. It has also been suggested that target organs are less sensittive to testosterone in the older man, due to change in receptor physiology, although this has not been confirmed.

With increasing age, the rates of production and of clearance of testosterone both fall, but production rates fall faster, resulting in a net decline in plasma testosterone levels. There are many causes for reduced rates of testosterone production in elderly men. The most important are thought to be at the level of the testes, where there is loss of leydig cells and reduction in the activity of the enzymatic processes involved in the production of the testosterone precursor dehydroepiandrosterone (DHEA). Most DHEA is present as its sulfate, DHEAS, which acts as a reservoir for testosterone. Although DHEAS is present at much higher concentrations than testosterone itself, it is level also declines with age in a parallel fashion.[14]

Another factor involved in the decline of testosterone production rates is decreased sensitivity of the tests to pituitary gonadotropins. Some longitudinal studies show that mean levels of LH, and even more of FSH, both increase moderately with age, especially after the age of 70 years. However, many elderly individuals have normal levels of both LH and FSH, suggesting that the effects are due both to a reduced sensitivity of leyding cells to LH. Taken together, studies on aging suggest that changes at all three levels of the HPG axis are implicated in the decline of testosterone levels with age, but testicular changes are probably the most dominant. The loss of the circadian rhythm of testosterone secretion that happens in elderly men is probably due to hypothalamic impairment, causing reduced LH secretion, together with reduced inhibin secretion by the Sertoli cells.

In short, the decline in testosterone plasma levels that occurs with age in many individual is probably due to the combined effects of reduced testicular function and age related changes in the dynamics of the HPG axis.[15]

Clinical features of late-onset hypogonadism:

In men, as in women, the incidence of hip fractures increases gradually with increasing age. In the USA, amongst men aged 65 or more years of age, 4-5 per 1000 break a hip each year. Approximately 20% of these aging men will die within 6 months and only about 40% will recover to their previous level of daily functioning. The root cause of hip fracture in the elderly is reducation of bone mineral density, also described as osteoporosis, which in men is thought to be due, in part at least, to testosterone deficiency.

Adverse effects on muscle status and body composition

As men grow older, their muscle become smaller and weaker and they develop more adipose tissue in the central and upper parts of the body. This condition of age-related muscle weakness is often referred to as sarcopenia and is associated with impaired functional performance, increased physical disability, increased dependency and increased risk of falls. Potential casual factors include decreased plasma levels of anabolic factors, decreased muscle protein synthesis, nervous system degeneration, as well as the pathological effects of malnutrition and chronic disease. Moreover, results from the New Mexico Aging Process Study have shown that, in relatively healthy aging men, there are significant correlations between total and free plasma testosterone levels and muscle strength.[16]

Significant associations have been reported in men between age, plasma testosterone levels and body

composition. Low plasma levels of testosterone and a low testosterone / estradiol ratio are associated with obesity. In addition, associations have been reported between distribution of adipose tissue and testosterone levels : testosterone levels are inversely associated with visceral adiposity, which was largely independent of the aging process itself. The increase of visceral adipose tissue with aging in men results in an increased free fatty acids drain on the portal vein. This results in an increase of plasma triglycerides, a decrease of high density lipoprotein cholesterol, impairment of insulin metabolism and reduction of insulin sensitivity. These metabolic effects are thought to contribute to an increased risk of type 2 diabetes and cardiovascular disease and mortality. Cross sectional studies showed that in aging men there are also positive correlations between testosterone and muscle strength parameters of upper and lower extremities, as measured by, amongst others, leg extensor strength and isometric hand grip strength. Moreover testosterone was positively associated with functional parameters, including the doors test as well as the 6-m wait, get up & go test, and 5-chair sit / stand test. In addition, in male nursing home residents a significant relationship was found between testosterone and activities of daily living. Low testosterone levels were associated with a higher degree of dependence.

Reduced libido and erectile dysfunction

Libido is a poorly understood subjective state shaped by biochemical, psychological and social influences. There is a remarkable increase of libido problems in men with increasing age: men aged more than 50 years report a threefold increase of the prevalence of libido problems, Predictors for libido problems in men are health and lifestyle factors such as alcohol use, poor health status and previous adverse sexual experiences in the past. Next to these contributing factors, the age-related decrease in plasma testosterone levels is often implicated in the increase of libido problem among aging men. There appears to be a minimum level of testosterone necessary for adequate sexual functioning, above and beyond which additional levels have no effects. Therefore, if plasma testosterone levels in aging men are below this threshold level, low libido may be prevalent. Moreover, it was demonstrated that, in men, a decrease of bioavilable testosterone was associated with a decrease of sexual desire and sexual arousal.

Reduced hematopoiesis :

Endogenous androgens are known to stimulate erythropoiesis; they increase reticulocyte count, blood hemoglobin levels and bone marrow erythropoietic activity in mammals, whereas castration has opposite effects. Testosterone deficiency results in a 10-20% decrease in the blood hemoglobin concentration, which can result in anemia. Young hypogonadal men usually have fewer red blood cells and lower hemoglobin levels than age matched controls, while healthy order men also may have lower hemoglobin than normal young men. The main androgen involvement in the mechanism of normal hematopoiesis is thought to involve direct stimulation of renal production of erythropoietin by testosterone. Moreover the latter may also act directly on erythropoietic stem cells.[17]

Depressed mood :

The prevalence of depressed mood in men appears to increase with aging and a relationship between testosterone levels and mood has been suggested in several studies. Testosterone levels in aging men are inversely correlated with depressive symptoms. In a well controlled study, it was reported that hypogonadal men have more depressed mood than normal men, whereas in the Rancho Bernardo Study a significant association was found between the age related reduction of bioavailable testosterone and increased depression scores. Moreover, in a subgroup of patients with confirmed clinical depression, bioavailable testosterone levels were 17% lower than in healthy men.

Memory loss and impaired cognition :

Studies in a mouse model have indicated that the age related decrease of plasma testosterone levels, which occurs in the SAMP8 strain, is associated with impairment of memory and learning capacity. The relationship between testosterone and cognition has been investigated in several studies in aging men and it appears that there is, in general a u-shaped

relationship. This means that both subnormal and supraphysiological plasma levels of testosterone are associated with poor cognitive performance. As a consequence, optimal cognitive performance might be expected with plasma testosterone levels within the normal range.[18]

Diagnosis :

The diagnosis of hypogonadism is essentially based on the medical history, measurements of testosterone and measurement of gonadotropins. The clinician should endeavor to discover the underlying pathology of the disease. Diagnosis on the basis of testosterone levels alone may be straightforward in extreme cases. However, in patients with total testosterone in the low normal range, perhaps with intercurrent chronic illness, the complexities of the circadian and pulsatile rhythms of testosterone secretion can make interpretation difficult.

Patients with low testosterone levels often present with the typical cluster of complaints that are associated with hypogonadism. In younger patients with classical hypogonadism, diagnosis is confirmed by measurement of plasma total testosterone levels, often in combination with measurements of LH and FSH. Although there is no uniform definition of classical hypogonadism, it is often recommended to start testosterone therapy in younger hypogonadal men if, at repeated measurements, plasma total testosterone levels are < 12 nmol/L (350 ng/dL). The aim of treatment should be restoration of plasma testosterone levels in the normal range of 12-35 nmol/L.

Diagnosis of late onset hypogonadism is based on assessments of both symptomatology and plasma testosterone levels. For symptom assessment a rating scale has been developed, the Aging Males Symptoms (AMS) questionnaire. In this standardized, easy to apply patient administered 17 item scale, the prevalence and severity of a variety of symptoms associated with aging in men over time are assessed. The AMS questionnaire was originally developed and validated in the German language and in 2001 the questionnaire was validated in the English language. It is however, unclear whether the AMS questionnaire can be used as a valid tool to evaluate the response to testosterone treatment. (19)

In symptomatic aging men, measurement of plasma total testosterone may not be the ideal measure for diagnosis of hypogonadism. Because of the age associated increase of plasma levels of SHBG, there is an increased binding of testosterone to this carrier protein. As a result, more testosterone is locked up thereby reducing the amount that is available to the target tissues. It has therefore been proposed that, in aging men, the testosterone fraction that is available for bioactivity should be determined. This fraction is called bioavailable testosterone and consists of free testosterone plus albumin bound testosterone. It has been proposed that, upon repeated measurement, aging men with a bioavailable testosterone plasma level < 2.5 nmol/L (70 ng/dL) should be considered hypogonadal.

Geriatrics Clinic experience: Forty six cases of LOH were treated with 80-160 mg/ per day of oral testosterone (TE). It has an excellent tolerability, 10-12% of patients after 8-9 weeks of therapy complained of Gastrointestenial complains such as nausea, vomiting, constipation, diarrhea. Three patients had to stop the drug, because of unpleasant GI side effects.

Conclusions :

Hypogonadism due to androgen deficiency may be inherited, acquired or a concomitant of old age. Many elderly men appear to suffer from late onset hypogonadism, which is associated with a range of clinical symptoms, including muscle wasting, increased central adipose tissue. bone loss, reduced sexual function and psychological disorders.

It has now been established beyond doubt that serum testosterone levels decline with increasing age in otherwise healthy men and it is likely that many of the clinical symptoms associated with late-onset hypogonadism are a result of this trend. Although the diagnosis of late onset hypogonadism is not clear-cut, practice guidelines, screening tools and diagnosis and treatment algorithms are being developed to assist the physician. The bioavailable testosterone plasma level seems to be a better marker for late-onset hypogonadism than total testosterone.

Testosterone in an oral formulation has been shown to restore plasma testosterone levels to the

physiological range in hypogonadal men. Trials have also established that oral TU can be used successfully to treat a variety of clinical symptoms in testosterone deficient men by improving body composition, libido and erectile function, reducing bone loss, and improving mood and well being. Furthermore, oral TU has been shown to be effective in the treatment of delayed puberty.

More than 20 years of clinical experience have shown that oral TU is well tolerated by both young and elderly hypogonadal men and is more acceptable for testosterone supplementation than intramuscular injections. It has a relatively small effect on the prostate (though it is contraindicated for pre-existing prostatic cancer) and there is no indication of liver toxicity after many years of continuous use. Contrary to theoretical considerations that testosterone supplementation in general would have adverse effects on the heart, studies now suggest that oral TU may have beneficial effects on the cardiovascular system.

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Current Concept

MULTIPLE MYELOMA: RECENT ADVANCES IN DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Multiple myeloma is a plasma cell dyscrasia which represents a malignant proliferation of plasma cells *derived from a single clone*. These clonal plasma cells, their products and the host response to them, result in a number of organ dysfunctions and symptoms e.g. bone pain or fracture,renal failure, anemia,hypercalcemia, susceptibility to infection, clotting abnormalities, neurological symptoms and manifestations of hyperviscosity.[1]

Multiple myeloma accounts for 1% of all malignancies and 13% of all hematological malignancies. In Western countries,age adjusted incidence is 5.6 cases per 1lac persons/yr.The median age at diagnosis is 70 yrs. Among all patients 37%- <65 yrs, 26%- 65 – 75 yrs ,37%- >75 yrs.[2]

In 2010 -no. of new cases of multiple myeloma was 20,180 and no. of death from multiple myeloma is 10,650 in United States.In India the exact prevalence and incidence of multiple myeloma is not known. The incidence of multiple myeloma and lymphoma is 3.2 per 1 lac population in India.

CLASSIFICATION:-

Multiple myeloma is classified into MGUS, Asymptomatic or Smoldering myeloma,Symptomatic myeloma. Criteria for diagnosis of SYMPTOMATIC MYELOMA are Presence of M-protein in serum and/ or in urine,Bone marrow clonal plasma cells e"10% or biopsy proven plasmacytoma, Evidence of Myeloma-related organ or tissue impairment (including bone lesions).[3]

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Table-1- ROTI : myeloma Related Organ or Tissue Impairment (CRAB-O)[4]

Clinical effects	Definition
HyperCalcemia	Corrected serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l (11mg/dl)
R enal insufficiency	Creatinine >173 µmol/l (2mg/dl)
A naemia	Haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
B one lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
O ther	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

INTERACTION BETWEEN PLASMA CELLS AND BONE MARROW IN MULTIPLE MYELOMA

To understand the mechanism of action of the recently introduced agents in the management of myeloma the interaction between the plasma cells and bone marrow cells must be clearly understood. The effects exerted by the plasma cells are mediated via production of various cytokines e.g. VEGF, RANKL, MIP-1α, DKK-1 or through adhesion with marrow stromal cells.(Fig.1)

Adhesion between plasma cells and stromal cells is mediated by cell-adhesion molecules, such as VCAM -1 and VLA-4. This interaction increases the production of growth factors, e.g. IL-6 and VEGF, which stimulate both plasma cells and angiogenesis.

The increased osteoclast activity is due to an imbalance in the ratio between RANK and OPG .It is due to enhanced production of RANKL and reduced production of OPG. Osteoblast activity is also suppressed by the production of dickkopf homolog 1 (DKK1) by plasma cells.[3]

DIAGNOSIS OF MULTIPLE MYELOMA :-

Clinical diagnosis is difficult. But the features which suggest the diagnosis of multiple myeloma are symptoms like - bone pain(mostly in the back and ribs), weakness, fatigue, loss of appetite and loss of weight, nausea, vomiting, increased thirst, headache, weakness or numbness of legs. The signs may be–anemia, tenderness over the site of bone pain,paraparesis or paraplegia .

TESTS TO BE DONE IN EVALUATION OF A PATIENT OF MULTIPLE MYELOMA[4]

Screening tests-

-CBC(anemia), very high ESR ,increased plasma Viscosity. -Elevated Blood Urea, S. creatinine, S.calcium. -Electrophoresis of serum and concentrated urine to find M protein. -X-ray of symptomatic areas for lytic lesions. ***Tests to establish diagnosis-*** -Bone marrow aspirate for BM plasmacytosis. -Trephine biopsy with plasma cell phenotyping. -Immunofixation (IF) of serum and urine. ***Tests to estimate tumour burden and prognosis-*** -FISH analysis for cytogenetic abnormalities -Quantification of Monoclonal protein in serum and urine -α2-microglobulin.

Tests to assess myeloma Related Organ or Tissue Impairment(ROTI)-

-Serum urea and creatinine, Creatinine clearance, S.Calcium , S.Albumin, Plasma viscosity -Tissue biopsy (or fat pad aspirate) for amyloid(if suspected)

Special tests indicated in some patients-

- SFLC i.e. serum free light chain assay .

Table-2- INTERNATIONAL STAGING SYSTEM (ISS) FOR MULTIPLE MYELOMA

Stage	Criteria	Median survival (months)
I (28%)	-Serum ß2 microglobulin <3.5 mg/l (296 nmol/l) and -Serum albumin ?3.5 g/dl (35 g/l or 532 µmol/l)	62
II (39%)	Neither I nor III	45
III(33%)	Serum ß2 microglobulin ?5.5 mg/l (465 nmol/l)	29

TREATMENT : WHOM TO TREAT & WHEN TO START?

Chemotherapy is indicated only in patients with symptomatic myeloma and those with presence of ROTI[3] .Early intervention in patients with asymptomatic myeloma is not required (Riccardi et al, 2000)[5]. Patients with asymptomatic myeloma should be monitored under close supervision .The overall risk of progression is *10% per year for the first 5 years* but interestingly declines in subsequent years (Kyle et al, 2007).[6]

The SFLC assay measures free κ (0.33-1.94 mg/dL) and free λ (0.57-2.63 mg/dL) light chains.The SFLC κ/λ ratio (0.26-1.65) is used to distinguish polyclonal elevations. The SFLC ratio (≤0.125 or ≥8) appears to be predictive of outcome. A RISK SCORE has been proposed with -BM plasma cell percentage,M-protein concentration and SFLC ratio (Dispenzieri et al, 2008) (*7*). Monitoring of patients with asymptomatic myeloma should include- regular 3-monthly clinical assessment for the emergence of ROTI and measurement of serum and urinary M-protein (and SFLC if possible).

HOW TO MEASURE THE RESPONSE TO THERAPY :-

Previously there had been so many different criteria to monitor the response to therapy, e.g. EBMT/ IBMTR/ABMTR criteria. But recently the best and most accepted one is INTERNATIONAL MYELOMA WORKING GROUP UNIFORM RESPONSE CRITERIA by Durie et al 2006 . It has been recently modified a little by Rajkumar et al ,2011

Changes introduced in the IMWG uniform response criteria :-

There are two new response categories sCR and VGPR. The criteria now incorporate changes in the SFLC assay to support the uniform reporting of clinical trials.The response category 'sCR' has been refined recently to incorporate the use of flow cytometry to detect Minimal Residual Disease (MRD) on the basis of the presence of an aberrant immunophenotype (Rajkumar et al, 2011)

Table-3- INTERNATIONAL MYELOMA WORKING GROUP UNIFORM RESPONSE CRITERIA[3,8]

Response sub-category	Response criteria
Complete response (CR)	• Negative immunofixation on the serum and urine ***and*** • Disappearance of any soft tissue plasmacytomas ***and*** • Bone marrow plasma cells < 5%
Stringent complete response (sCR)	CR as defined ***plus*** • Normal SFLC ratio • Absence of phenotypically aberrant plasma cells (by flow cytometry)
Very good partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis ***or*** • ?90% reduction in serum M-protein ***plus*** reduction in 24-h urinary M-protein by ?90% or to <100 mg/day
Partial response (PR)	• ?50% reduction of serum M-protein ***plus*** reduction in 24-h urinary M-protein by ?90% or to <200 mg/day
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR or progressive disease

MANAGEMENT OF MULTIPLE MYELOMA :-

Basing on several factors like old age, less fit patients or financial capacity the initial standard treatment for a newly diagnosed myeloma patient *depends* on whether the patient is a candidate for ASCT or not.Because of financial constraints most of the Indian myeloma patients come under Transplant ineligible group.The treatment plan is different in the two groups.

TREATMENT PLAN IN TRANSPLANT INELIGIBLE PATIENTS :-

INDUCTION THERAPY

The oldest regimen is MP introduced in 1960 .It contains *Melphalan- 9mg/m2/day on Day 1-4 + Prednisolone – 100mg/day on Day 1-4* each 4 week.In this regimen the Response Rate(RR) is 46-60% and median survival is 18-42 months.[9]

After that, several multidrug chemotherapy regimens have been tried with or without anthracyclines using melphalan, cyclophosphamide, vincristine, carmustine, lomustine, doxorubicin.e.g. MCP, CCP, MCBP, VMCP, VBMCP, MAP, CAP, VCAP. A meta analysis of multidrug CT Vs MP performed by Myeloma Trialist Collaborative Group, involving 6633 patients in 27 RCTs ,revealed that though there is superior Response Rate (60.2 Vs 53.2% ,p<0.000001) but no overall survival benefit. Rather the toxicity risk is more.[10]

NOVEL AGENTS :- THALIDOMIDE & LENALIDOMIDE

After nearly 4 decades of the introduction of MP regimen in 1960, there came a revolution when in 1999, Singhal et al reported the role of a forgotten drug THALIDOMIDE in the treatment of multiple myeloma.This came after the recognition of the role of increased angiogenesis in the pathogenesis and progression of myeloma and evidence of Thalidomide's antiangiogenic properties.Fig.2[11]

Mechanisms of action of *Thalidomide* in myeloma are inhibition of angiogenesis, modulation of adhesion molecules of myeloma cells and their surrounding stroma , modulation of cytokines and stimulates natural killer cells, it has some role in induction of apoptosis and G1 growth arrest in myeloma cells. LENALIDOMIDE has similar mechanism of action but it is more potent than Thalidomide in mediating direct cytokine related and immunomodulatory effects against multiple myeloma cells. (Fig.3)

Thalidomide based regimens :-

1- MPT :- It contains –Melphalan-0.25mg/kg on day 1-4,Prednisolone-2mg/kg on day 1-4 every 6 weeks and Thalidomide-200mg/day. Most of the trials

comparing MPT with MP have shown better CR and longer progression free survival(PFS) and overall survival (OS).[12]

2- TAD- Thalidomide-200mg/day + Doxorubicin 9mg/m2 on day 1-4 + Dexamethasone-40mg/day on day 1-4,9-12,17-20.

3- TD – Thalidomide-50-100mg/d + Dexamethasone-40mg/d on day 1-4,9-12,17-20.

In HOVON 50 trial a comparison of outcome was done between TAD vs VAD, showing better overall response rate(80 vs 63%,$p<0.001$) and complete response(7 vs 3%,$p<0.1$).(13) Ludwig et al compared outcome of TD vs MP and found higher response rate using TD(52 vs 35% ,$p<0.05$).[14]

Lenalidomide based regimens :-

1- Len-Dex – *Lenalidomide-25mg/d, day 1-21 + Dexamethasone 40 mg/d on day 1-4,9-12,17-20* repeated every 4 week. The overall response rate with this regimen was 91% ,CR in 6% and VGPR in32%.[15]

2- BiRD- *Lenalidomide (25 mg/d) orally on days 1–21+ Clarithromycin (500 mg) twice daily + Dexamethasone (40 mg) once weekly* every 28 days.

In this regimen Clarithromycin is used because it inhibits the hepatic metabolism of the other two drugs thereby increasing therapeutic effects.The CR rate was 38.9% and a VGPR in 32.7%.[16]

Novel agents:-proteasome inhibitors – BORTEZOMIB

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells.The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. By this mechanism Bortezomib is cytotoxic to cancer cells.(Fig.4)

Table-4 : Bortezomib based regimen[12,17]

Regimens	Dose	CR (%)	PR (%)	VGPR (%)	OR (%)
BMP Mateos et al	B-1.3mg /m2 on day1, 4,8, 11, 22, 25, 29, 32 M-9mg/m2 on days 1-4 P-60mg/m2/day on days1-4 6 WEEK CYCLES x 4	32	45	11	88
PAD Oakervee et al	B-1.3mg /m2 on days-1, 4,8, 11 A-4.5 mg/m2/day as CI over 4 days D-40mg on days 1-4 and 15-18 3 WEEK CYCLE x 4	24	71		95
Low Dose-PAD Popat et al	B-1mg /m2 on days-1, 4,8, 11 A-9 mg/m2/day as CI over 4 days D-40mg on days1-4 9-12and 17-20 for 1st cycle then only for days 1-4 3 WEEK CYCLE x 4	13	53	23	89

In the VISTA trial(2008),San Miguel et al compared BMP regimen with MP regimen and found better CR(30 vs 4%), longer PFS and OS(79 vs 53%).(Table-4)[12,17]

TREATMENT PLAN IN TRANSPLANT ELIGIBLE PATIENTS :-

The treatment plan in the young patients who are transplant candidates includes: 3-6 cycles of induction therapy, stem cell collection, conditioning by high dose chemotherapy, consolidation with ASCT, maintenance therapy.

Fig.1 : Interactions of Myeloma Cells inside Bone marrow[2]

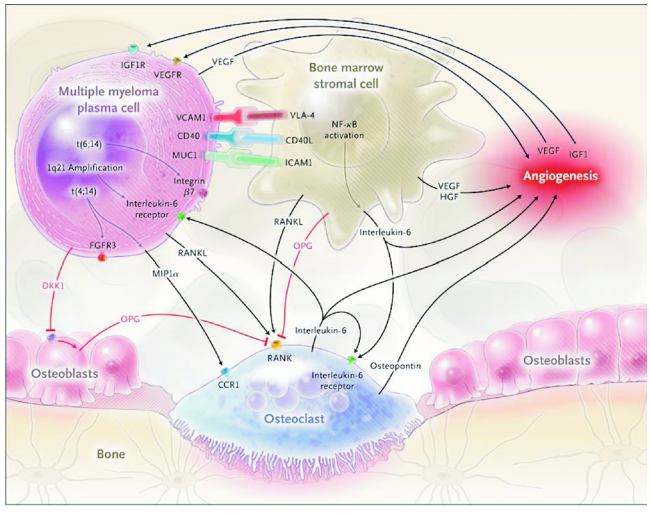


Fig.2 : Angiogenesis & progress of Myeloma[2]

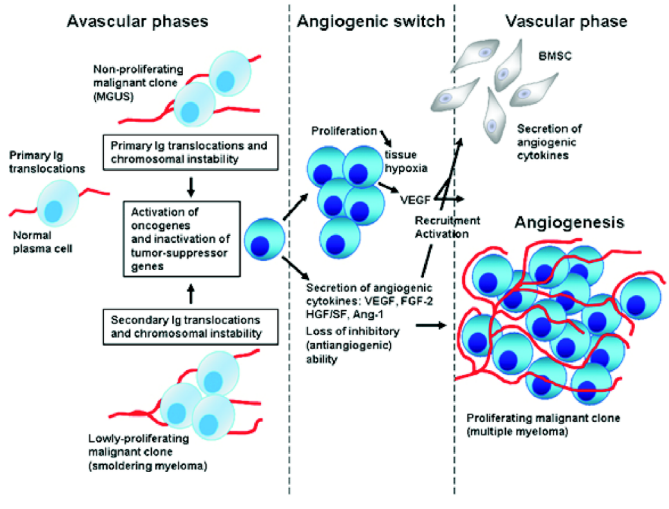
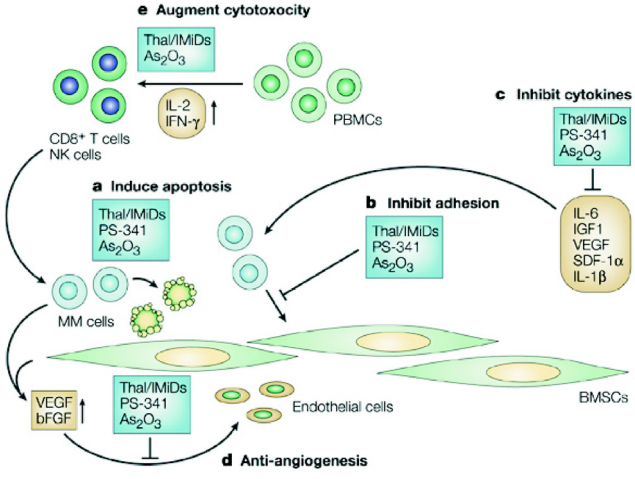


Fig.3 : Mechanism of action of novel agents[11]



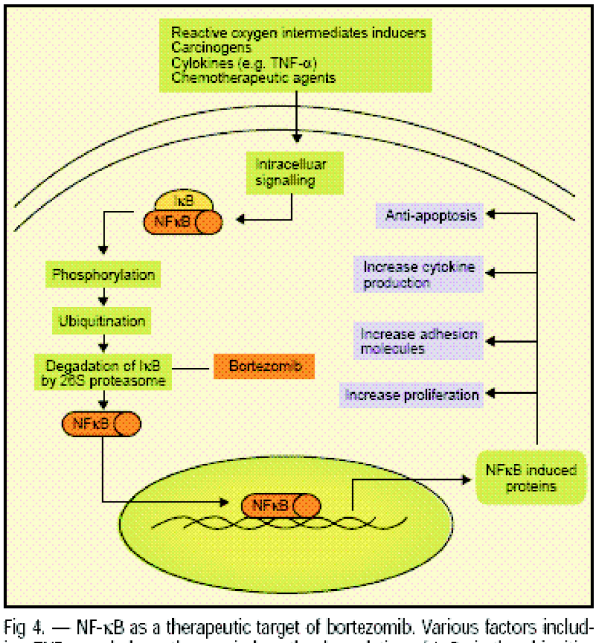
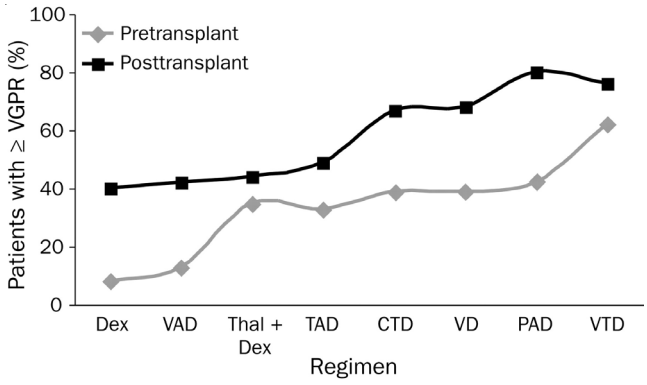


Fig 4. — NF-κB as a therapeutic target of bortezomib. Various factors including TNF-α and chemotherapy induce the degradation of IκB via the ubiquitin-proteasome pathway, resulting in the activation of NF-κB and its subsequent translocation in the cell nucleus where it transcribes genes that contribute to the growth and survival of myeloma cell, their resistance to chemotherapy, and enhances their interaction with the bone marrow microenvironment. Bortezomib blocks the degradation of IκB by the 26S proteasome and hence abrogates the oncogenic effects of NF-κB activation.



Outcome with or without ASCT[2]

Step-1 : Induction therapy prior to ASCT :-

In transplant eligible patients the induction regimens should contain drugs which would not affect the stem cell harvesting. Hence the alkylating agents should best be avoided.Thalidomide or Bortezomib combinations do not affect stem cell collection or granulocyte and platelet recovery after transplantation. The VAD regimen was long been considered as the gold standard as an induction prior to ASCT. However novel drug combinations like TD, TAD, BD, BTD, LD appear to be superior to VAD-like regimens in several recent trials. The majority of patients achieve maximum response to induction therapy after *four to six cycles*. Switch over to an alternative regimen if there is evidence of progressive disease after two cycles or less than PR after 4 cycles.

Step 2 : Hematopoietic stem cell collection :-

These days instead of bone marrow the stem cells are collected from the peripheral blood which has the advantages of- less contamination with myeloma cells and rapid engraftment.The absolute number of CD 34+ cells/kg is the most reliable and practical method for determining the adequacy of stem cell collection.

Step 3 :- Conditioning therapy prior to ASCT :-

This is done to reduce the myeloma cell burden. High dose Melphalan (200 mg/m2) remains the standard conditioning prior to ASCT. The recently reported IFM phase II study with 54 new patients receiving Bortezomib(1 mg/m2 x 4) and Melphalan (200 mg/m2) as conditioning regimen (Roussel et al, 2010). The response reported is VGPR in 70% and CR in 32% .In patients with severe renal impairment (GFR<30 ml/min) the dose of melphalan should be reduced to a maximum of 140 mg/m2.[3]

MAINTAINANCE THERAPY :-

Once the patient attains remission and enters into the plateau phase after induction or ASCT, there is no necessity to continue the induction regimen. Rather it may lead to development of resistance to chemotherapy or development of myelodysplasia or acute leukemia. So it is wise to switch over to a maintainance regimen. Maintainance can be done by monotherapy with IFN -á2 , alt day Prednisolone 50mg, Bortezomib or Lenalidomide.[18,19]

TREATMENT OF RELAPSE IN MULTIPLE MYELOMA :-

If relapse occurs in a patient of age < 55 yrs then the interval between response to treatment and relapse is important. In case of *early relapse <1 yr* the patient is considered as high risk and in order to overcome drug resistance, he is rescued with either a *combination of all effective drugs* (BTD) with cisplatin, adriamycin, cyclophosphamide; or BLD *or alt. cycles of 2 combinations of non cross resistant agents* e.g.BCD with Len. In case of *intermediate relapse (1-3yrs)*, rescue with novel agents in a sequencial manner i,e. starting with one and then shifting to second line and so on. In *Late relapse >3yrs* , reinduction is done with the initial treatment or other novel agent-combination followed by a 2nd ASCT.[12]

In a patient of >55yrs, if it is the 1st relapse, a regimen based on novel drugs (thal, len, bort) and different from that used in induction should be given. In Second or subsequent relapses i.e. he has already failed B and one IMiD ,give experimental agents or palliative treatment with Cyclophpsphamide and alt day Prednisone.[12]

MANAGEMENT OF COMPLICATIONS OF MYELOMA[3]

1. MYELOMA BONE DISEASE (50%)-

The patients should be followed up periodically with radiograph every 6-12 months. MRI can be used as a follow up tool.Mainstay of treatment is BISPHOSPHONATES.The bisphosphonates inhibit dissolution of hydroxyapatite crystals and down regulate

osteoclast formation. They make the osteoclasts unable to form the ruffled borders of their membrane which is required to activate bone resorption. The agents tried in this context are *monthly intravenous administration of PAMIDRONATE (90mg over 4 hrs) or ZOLENDRONATE (4-8mg over 15mins)*. Dose modification is not required for Zolendronate in renal failure.

2-HYPERCALCEMIA (30%):-

-Mild hypercalcaemia(10.5-12mg/dl)- re-hydrate with oral and/or iv fluids.Moderate to severe hypercalcaemia (> 12 mg/dl) - re-hydrate with intravenous fluids and give furosemide. Zoledronic acid is the bisphosphonate of choice .

3-RENAL FAILURE –(20-25%): - Hemodialysis or peritoneal dialysis.

4-HYPERVISCOSITY- Symptomatic patients treated with urgent plasma exchange.If plasma exchange facility not immediately available then Isovolemic venesection is an option.

5-INFECTION :-

-Any febrile myeloma patient should be treated with broad-spectrum antibiotics.Intravenous antibiotics recommended for severe systemic infection or neutropenic sepsis.Aminoglycosides should be avoided.The routine use of prophylactic antibiotics is not recommended.

PROGNOSTIC MARKERS :-

1- α2-microglobulin-It is the strongest & most reliable prognostic marker and is easily available.It reflects the tumor burden; its elevated value predicts early death.

2-CRP and LDH- their high level indicates poor outcome of the disease and low level indicates good outcome from chemotherapy.

3-BM plasma cell no & morphology-

Marschalko type and small cell type –good prognosis ;(OS 40 months),cleaved and polymorphonuclear type – intermediate prognosis;(OS 20m).plasmablastic type of cell – poor prognosis ;(OS 8 months)

4- Plasma Cell Labelling Index (PCLI) :-

It is determined by an immunofluorescence slide based assay. Cells in S-phase of the cell cycle incorporate Bromodeoxy-uridine which can be recognised by using a monoclonal antibody. S-phase cells are then marked with a second Ab. Plasma cells are recognised by morphology and reactivity with anti human Ig ê and ë light chain. An increased PCLI > 3% predicts a short survival and short remission to therapy.

5- Immunophenotype- Better prognosis- CD45, CD56, CD117. Worse prognosis- CD28 ,CD44

6- Cytogenetics (by FISH & flow cytometry) – del 13q, t(11;14) and Hyperdiploidy like trisomies are not unfavourable but del 17p ,t(4;14),t(14;16) and hypodiploidy are associated with worse prognosis.

CONCLUSIONS :-

Multiple myeloma is a disease of old age; the mean age at diagnosis is 70 yrs. At the time of presentation,most of the patients have already developed ROTI . Only symptomatic and those with ROTI should be treated. Asymptomatic patients should not be treated and they should be followed up every 3 months. Treatment plan is mainly dependent on the fact that whether the patient is a candidate for ASCT or not. For patients <65 yrs ASCT is best. In transplant candidates,alkylating agents are avoided before stem cell harvesting. Novel agents have brought revolution in the treatment of multiple myeloma. The regimens containing the novel agents should be prefered. For very poor patients OLD (MP regimen) IS GOLD.In our country with transplant facilities less available and less affordable, MPT ,TD and BMP are the best regimens.VGPR should be the target of treatment, not CR.

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Case Report

HAIR DYE (SUPER VASMOL 33) POISONING – REPORT OF 3 CASES

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ABSTRACT

Super-Vasmol 33 an inexpensive easily available hair dye is a major cause of suicidal and accidental poisoning in India. It contains multiple potential toxins which can result in acute renal failure, rhabdomyolysis, intravascular hemolysis, hepatic injury and metabolic complications such as hypocalcemia and acidosis. We report 3 cases of hair dye poisoning which reflect the combined toxicities of different ingredients and risk of mortality. ***Key wards****: Hair dye poisoning, paraphenylene diamine (PPD), resorcinol, rhabdomyolysis, acute renal failure.*

INTRODUCTION

Hairdye poisoning is common in developing countries like India[1]. It is available both in liquid (Super Vasmol 33) and powder (Super Vasmol) form. Both of these forms contain substances like paraphenylene diamine (PPD), resorcinol, ethylene diamine tetra acetic acid (EDTA), propylene glycol, liquid paraffin, cetostearyl alcohol, sodium louryl sulphate liquid, herbal extracts, preservatives, almond protein and perfume. PPD is the most toxic active ingredient among the above substances. Ingestion of this preparation can cause severe cervico-facial inflammatory edema, rhabdomyolysis, intravascular hemolysis, renal failure, hepatic injury, metabolic acidosis, hypocalcemia, seizure and death[2]. We present here a report of 3 cases from a teaching hospital in Western Odisha.

Case- 1

A 36 year female came to this hospital after 4 hours of consuming 2 bottles (100ml) of Super Vasmol 33. On examination the patient had swelling of face, mouth and neck. She had dyspnea with tachypnea (RR-32/min), pulse rate 80/min, blood pressure 150/90mmHg. On systemic examination no specific respiratory abnormality except tachypnea was noted. Cardiovascular system, central nervous system and abdominal examination revealed no abnormality at outset. On 2nd day urine was dark in colour. Urine volume decreased to less than 100ml in 24 hours by 3rd day with raised blood urea (187mg/dl) and serum creatinine (9.5mg/dl) suggestive of acute kidney injury. In addition, she had elevated liver enzymes (AST=1175 U/L, ALT-1335U/L, ALP-64U/L) but a normal serum bilirubin level (0.5mg/dl), Hb 11.8gm% and TLC-18600/cmm (with neutrophil 89%). Patient was put on hemodialysis twice (on 6th and 8th day of poisoning) in addition to injection dexamethasone and ceftriaxone. But after the second hemodialysis, she left the hospital against medical advice. Eight days later she again presented with oliguria, dyspnea, edema, ascites and crepitation all over the chest. This time she was treated with oxygen, injection hytrocortisone, injection furosemide, injection theophylline and etophylline, salbutamol and ipratopium bromide nebulisation and hemodialysis for 2 more times. At that time haemoglobin level was 5.6 gm % which dropped from its initial level of 11.8gm%.Hence, one unit of blood was transfused. The urine output gradually increased and serum creatinine, blood urea level reduced to 2.5mg/dl and 148mg/dl respectively and on 9th day

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of readmission the patient was discharged. At follow up after 15 days she was asymptomatic and her serum creatinine and blood urea level were normal.

Case -2

An eighteen year female presented to the emergency department of our institution 7 hours after consuming Super Vasmol 33 liquid with complaints of throat pain, bodyache, difficulty in swallowing and breathlessness. On examination the patient was dyspneic, oral cavity was congested and oropharynx was full of secretions. On investigation hemoglobin was 10.6gm%, TLC-24200/cmm with 86 % of neutrophil, normal blood urea (23mg/dl) and serum creatinine(1.0 mg/dl) and raised serum LDH (31500 IU/L). On the 2nd day urine was chocolate brown coloured with hematuria and proteinuria. The patient developed hypocalcemic tetany (serum calcium of 6.1mg/dl). On the 3rd day the patient developed renal failure evidenced by urine volume less than 50 ml and raised blood urea (135mg/dl) and serum creatinine(7.5mg/dl). Liver enzymes were elevated (AST=6400U/L, ALT-2170U/L, ALP-28U/L) with normal serum bilirubin level (0.7mg/dl). The patient was treated with one sitting of hemodialysis.Other treatment included injection hydrocortisone, injection furosemide, injection theophylline and etophylline, salbutamol and ipratopium bromide nebulisation. However, patient detoriated and died on 4th day of admission.

Case -3

A 23 year female was admitted to our hospital after 5 hours of consuming Super Vasmol 33 liquid with complaints of difficulty in swallowing, throat pain and breathlessness. On examination oropharyngeal mucosa was congested with oral cavity full of secretions, pulse rate 80/min, BP 120/70 mm Hg. Chest examination revealed no abnormality. She had Hb- 10gm%, TLC-10500/cmm with neutrophilia (90%), normal blood urea (54mg/dl) , serum creatinine (0.96mg /dl.) and raised serum CPK (16440 IU/L). On 2nd day her liver enzymes (AST=1734U/L, ALT-855U/L, ALP-103U/L) were found to be elevated with normal serum bilirubin level (0.84mg/dl). Repeat tests for blood urea, serum creatinine, and liver enzymes were normal on 7th day. During the hospital stay the patient was treated with injection hytrocortisone, injection furosemide and IV fluid. The patient improved with conservative management and was discharged on 8th day. At follow up after 15 days she was asymptomatic

DISCUSSION:

Super-Vasmol 33, an inexpensive easily available hair dye is not an uncommon cause of suicidal and accidental poisoning [3]. It contains potential toxins including PPD, resorcinol, EDTA, propylene glycol which can result in multi-organ dysfunction. In all three reported cases oropharyngeal inflammation was noted, which may be due to PPD or corrosive effect of resorcinol present in the hair dye. Two patients had difficulty in breathing which is possibly due to laryngeal inflammation and edema resulting from resorcinol. Two cases developed acute kidney injury (AKI). This could be due to nephorotoxic effect of propylene glycol[1, 6, 7] or due to rhabdomyolysis[9] induced by PPD. All the three cases manifested features of anicteric hepatic dysfunction[4, 5] possibly due to toxic effect of PPD. One patient had intravascular heamolysis as evidenced by chocolate brown coloured urine, high serum LDH level (31500IU/L) and hemoglobinuria. The same case had hypocalcemia[6] which may be due to sodium EDTA in the hair dye or may occur in the setting of severe rhabdomyolysis[9]. This patient died inspite of hemodialysis and intensive care. The cause of death could be multifactorial including acute renal failure, hypocalcemia and hemoglobineuria. P Bhargava et al[10] , Chrispal A et al[11] and Verma R et al[1] also reported cases of super vasmol 33 poisoning presenting with similar clinical features as in our patients. Verma R et al[1] also described one case of death due to renal failure, acidosis and convulsion in super vasmol poisoning.

CONCLUSION:

Super-Vasmol 33 contains a combination of potentially dangerous toxins which can result in multi-organ dysfunction and death. Early, effective and

aggressive management like tracheostomy or ET tube insertion for respiratory distress and hemodilysis for acute renal failure and correction of hypocalcemia may be live saving in these casess.

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Case Report

EXTRAPONTINE MYELINOLYSIS

P.K. Jena*, S. Patro**

ABSTRACT

Osmotic demyelination usually occurs in patients with rapid correction of hyponatremia. It is a disease of the central nervous system and can involve the pontine or extrapontine areas. It is usually irreversible and can only be managed by prevention. The rate of increase in the plasma sodium level per hour and within twenty four hours are the key points for preventing osmotic demyelination. We report a 54 year old man in whom osmotic demyelination occurred in the extrapontine area (extrapontine myelinolysis) after rapid correction of hyponatremia. ***Key words:*** *Extrapontine , pontine, myelinolysis, hyponatremia, osmotic demyelination.*

Case Report:

A 54-year-old man attended casuality of KIMS, Bhubaneswar with the history of drowsiness and stiffness of both upper and lower limbs for last six days. He did not have any other systemic diseases. Physical examination revealed mild drowsiness, but he could be aroused (GCS -E3V3M4). The upper and lower limbs had generalized rigidity and brisk deep tendon reflexes. All the brain stem reflexes were normal. His skin was dry and his ankles were not edematous. His blood pressure was 110/72 mm Hg in arm in supine position. Pulse rate and respiratory rate were 98 beats per minute and 14 per minute respectively. His body temperature was 98.8^0 F. No other clinical abnormalities were found on physical examination. The laboratory data showed blood haemoglobin 11.4 gm./dl, white cell count 10,700 cells/ ì L., blood urea nitrogen 63 mg/dl., creatinine 1.7 mg/ dl., sodium 136 mmol./L and potassium 3.5 mmol./L.

Few days prior to admission to our hospital, patient was admitted to some other hospital with complains of repeated vomiting and was treated with antiemetics and sodium containing fluids. At that time serum sodium level was 113mmol./L and 128mmol./L on the day of admission and on the 2^{nd} day respectively(after sodium replacement therapy). On 5^{th} day of admission in the same hospital patient started developing rigidity of limbs and difficulty in swallowing.

Because of this background history, patient was further evaluated with magnetic resonance imaging study of brain .This imaging study showed abnormal signal intensities in the striatum and thalamus , but there was no abnormalities in the brainstem including the pons (Figure-1,2&3).

The clinical course and radiological findings were compatible with extrapontine myelinolysis.

As the patient was not improving, relatives took away the patient from the hospital against the medical advice.

DISSCUSION:

CPM (central pontine myelinolysis) was described by Adams and colleagues in 1959. In 1976, pontine and extrapontine myelinolysis were first found to be associated with rapid correction of low serum sodium levels.[1, 2] The sequelae of rapid correction of hyponatremia usually follow a biphasic clinical course, with initial encephalopathy or seizures from hyponatraemia, followed by a rapid recovery as normonatremia is restored, with deterioration several days later. In CPM, the initial signs include dysarthria

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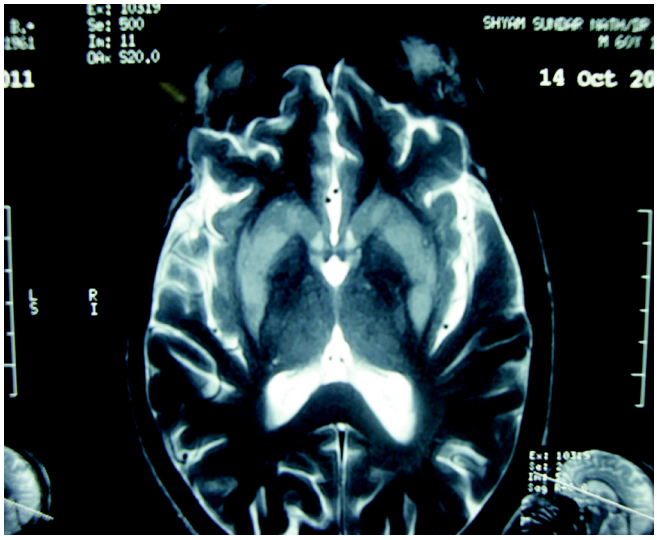
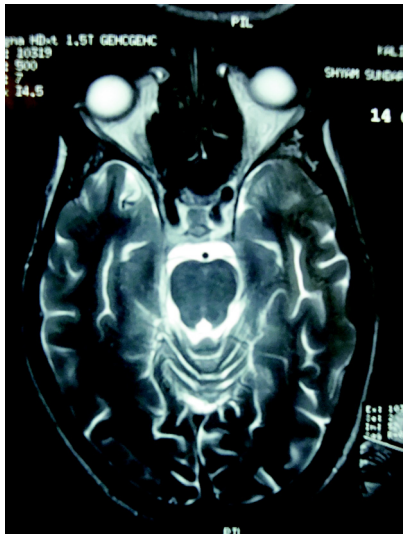
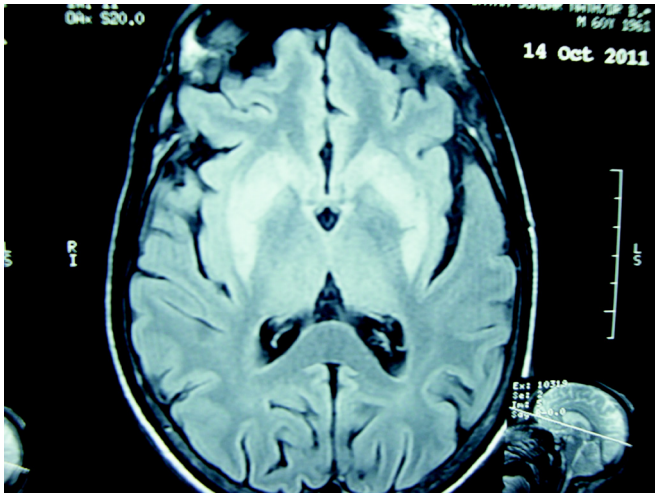


(Hyperintentse signal in bilateral basal ganglia region in T-2 weighted SEQUENCE) (Figure-1)



(Normal signal in pontine region in T-2 weighted SEQUENCE) (Figure-3)



Hyperintentse signal in bilateral basal ganglia region in FLAIR SEQUENCE) (Figure-2)

and dysphagia (secondary to corticobulbar fiber involvement), and flaccid quadriparesis (from corticospinal tract involvement) which later becomes spastic, all from involvement of the basis pontis. If the lesion extends into the tegmentum of the pons, pupillary and oculomotor abnormalities may occur. There may be changes in the level of consciousness.[4]

EPM has identical pathological findings but the involved areas are extrapontine, so there are different clinicalmanifestations.[5] Because EPM is rare, its manifestations continue to attract further study. It may manifest as postural limb tremors, myoclonic jerks, a parkinsonian picture, catatonia, dystonia, or pyramidal dysfunction (secondary to the different areas involved). These may resolve completely or partially over months or they can become permanent.[2]

The most common causes of hyponatremia are therapy with thiazides, syndrome of inappropriate secretion of antidiuretic hormone in postoperative state, polydipsia in psychiatric patients, gastrointestinal fluid loss, ingestion of dilute fluid ,and accidental ingestion of excessive water.[6,7]

These cases are mostly hypotonic hyponatremia, as seen in our patient. The most important aspect of hyponatremia management is a proper rate of correction. In the emergency setting, no matter what the cause of hyponatremia may be, the rate of correction of sodium depends on the absence or presence of neurologic dysfunction.

When hyponatremia develops rapidly and is accompanied by neurologic symptoms, more rapid correction is required. When hyponatremia develops slowly, slow correction is needed.[8,9] In general, acute symptomatic hyponatremia should be treated by hypertonic saline, and the plasma sodium level should

be raised by only 1-2 mmol./L /hour and no more than 10-12mmol/L during the first24 hours. In chronic asymptomatic hyponatremia, the plasma sodium level should be raised more slowly, and no more than 8 mmol./L during the first 24 hours.[3] The rate of increase in the sodium level is usually rapid if 3% saline is used intravenously, but it can also occur rapidly with only intravenous normal saline if the initial sodium level is profoundly low.[10] If the sodium level increases too rapidly, intravenous dextrose water or oral water can be administered to re-lower the sodium level to a "safe" level. [11,12]

In our patient, the rate of correction was 16mmol./L in the first 24 hours; which was beyond the safe level.

CONCLUSION:

Hyponatremia is a manifestation of various disorders that are faced and treated in everyday clinical practice. However, if attention is given to the benefits and harm of management of hyponatremia, osmotic demyelination is preventable.We suggest that correction of hyponatremia should not exceed a rate of 1-2 mmol./L/hour and no more than 10-12 mmol/L/day. During treatment for hyponatremia , (especially when using intravenous 3% saline), the plasma sodium level should be checked frequently. If the sodium level increases too rapidly, water can be administered intravenously or orally to re-lower the sodium level.

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Case Report

CONVERSION OF ESSENTIAL THROMBOCYTHAEMIA TO CML

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ABSTRACT

We are here reporting a case who initially suffered from essential thrombocythaemia (ET) which proceeded to chronic myeloid leukaemia within a period of two years. ***Keywords :*** *Essential Thrombocythaemia, Chronic Myeloid Leukemia, Conversion, Myeloproliferative disorders.*

Introduction:

All varieties of malignancies occur due to genetic alterations. Various factors bring on these changes. Development of a second malignancy in cases of lymphoma and leukaemias while on treatment is known[1]. But spontaneous conversion of one form of malignancy to another is rare.

Case Report:

Sunasir Mahapatra 33 years Hindu male presented with dyspnoea, fever, cough of 2days duration. His past history revealed he had developed stroke twice within one year in 2007. To evaluate this he had gone to Satyasai Institute of Higher Medical Sciences where he was diagnosed as essential Thrmbocythaemia. All the investigation reports were reviewed including the bone marrow study. The two episode of strokes he had; one was ischaemic and the other was haemorrhagic. This is possible in ET. He was given treatment of hydroxyurea which he consumed for just three months and then discontinued.

On examination his pulse was 120/minute, Blood Pressure was 110/80mmHg, respiration rate was 42/ minute, and temperature was 101^0F. The patient was pale; there was no cyanosis, no significant lymphadenopathy. He had splenomegally of 17cm and liver was enlarged 4cm. Respiratory examination showed bronchial breathing over right lower lobe and crepitations over right upper lobe; left side was normal.

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His blood examination revealed a TLC of 284000/cmm; Hb was 7.7gm%; DC showed Myeloblast: 3%, Promyelocyte: 22%, Myelocyte:30%, Neutrophil: 4%, Basophil: 5%, Lymphocyte:7%, his platelet count 3,60,000/cmm. His other metabolic parameters were normal. His X-ray chest showed consolidation right lower lobe with patchy consolidation over right upper lobe. So his diagnosis was chronic myeloid leukaemia complicated with pneumonia.

He received treatment for pneumonia which resolved fast; fever subsided by fourth day, dyspnoea subsided by seventh day. After two weeks there was radiological clearance of the shadow. What remained was the chronic myeloid leukaemia.

Discussion:

So far as pneumonia is concerned there is nothing interesting. The interesting part is conversion of ET to CML within a period of two years. Second malignancy has been reported in patients receiving treatment for lymphoma or leukaemia mostly following chemotherapy and radiotherapy. The present case initially presented with ET. He received treatment with hydroxyurea just for three months. It is difficult to comprehend that the change to CML is the effect of drug. It is more likely to be spontaneous conversion of ET to CML. Conversion of all forms of myeloproliferative disorders(MPD) to myelofibrosis (Agnogenic myeloid metaplasia) is described.[2,3,4] Conversion of ET to CML must be rare. Conversion of ET to Polycythaemia Vera and AML has been

reported.[3,4] As conversion of ET to other forms of MPD has been reported, so spontaneous conversion of ET to CML is also a possibility as happened in this case. This conversion appears to be good for the patient. Because, the chances of developing stroke decreases in comparison to essential thrombocythaemia.

Conclusion:

From the literature and from our case we can conclude that all forms of myeloproliferative disorders are interconvertible. But under what circumstances this occurs needs study. Whether there is any specific pattern in these conversions or the conversion occurs at random is to be explored. It is also required to be known if any specific genetic change brings on the conversion.

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PULMONARY METASTASIS OF GIANT CELL TUMOR OF BONE DIAGNOSED BY IMAGE GUIDED FNAC

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

ABSTRACT

A 25 yr female who presented to us with progressive breathlessness for 1 month associated with cough and significant weight loss was evaluated and was found to have massive left sided pleural effusion. She suffered from Giant cell tumor(GCT) of lower end of right radius (Biopsy proven), associated with fracture four years back. On contrast enhanced CT(CECT) scan of thorax, multiple pulmonary metastasis were detected and CT guided FNAC from the pulmonary lesions with cytosmear study confirmed the lesions to be of giant cell tumor origin ,proving the metastasis of GCT. The case being reported here in view of rarity. ***Keywords :*** *Giant cell tumor, pulmonary metastsis, Benign.*

INTRODUCTION :

Giant cell tumor(GCT) of bone is a benign but aggressive lesion that behaves in an unpredictable fashion.These tumors recur locally and may even metastasize.The frequency of metastasis is approximately 2-3 percent[1]. Most metastasis are to lung.The incidence of lung metastasis from a histologically proven benign GCT is rare and ranges from 1 to 9 percent.[1]Metastasis to other sites are extremely rare. A case of benign GCT of distal radius(right side) which presented after four yrs of its initial detection with bilateral multiple pulmonary metastasis and massive left sided plural effusion is reported here due to its rarity of occurrence.

CASE REPORT

A twenty five year old woman was admitted to our hospital with history of cough, progressive breathlessness and low grade fever for one month.There was associated significant weight loss, reduced appetite and generalised weakness. Cough was nonproductive and there was no history of hemoptysis, orthopnea or paroxysmal nocturnal dyspnea(PND).There was no history suggestive of Rheumatic heart disease or contact history of pulmonary tuberculosis. She was non-diabetic and non-hypertensive and was working as a staff nurse.Four years back ,She had a sweeling over the lower end of right forearm followed by fracture after falling down from a bicycle. She was diagnosed to have Giant cell tumor of lower end of radius as evidenced from biopsy study of the curretage specimen from the mass.Mass was excised followed by bone grafting. She did not receive any chemotherapy or radiotherapy at that time. Post opperatively she didn't have any significant local or systemic complaint.She was unmarried and there was no significant menstrual history. On general examination, she was cachectic with body weght of 32 kg and height of 150 cm, pulse 110/ min, BP 110/70mm of Hg and was tachypneic with respiratory rate of 25/min. There was pallor, pedal edema and JVP was 4cm elevated. No icterus, cyanosis, clubbing or significant lymphadenopathy was present. On examination of respiratory system, massive pleural effusion was found on the left side along with gross shifting of mediastinum to right. Cardiovascular system examination revealed no abnormality. On examination of abdomen there was no organomegaly or free fluid. On local examination of lower end of right forearm there was a linear healthy scar of 5 cm.With a provisional diagnosis of left sided pleural effusion of tubercular/

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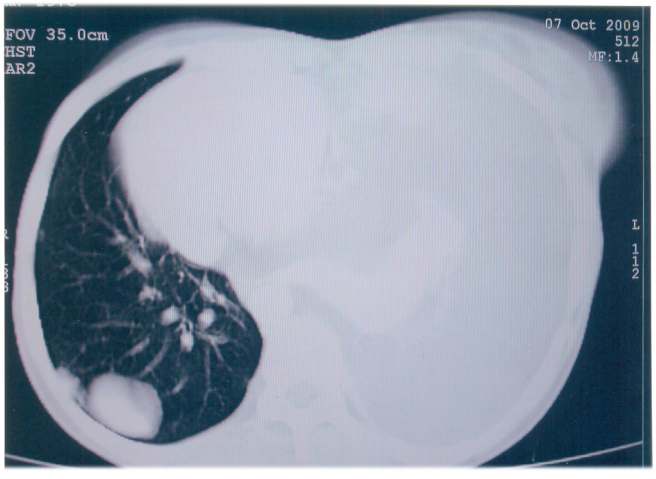

Fig.1

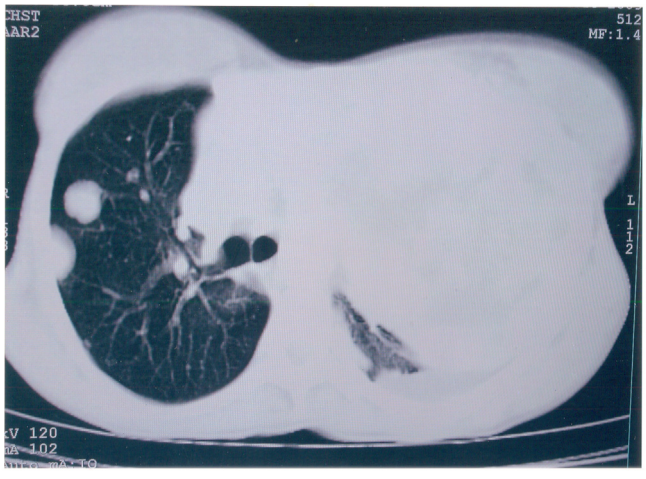

Fig.2

CECT Thorax showing multiple pulmonary nodules in the right lung with a large variegated mass on the left side.

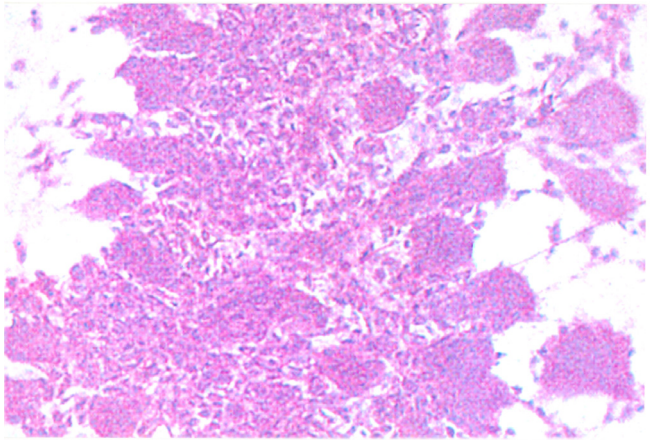

Fig.3
Aspiration cytosmear from left lung mass

malignant etiology, following investigations were carried out.

INVESTIGATIONS:

On routine haemogram, hemoglobin was 6gm%, ESR was 50mm and other parameters were within normal range. Mantoux test was negative. X-ray of chest showed massive pleural effusion on left side and ultrasonogram of abdomen and pelvis revealed no significant abnormality. Pleural fluid examination on two repeated occasions did not show any malignant cells and was transudative in nature with only lymphocytic cells. Sputum test for AFB was negative in three consecutive specimens. In view of persistent cough and rapid reaccumulation of fluid a Contrast enhanced CT scan (CECT) of thorax was advised Which showed multiple pulmonary nodules in the right lung with a large variegated mass on the Lt.side (fig.1,2).CT guided FNAC was done from the mass on left side and yielded particulate material diluted with peripheral blood. Aspirated material was cytologically evaluated. Aspiration cytosmears were moderately cellular, showing both dispersed cells and cohesive cells clustering with many multinucleated giant cells having abundant cytoplasm and many uniform nuclei (20-60) along with spindle,oval and round mononuclear stromal cells with similar nuclei and less distinct cell borders. Many giant cells were seen chracteristically attached to the periphery of the cohesive clusters stromal cells (fig.3). Few bi and trinucleated osteoclastic/ histiocytic cells were present discretely. No cytological features of malignancy was noted. A diagnosis of benign metastatic giant cell tumor(GCT) with bilateral pulmonary metastasis and left sided pleural effusion was made after correlating with the past history. Chemotherapy was started in the Dept. of Oncology along with blood transfusions and thoracentesis whenever required. She responded well initially with improvement in general condition but she discontinued

treatment and died after six months of initiation of chemotherapy.

DISCUSSION

Tumors that metastasize are considered 'malignant' by definition. However,benign GCT is one of the exceptions because of the potential for histologically benign tumor to metastasize. GCT is a benign but locally aggressive tumor that primarily affects epiphysis of long bones of young adults.Pulmonary metastasis in GCT is rare(about 1-9%)[2].Many authors have done painstaking studies to assess agressiveness, reccurence and metastasis of GCT which are histologically benign.It has been stressed that complains of pain,swelling and radiological demonstration of infiltration of the tumor into surrounding soft tissue with cortical destruction are very suggestive of aggressiveness of these lesions rather than the cytological features described under microscope. [1]

Guoping Cai et al [2] reported a similar case of metastatic GCT who had a previous history of GCT of distal femur.All multinucleated cells showed immunoreactivity to KP -1 antibody,a histiocytic marker (not lineage specific).20% of mononuclear cells also displayed increased Ki-67 and p^{53} protein expression.

Dahlin [3] described his experience with 407 cases of GCT seen at the Mayo clinic.Eight of these patients developed pulmonary metastasis and two of these died of tumor.His study reinforced the facts that[1] GCT has a predeliction for the ends of major tubular bones in patients with mature bone growth[2] GCT is a locally aggressive lesion that has a prominent tendency to produce local recurrence[3] GCT may metastasize as a histologically benign lesion(observed in 2% of his cases) and[4] radiation is probably important in " triggering" malignant transformation of this tumor.Malignant change occurred in 24 of the 407 cases.

Viswanathan et al[4] in a study of 470 patients with GCT during a period of 20 years identified distant metastasis in 24 patients.Medium age of presentation of these patients was 26 years(range 16-76 years).Metastasis occurred at a mean within two years after initial diagnosis. Sites for metastasis were lungs (21 out of 24 patients), scalp, calf muscle and regional lymphnodes.Although overall outcome was favourable,metastatectomy is recommended where possible.

Authors have noted that multiple operative interventions on the primary tumor seemed to promote pulmonary metastasis. For therapy,a thoracotomy and a complete excision of the pulmonary nodules has proved successful,and the literature strongly favors the surgical extirpation of all pulmonary nodules.[1]

CONCLUSION :

The present case is an additional evidence and a reminder that microscopically benign appearing giant cell tumors of bone may occasionally metastasize and hence called 'Benign' metastasizing GCT.

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Case Report

WILSON'S DISEASE PRESENTING AS DECOMPENSATED LIVER DISEASE & PSYCHIATRIC MANIFESTATIONS

P. Jena* B. L. Parija, G. Ray*****

ABSTRACT

Wilson's disease is a rare but important autosomal recessive disorder of copper metabolism that is caused by a variety of mutations in the gene ATP 7B on chromosome 13. Total body copper is increased with excess copper deposited in various organs like Liver, Basal ganglia, Eyes, Bone, Kidney. We report here a case who presented with decompensated liver disease, kayser -fleischer ring in the cornea with psychiatric manifestations. ***Key words****: Wilson's disease, kayser fleischer ring, Decompensated liver disease.*

INTRODUCTION:

Wilson's disease is an inherited disorder of copper homeostasis first described in 1912. It is an autosomal recessive disorder caused by mutations in ATP 7B gene on chromosome 13.

The frequency of the disease is 1 in 30,000 to 40,000. Due to this mutation involving P-type ATPase, export of copper from the hepatocytes does not occur resulting in positive copper balance, hepatic copper accumulation & copper toxicity from oxidant damage. Excess hepatic copper is initially bound to metallothionein but as this storage capacity is exceeded liver damage begins. Defective copper incorporation into apoceruloplasmin leads to excess catabolism & low blood levels of ceruloplasmin. As the disease progresses, non ceruloplasmin serum copper ("free" copper) level increase resulting in accumulation of copper in other parts of body such as brain, cornea etc, leading to neurological & psychiatric manifestations.

CASE REPORT :

A 18 years old male patient admitted into the medicine dept. of S.C.B. Medical college, Cuttack in December 2010 with chief complaints of progressive swelling of abdomen for two months, swelling of both lower limbs for 8 days & Melena for 4 days. There was h/o jaundice at the age of 2 years. Developmental milestones were normal. There was no h/o alcoholism, Acid peptic disease, intake of toxic food stuffs, any hepatotoxic drug intake. Parents gave h/o writing difficulties & impulsive behaviour since 1 year.

On examination, the patient was of average body built, mild pallor, mild icterus, B/L pitting pedal edema, no clubbing/cyanosis/ lymphadenopathy. Pulse -96/min regular, BP-130/86mm Hg, Respiration rate – 30/min, temp.99'F. Abdominal examination showed no superficial venous engorgement. Liver is not enlarged, spleen is 3cm. palpable, Ascitis present. Respiratory, CVS, nervous system examination revealed no abnormality. On examination of eyes there was keyser-Fleischer rings present on cornea of both sides. Which later confirmed by slit lamp examination. On psychiatric examination there is emotional liability, depression & evidences of impulsive behavior.

Laboratory investigations were Hb-6gm%, TLC-10800/cmm. DC=> N-80%, L-14%, E-3%, ESR -60mm in 1st hr, FBS-95mg/dl, Blood urea-20mg/dl, Sr Cr-0.9mg/dl, Sr Na+- 125meq/lit, Sr k+3meq/lit. Sr Billirubin(T)-1.8Mg/dl, D-1.1Mg/dl,SGOT-194 iu/lit, SGPT-667 iu/lit. total Sr Protein-5.9gm/dl, Sr Albumin-2.0gm/dl. PT->14 sec, HBs Ag(-) HCV(-) HIV(-). USG Abdomen & Pelvis-> Liver-11.7cm, coarse & nodular echotexture, irregular margin, portal vein-13mm, Spleen-16.1cm,

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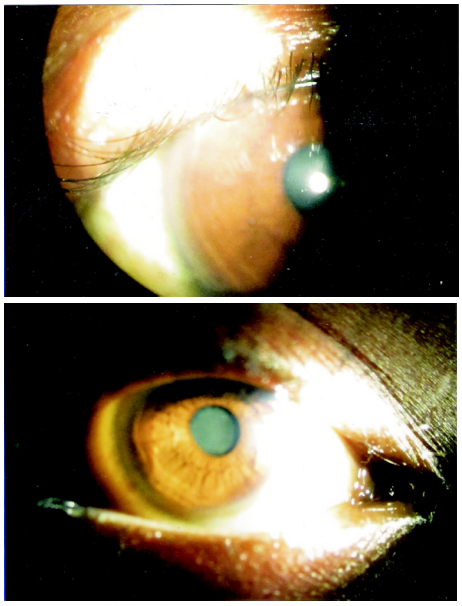
normal echotexture, spleenic vein-12.6mm(dilated) & contains collaterals. Presence of gross free fluid in the peritoneal cavity. Impression – cirrhosis of liver with portal hypertension. Upper GI Endoscopy- esophageal varices of Grade l-ll, Fundic varices ,congestive gastropathy, 2D Echo-Diastolic dysfunction. Ascitic fluid study showed: Protein-0.5gm/dl, sugar-102mg/dl. ADA -10.2 iu/lit. occasional Lymphocytes & few histiocytes only. Sr ceruloplasmin <9mg/dl(Normal->20mg/dl), 24hr urinary copper->92.5microgram CT scan of Brain was normal with falx calcification.



KAYSER FLEISCHER RINGS

DISCUSSION:

The clinical presentation of Wilson's disease is variable & includes hepatitis, cirrhosis or hepatic decompensation. Hepatic decompensation is associated with increased serum Billirubin, decreased serum albumin & coagulation factors, peripheral edema, ascitis & hepatic encephalopathy. Hemolytic anemia may occur in severe hepatic failure due to release of large amount of copper into blood stream from hepatocellular necrosis. In our case hepatic decompensation had taken place with cirrhosis , ascitis ,hypoalbuminemia(2gm/dl), raised S.billirubin (1.8 mg/dl), raised PT/INR & peripheral edema. Anemia with Hb-6gm% was present although it was not completely investigated.

Neurologic manifestations typically occur in patients in early twenties. The three main movement disorders includes dystonia, incoordination & tremor. Dysarthria , dysphagia are also common. Autonomic disturbances may include orthostatic hypotension, sweating abnormalities, bowel, bladder & sexual dysfunction. Memory loss, seizures may occur. Sensory abnormalities & muscular weakness are not the feature. Patients have difficulties focusing on tasks but cognition usually not grossly impaired. In our case cognition & focusing on tasks were normal. Since he was just 18 years of age, probably he had not developed the neurological problems.

A h/o behavioral disturbances, with onset in the 5years before diagnosis is present in 50% of patients with neurologic disease which includes loss of emotional control(temper tantrums, crying bouts), depression, hyperactivity or loss of sexual inhibition. Our case has h/o behavioral disturbances including loss of emotional control, depression & hyperactivity but no neurologic disease.

Some female patients have repeated spontaneous abortions & most become amenorrheic prior to diagnosis. Sun flower cataracts & kayser Fleischer rings(greenish brown discolouration) of the corneal margin are usually seen. Our case had KF rings in both the eyes.

Serum ceruloplasmin levels should not be used for definitive diagnosis because they are normal in 10% of affected patients & decreased in 20% of carriers. In our case S.ceruloplasmin level is very low (<9mg/dl). In most cases although KF rings are visible to naked eye they can only be dignosed definitively by an ophthalmologist using a slit lamp. In our case it is visible to naked eye. 24 hr urinary copper estimation is an important diagnostic tool. Symptomatic patients invariably have urine copper level >100micro gm/24hr. In our case it is towards higher limit of normal. The Gold "standard" for diagnosis is liver biopsy with quantitative copper assay. Genetic testing is limited by the existence of multiple genetic defects but may be useful in screening families of the affected individual.

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Case Report

ISOLATED PULMONARY VALVE ENDOCARDITIS FOLLOWING DILATATION & EVACUATION IN A FEMALE

B.P.Behera*, D.Saw*, S.K.Behera*, P.C. Patra*, N.Dhal, P.K. Rathor**, R.Mohanty***, D.N.Maharana******

ABSTRACT

Right-sided infective endocarditis (IE) is mainly a disease of intravenous drug abusers, it can occur also in non-drug addicts. Abortions and deliveries are frequently reported as a cause of right sided infective endocarditis is underdeveloped countries. ***KEY WORDS:*** *Infection, endocarditis, pulmonary regurgitation*

INTRODUCTION:

Infective endocarditis involving the pulmonic valve is extremely rare, accounting for only 1.5 to 2.0% of hospital admissions for infective endocarditis. [1] Although right-sided infective endocarditis (IE) is mainly a disease of intravenous drug abusers, it can occur also in non-drug addicts and involves the tricuspid valve in majority of subjects. Compared with the left-sided heart valves, the involvement of pulmonic valve infection tends to affect younger patients and more than 80% of affected subjects are normally male. In this case report we are reporting a case of isolated pulmonary valve endocarditis in a non-drug addict female following D&E.

CASE HISTORY:

A female patient aged 23 years was admitted with chief complains of continued high grade fever for 14 days and chest discomfort for 2 days. She had undergone D&E 2 weeks prior to this for threatened abortion in a local health care facility, which was not associated with any acute complication. She is a non diabetic and non hypertensive; there was no history suggestive of any congenital or rheumatic cardiac disease. She is not a known smoker or IV drug user. On examination she was found to be conscious, oriented, febrile (102.6°F), pulse rate of 144/min, regular, blood pressure 114/72 mm of Hg. There was presence of pallor and JVP was raised. Cardiovascular system examination revealing normal first heart sound, loud pulmonary component of 2nd heart sound. There was presence of ejection systolic murmur of grade 3/6 heard over pulmonary area. Other system examination was normal. Her routine haematological and biochemical parameter were Hb- 9.6gm%, TLC- 6400/cmm, DC- N 61%, L 37%, M 2%, ESR- 90 mm in 1st hour, Urine Routine/Microscopy: Albumin/Sugar- Absent, RBC- nil, Pus cell- 0-1/hpf; Fasting blood sugar- 87mg/dl; Blood Urea-18 mg/dl, Sr creatinine- 0.7mg/dl, MP (Slide/ICT) – Negative, Widal – Negative, Chest X-Ray (PA view) revealed no abnormality.(Pic-1) Blood culture done on 3 occasions was found negative after 7th day of aerobic incubation. Ultrasound of Abdomen/pelvis was normal. Echocardiography showed presence of a freely mobile vegetation of size 13x10 cm attached to ventricular side of pulmonary valve (Pic.2&3). LV function was normal with ejection fraction of 60%. With above findings a diagnosis of isolated pulmonary valve endocarditis was made and treatment was started with inj. Benzyl Penicillin, and inj. Gentamycin. Pt showed steady improvement and review ECHO done after 15 and 30 days showed progressive decrease in size of vegetation.

DISCUSSION:

Right-sided infective endocarditis (IE) is mainly a disease of intravenous drug abusers and involves the tricuspid valve in majority of subjects; however it can

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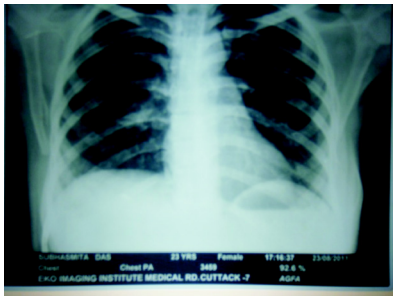
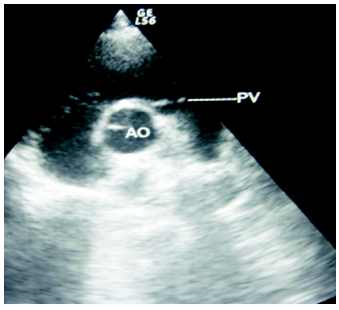
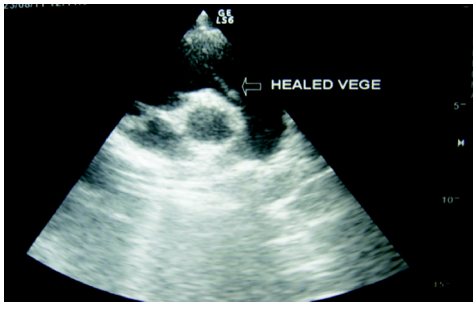


Picture.1
Normal chest x-ray



Picture.2



Picture.3

2D-ECHO showing pulmonary valve vegetation.

occur also in non-drug addicts. A search of the literature from 1960 through 2000 identified only 38 cases (including the present case) of isolated pulmonic valve endocarditis occurring on structurally normal hearts. [2] Compared with left-sided heart involvement, pulmonic valve infection tended to affect younger patients, and more than 80% of affected subjects were male. The vast majority of infections were community-acquired. Predisposing factors included intravenous drug abuse (28%), alcoholism (13%), sepsis (7%), central line infection (7%) or other catheter-related infection (5%), gonorrhea (5%), dental extraction (2.6%), bowel surgery (2.6%), liver or renal transplantation (2.6%), and colonic angiodysplasia (2.6%). In 28% of cases, no predisposing factor was identified. Abortions and deliveries are frequently reported as a cause of right sided infective endocarditis in underdeveloped countries.[3, 4]

In the 38 reviewed cases in which no pulmonic valvular abnormality was noted before infection, Staphylococcus aureus was the most common microorganism recovered from blood cultures (44%), followed by streptococci (13%), Streptococcus bovis (5%), gonococcus (5%), pseudomonas (5%), E. coli (5%), Candida albicans (5%), Bacteroides fragilis (2.6%), Haemophilus influenzae (2.6%), and E. faecalis (2.6%).[2] However, no organism was cultured in 10% of the cases. Transthoracic echocardiography was sensitive in detecting pulmonic valve vegetations (29 of 38 cases, or 76%). [2] In our case in view of continued fever and suspected cardiac lesion a 2-D Echo was done for detection of infective endocarditis, which showed vegetation attached to the pulmonic valve. Patient was having features of acute carditis as evidenced by disproportionate tachycardia and features suggestive of right heart failure as raised Pulsatile JVP and tender hepatomegaly. Although Blood culture of the patient was negative patient responded to the infective endocarditis regimen as further confirmed by reducing size of vegetation in follow up echocardiography. Patient had no history of IV drug abuse or any other predisposing factors but she had undergone D&E 2 weeks prior to the onset of features which may be attributed as the cause of Infective endocarditis in our case.

CONCLUSION :

This case is reported here in the view of its rarity of occurrence and to remind the fact that Right sided IE may complicate a D&E procedure.

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Case Report

HEPATOBILLIARY ASCARIASIS – 3 CASE REPORTS

B.D. Sahoo*, B. Sahu**

ABSTRACT

Three cases of hepatobiliary ascariasis are reported here. One of them presented as obstructive jaundice, 2nd one presented as acute colecystitis and the third case presented as acute abdomen.In all these cases single or multiple round worms were detected in hepatobiliary system by ultrasonography. All the three patients were treated by anthelmintic drugs and recovered within 24 to 72 hours of initiation therapy. ***Key words*** *- Ascariasis, Ultrasonography, Hepatobiliary.*

INTRODUCTION :

Ascariasis is endemic in developing countries, especially in village people. From GI tract roundworm may enter the hepatobilliary tree and produce obstructive jaundice, acute pain abdomen, acute cholecystitis, acute cholangits, acute pancreatitis and liver abscess. It can be diagnosed by USG or CT scan. Ultrasonography is an excellent modality to diagnose hepatobilliary ascarisis. 3 cases of hepatobilliary ascariasis were diagnosed by in NTPC hospital, Kaniha and were successfully treated.

CASE – 1

20 years old male, a cook by occupation presented with features of obstructive jaundice. Ultrasonography of abdomen revealed mobile elongated structure in common bile duct and intrahepatic billiary canaliculi with non homogenous echo texture. The structure showed inner hypoechoic and outer hyperechoic areas. Gall bladder was dilated and GB wall was thickened. The motility of structure was not related to respiration or postural change. Double tube sign was present in this case and was due to hypoechoic elementary canal seen within the round cross section of the worm. This confirms the diagnosis of hepatobillary ascarisis. Patient was treated with albendazole 400 mg OD for 3 days and showed the sign of clinical improvement three days after initiation of anthelmintic therapy. Repeat ultrasonography after 3 days revealed disappearance of the worm from CBD.

CASE – 2

A 40 years old lady had been admitted with severe pain abdomen and was on IV fluid, antibiotics,metronidazole and antispasmodic drugs for one day and there was no jaundice. USG of abdomen revealed a round cord like structure inside the gall bladder and partly in cystic duct. It had same double tube sign and the structure was motile which confirms the diagnosis of round worm in gall bladder and cystic duct. There was mild hepatomegaly and G.B wall was thickened. Patient was given anthelmintic drug and her pain subsided within 24 hours.

CASE – 3

11 years old boy, son of one CISF employee was admitted with diagnosis of acute abdomen and ultrasonography of abdomen revealed multiple round worm in gall bladder and at beginning of cystic duct producing acute cholecystitis. They had outer hyperechoic and inner hypoechoic structure and were motile. Diagnosis of hepatibiliary ascarisis was done and treated with anthelmintic drugs. On next day USG of abdomen revealed impacted elonged structure in GB. The patient gradually improved.

DISCUSSION

Suri et al (1) published a case of hepatobiliary ascariasis in which they had detected by USG one round worm in GB and three round worms in CBD

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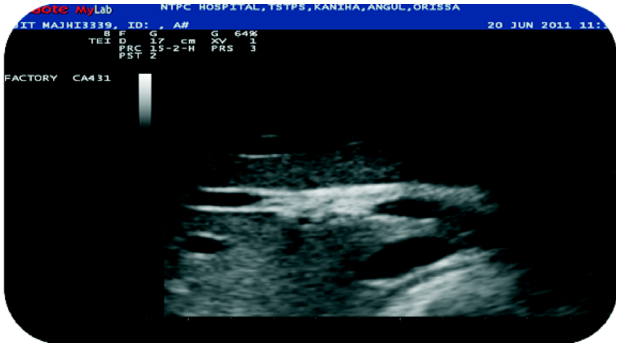

FIG-1 -ROUND WORM IN CBD

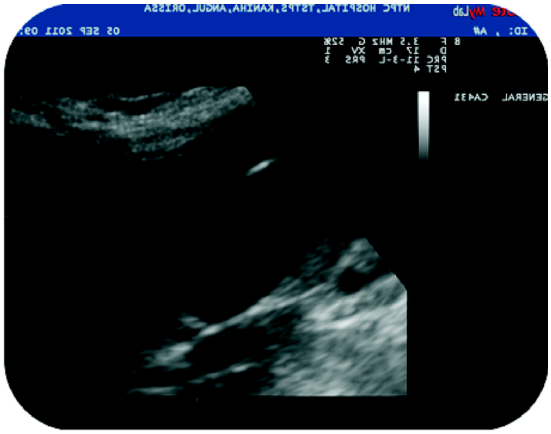

FIGURE-2 ROUND WORM IN CYCTIC DUCT

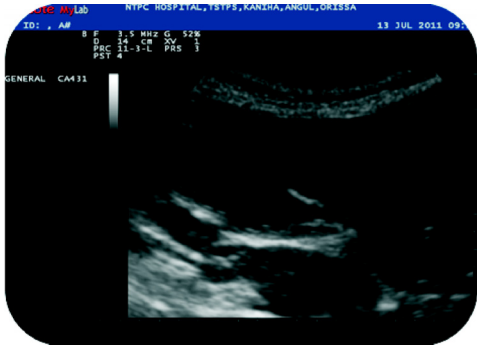

FIGURE-3 ROUND WORM IN GB

producing acute cholecystitis and obstructive jaundice. Patient was treated with albendazole, but did not improve and round worms were removed surgically. Khuro et al (2) have outlined several sonographic appearences of round worm in CBD like spaghetti appearance, bull's eye sign, impacted worm sign etc. Linear or curvilinear structures, single or multiple, with or without acoustic shadowing in USG are typical of Biliary ascariasis (4) . Some times when USG fails CT scan can detect round worm in CBD,ampula or neck of GB (3) . D A Lloyd et al had reported 9 cases of massive hepatobiliary ascariasis in childhood in which they have mentioned USG, intravenous cholangiography and endoscopic retrograde cholangiography are different modalities of investigation for diagnosis of hepatobiliary ascariasis.

CONCLUSION:

Ultrasonography is a noninvasive, cheap, accurate modality to diagnose and follow up of hepatibilliary ascariasis. Linear or curvilinear structures, single or multiple, with or without acoustic shadowing is typical of hepatobilliary ascariasis. Various signs described to diagnose ascarias includes bulls eye sign, inner tube or double tube sign, impacted worm sign etc. Movement of the worm is the most important appearance for diagnosis of hepatobiliary ascariasis. This movement should be differentiated from that of breathing and change in posture of the patient.

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Case Report

UNUSUAL PRESENTATION OF DENGUE

S N Das*, P K Thatoi, A Acharya***, S K Dutta******

ABSTRACT

Dengue is due to a flavivirus transmitted by the bite of Aedes mosquitoes[1]. Dengue infection may range from asymptomatic to severe haemorrhagic fever or dengue shock syndrome[1]. Out of 167proved dengue patient admitted to 7th unit Department of Medicine, SCB Medical College during the period August-September 2011. Most cases presented with fever, myalgia and rashes. Usually fever subsided after 5 days with or without paracetamol. Some cases (5-10%) needed 1 to 2 platelet transfusions. Here we are presenting some unusual cases. One presented with pleural effusion (pleural fluid Dengue IgM positive), one case with convulsions, one case with quadriparesis diagnosed in the emergency as GB Syndrome, one with severe thrombocytopenia (TPC -7200/cmm) subconjunctival haemorrhage, acute renal failure and hepatopathy. ***Keywords :*** *Dengue fever, Dengue Haemorrhagic fever, dengue shock syndrome, unusual presentation.*

INTRODUCTION:

The dengue viruses (type 1, 2, 3, 4) are enveloped ssRNA viruses of the flavividae family transmitted by the mosquito *Aedes aegypti*[2].

The incubation period is 5 to 8 days[1]. Dengue infection presents clinically as 3 overlaping syndromes. Undifferentiated fever (mild febrile illness lasting 1-3 days), dengue fever syndrome and dengue haemorrhagic fever or dengue shock syndrome (fever, thrombocytopenia, elevated haematocrit and hypotension)[2]. Some unusual presentations of dengue were observed during this present epidemic.

CASE 1: A 35 years old man admitted with fever, headache and pain abdomen for 3 days, on examination he had mild pallor, pulse 76/min, and BP 100/60 mmHg, no hepatosplenomegaly and grossly diminished vescicular breath sound in right infrascapular, infra axillary and mammary area without any added sound. Hb was 11 gm%, TLC 9500/cmm (N66, L28, E4, M2), TPC 1.5 lacs/cmm, serum urea 24mg/d, creatinine 0.9 mg /dl, Dengue NS-1 antigen and IGM ELISA was positive. X RAY chest showed moderate right pleural effusion. Pleural fluid aspirate revealed pale yellow fluid with lymphocyte 75%, histiocyte 25%, no polymorphs, pleural fluid sugar 102mg/dl and protein 3.1 gm/dl. Pleural fluid dengue IgM ELISA was positive. Patient was treated with antipyretics and discharged. Ten days after discharge X RAY chest was completely normal on follow up.

CASE 2: A 23 yr male presented with fever, rash, headache for 5 days. He was not an alcoholic, no history of trauma to head or no past h/o seizure. Patient was conscious, febrile, pulse 88/min, blood pressure 120/70 mm Hg. There were rashes over the trunk, back and legs. There was no hepatosplenomegaly. Patient was conscious, no neck stiffness, B/L plantar were flexor. Routine investigations showed Hb 12 gm%, TLC 8900/cmm (N68, L28, E2, M2) urea 28mg/dl, creatinine 1 mg/dl, serum Na^+139mg/dl, serum K^+ 4.2mg/dl, RBS 118mg/dl. Dengue NS1 Ag and IgM ELISA was positive. He was treated with paracetamol. On day 3 patient had GTCS & was treated with inj phenytoin. Repeat Serum Na^+144 mg/dl, K^+ 3.8 mg/dl, RBS 96 mg/dl. CT SCAN brain was normal. On day

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4 patient had another episode of GTCS and inj valproic acid was added. Observing 3 days without convulsion patient was discharged with oral valproic acid. Patient is seizure free after 2 months.

CASE 3: A 40 yr old male presented with fever for 3 days, unable to stand for 2 days and unable to lift his hands for 1 day. He was conscious, oriented, pulse 76/min, BP106/70 mmHg, mild pallor was seen without hepatosplenomegaly. CNS examination revealed cranial nerve deficit. Power of B/L upper limb 3/5, B/L lower limb 2/5, absent DTR in all 4 limbs. B/L plantar were non responsive. Bladder & bowel were not involved. Patient was diagnosed as GB syndrome. EMG and NCS reports were normal. All routine investigations were within normal limits. On day 4 suspicion of dengue was proved as NS1 Ag came positive. TPC was 1.3 lacs/cmm. Patient was treated with IV fluid and analgesics improved gradually and was discharged with full recovery of muscle power.

CASE 4: A 34 yr male referred from IGH Rourkela as viral fever for 5 days had severe subconjunctival haemorrhage, severe pallor and icterus. There was rashes all over the trunk and back. Pulse 88/min BP 110/60 mmHg, no hepatosplenomegaly, urination with gross haematuria was only 100 ml/24 Hrs. Investigations: Hb 4.8gm% TLC 5600/cmm, TPC 7200/Cmm, RBS 69mg/dl, serum urea 106mg/dl and creatinine 5.4 mg/dl, S Na^+ 143meq/l, K^+4.6meq/l.LFT: total bilirubin 4.5mg/dl. SGOT 196mg/dl, SGPT 148mg/dl. Dengue IgM was positive. He received 9 units of RDP (random donor platelet) and 3 units of fresh whole blood. On day 3 Serum urea was154mg/dl & creatinine 9.6 mg/dl. USG abdomen and pelvis report was acute medical renal disease. Then he was planned for haemodialysis. Three sittings of haemodialysis were done and on day 9 urination increased 2100ml/24 hrs. Gradually he improved and was discharged with creatinine 2.4 mg/dl.

DISCUSSION:

In this recent epidemic we saw most of cases (90%) of dengue presenting with fever myalgia arthalgia and rash that improved with or without paracetamol. Here we had one case of dengue fever with right sided pleural effusion (pleural fluid dengue IgM positive) that is described by Suchitra Nimmannitya et al[3]. Suchitra nimmannitya et al also described neurological manifestations of dengue as convulsion, encephalopathy or acute transverse myelitis as unusual presentations[3]. Wayne X shandera et al described neurological manifestation of dengue as convulsion, quadriparesis and encephalopathy[1,7]. We got one of the dengue fever with convulsion as dengue encephalopathy. Scott and Halstead et al described renal failure as an extreme manifestation of dengue[2,4,7]. We got one case of dengue with severe thrombocytopenia (TPC-7200/cmm) and acute renal failure. Patient improved with platelet transfusion and haemodialysis.

CONCLUSION:

Most cases of dengue present with fever, arthalgia, myalgia and rash. But deviating from usual presentations, dengue patients may present with pleural effusion, convulsion, acute onset quadriparesis or acute renal failure.

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Case Report

AUTOIMMUNE HYPOTHYROIDISM WITH SJOGREN'S SYNDROME

L Mohanty*, S Tripathy, R.P Sahoo***, L.Toppo******

ABSTRACT

Sjogren's syndrome is a chronic slowly progressive autoimmune disorder that mainly affects the exocrine glands. Sjogren's syndrome has an incidence of 4 cases in 100000. It is classified as primary or secondary depending on its association with other systemic autoimmune diseases like rheumatoid arthritis, systemic sclerosis, or systemic lupus erythematosus. We report a case of secondary Sjogren"s syndrome in a 38 year old lady, who was already under treatment for hypothyroidism. The diagnosis was made on the basis of suggestive clinical picture, autoimmune markers and radio-isotope study. ***Key words*** *: Sjogren's Syndrome, Autoimmune hypothyroidism.*

INTRODUCTION

Sjogren's syndrome is a chronic slowly progressive systemic autoimmune disorder that mainly affects exocrine glands and usually present as persistent dryness of mouth and eyes due to functional impairment of salivary and lacrimal glands. When sicca features are found in association with another systemic autoimmune disease like Rheumatoid arthritis, Systemic sclerosis or SLE, it is classified as secondary Sjogrens syndrome. When sicca features are found in otherwise healthy people it is called primary Sjogrens syndrome .Prevalence of secondary sjogrens syndrome is between 11%to19% in SLE patients and about 7% in RA patients. Incidence of sjogrens syndrome as a whole is 4 cases in 100000. Sjogrens syndrome primarily affects perimenopausal women with a female to male ratio ranging from 14:1 to 24:1 .

CASE REPORT

A 38 year old lady presented to KIMS Medicine OPD with decreased lacrimation , severe dryness, itching of both the eyes and inability to take dry food . Her symptoms started gradually and progressively over the last one and a half year. She also complained of intermittent low grade fever, easy fatiguability, arthralgia.

Her past history revealed that she has got hypothyroidism and is on l-thyroxine 100 µgm daily since 1996. There was no history of pain abdomen, breathlessness, constipation, dyspareunia, painful swelling of the lymph nodes, or any skin lesion. Her menstrual history is currently regular, normal cycles. Last child birth 3yrs back. General examination of the patient revealed mild pallor, puffy face, dry skin. There was no lymphadenopathy, no swelling or deformity of the joints, no thyromegaly.

Examination of the oral cavity revealed severe dryness of oral mucosa with caries affecting almost all of the teeth of all 4 quadrants. Pulse-62/min., regular. BP-110/80 mm Hg, wt-62 kg. Systemic examination revealed no abnormal finding. Provisional diagnosis of Hypothyroidism (possibly autoimmune origin) with Sjogren's syndrome was made. The patient was hospitalized for further investigation.

On laboratory investigation routine examination were within normal limit except high ESR-60 mm/1st hr, Rheumatoid Factor positive; Titre>10 IU/ml , CRP-Negative. Other investigations including ECG, Chest X-ray PA , USG A/P revealed no abnormality .Specific tests were sent in the line of autoimmune hypothyoidism and Sjogren"s syndrome which revealed –ANA-positive(4+) ,Anti RO/SS-A Ab-positive(titre >61.03) (normal<20) ,Anti LA/SS-B Ab-negative, TSH-2.699

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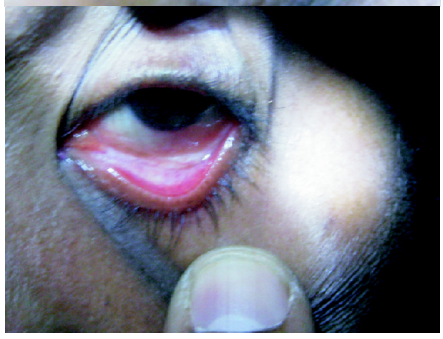
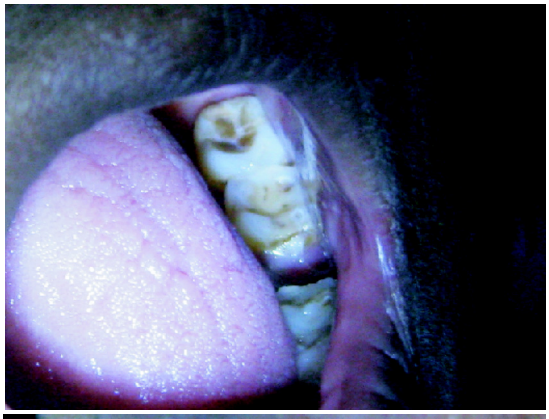
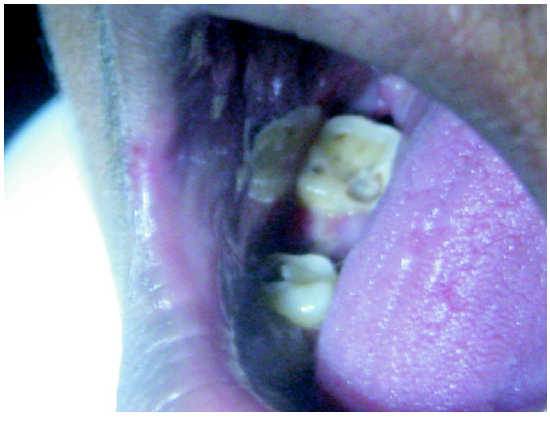
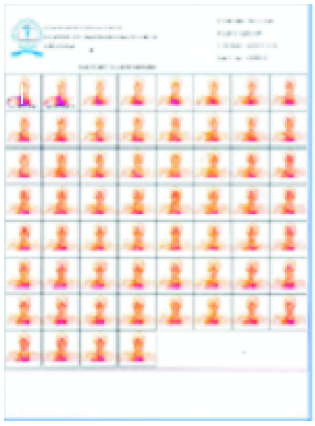


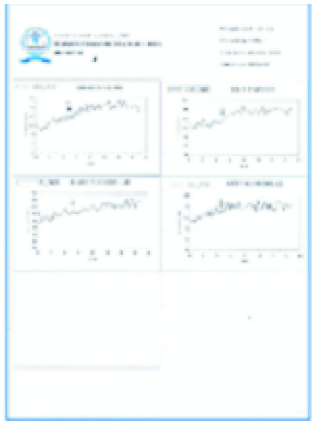
SCHIRMER I TEST-
SEVERE DRY EYES, B/L <3mm



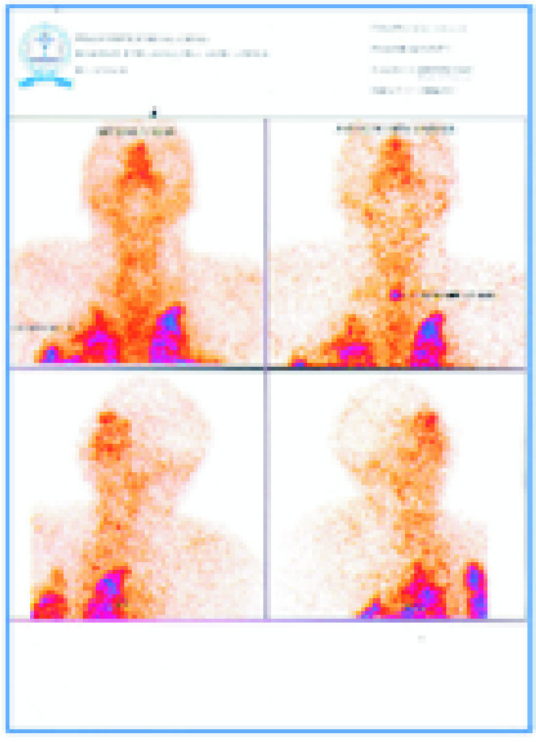


GROSSLY DECAYED MOLAR & PREMOLAR TEETH





SALIVARY SCINTIGRAPHY(Tc99Mo4 under gamma camera) of both parotid & submandibular glands revealed very poor tracer concentration in the glands showing no reaction to the stimulus.



THYROID SCAN revealed faintly visualized thyroid gland. **THYROID** to **PAROTID RATIO(TPR)** calculated to be 1.0(normal up to 2.5)

μIU/ml ,FT4 1.01 μIU/ml ,Anti TPO Ab-1300 U/ml(normal<60). Ophthalmic examination -Schirmer I test –severe dry eyes B/L, <3mm. Slit Lamp Exam – revealed no corneal ulcer. Dental examination showed grossly decayed molar / premolar teeth along with apical periodontitis. Extraction of the right lower molar and pre-molar was done by the dentist.

Salivary Scintigraphy (Tc99Mo4 under gamma camera) of both parotid & submandibular glands revealed very poor tracer concentration in the glands showing no reaction to the stimulus. thyroid scan revealed faintly visualized thyroid gland. Thyroid to Parotid ratio (TPR) calculated to be 1.0(normal up to 2.5).

Based on the above clinical and laboratory findings a final dia Secondary Sjogren's syndrome was made.

Patient was discharged with advice of tablet eltroxin 100μG daily, tablet pilocarpine 5mg thrice daily, taking frequent sips of water, sugar free lozenges or gums, proper dental hygiene, artificial tear drops to use.

DISCUSSION

Major clinical manifestations of sjogren syndrome are xerostomia, periodontal disease, oral candidiasis, parotid swelling, ocular involvement, Renal Tubular Acidosis, glomerulonephritis, myelopathy, sensorineural deafness, autoimmune thyoroditis and general symptoms like fatigue, fibromyalgia, polyadenopathy etc.

Lymphoma is a late manifestation of Sjogren syndrome.(B cell Lymphoma).[1]

Nearly one third of patients with primary sjogren's syndrome have thyroid disease .Subclinical hypothyroidism is the most frequent finding especially in patients with anti-thyroid antibody suggesting Hashimotos thyroiditis.

In our case Autoimmne Thyroid Disease was not concomitant, rather it preceded Sjogren's syndrome by a period of 13 yrs.

Treatment of Sjogren's syndrome is usually aimed at symptomatic relief with artificial tear drops, cholinomimetic drugs like pilocarpine, cevimelline (not available in India).

HCQS is helpful in patients with symptomatic arthritis. Corticosteroids are indicated only for systemic vasculitis.[4]

Anti CD20 monoclonal Ab along with classic CHOP regimen increases the survival in patients with lymphoma.

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Case Report

UNUSUAL CASE OF POLYARTICULAR GOUT

B.K. Barik*, P. Padhan, N. Mohapatra*****

ABSTRACT

Gout is a common inflammatory arthritis caused by deposition of monosodium urate crystals in the joints. It classically affects the first metatarsophalangeal joint and less commonly other joints, such as wrists, elbows, knees and ankles. We report the case of a 65-year-old man with tophaceous polyarticular gout, soft-tissue involvement of elbow joint with secondary infection leading to septicemia. ***Key words :*** *Gout, monosodium urate crystals, tophi, arthropathy, Febuxostat, Colchicine.*

INTRODUCTION

Gout is a common disorder of uric acid metabolism, characterized by recurrent episodes of inflammatory arthritis, tophaceous soft tissue deposits of monosodium urate crystals, uric acid renal calculi and chronic nephropathy. We report the case of a 65-year-old man suffering from tophaceous polyarticular gout and soft-tissue involvement, presenting with ulcerated tophi overlying the left elbow. We also emphasize the disabling effects of the untreated hyperuremic arthropathy.

Case presentation

A 65-year old man with a long-standing history of tophaceous gout and several recurrent episodes of arthritis during the past five years presented with a large, painful, ulcerated tophus located on the left elbow joint to the emergency department. He was given a course of non-steroidal anti-inflammatory drugs (NSAIDs) without improvement.

On physical examination he had mild fever (37.8°C). A grayish, voluminous and ulcerated nodule containing chalky white material was located on the left elbow. Further examination revealed multiple tophi overlying the 4th and 5th PIP joints (proximal interphalangeal joint) of his right hand and the first interphalangeal joints of his left hand(Figure 1). Other joints involved were wrists, elbows, ankles, interphalangeal and metatarsophalangeal joints of the feet and heels. Many joints were also deformed. The first metatarsophalangeal joint of his left foot was totally nonfunctional.

Laboratory workup revealed leukocytosis (11.000/mm^3), elevated C-reactive protein (60.21 mg/dl) and elevated serum uric acid (11 mg/dl) and normal serum creatinine (0.9mg/dl). Radiographs of the hands showed showing soft tissue swelling and destruction of both wrist, left IP thumb, right 4th and 5th PIP joints, calcified tophi seen in right 2nd MCP joint(meta carpo phalangeal joint)(Figure 2). A culture from the ulcerated tophus was positive for staphylococcus aureus (Methicillin sensitive). Two days after admission, the tophus burst releasing a viscous, chalk-like material. Polarized microscopy confirmed presence of needle shaped monosodium urate crystals (Figure 3).

Antibiotic treatment with IV Ciprofloxacin (1000 mg/day) and intravenous administration of NSAIDs (Diclofenac 100 mg/day) was initiated.

A surgical debridement with lavage of the joint was performed. Debridement was also performed on the minor ulcers. Five days after admission treatment with Febuxostat (80 mg/day) along with Colchicine 0.5mg twice daily was initiated. The patient improved clinically and was discharged two days later. Six months after treatment, he remains symptom free.

* Professor, Medicine, IMS & SUM Hospital, Bhubaneswar.
** Consultant Rheumatologist & Immunologist, Apollo Hospital, Bhubaneswar.
*** Histopathologist,Apollo Hospital, Bhubaneswar.

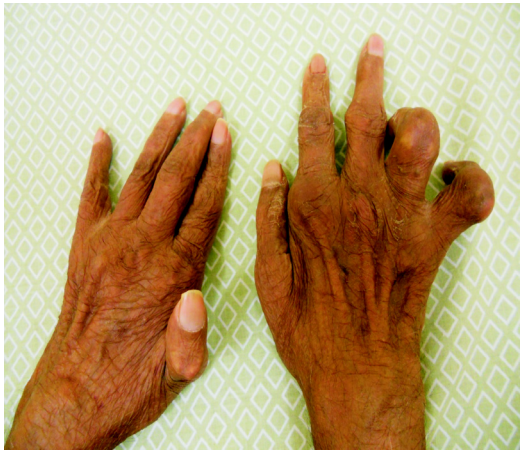

Figure 1 : showing small tophi over left IP thumb and right 4th PIP joints

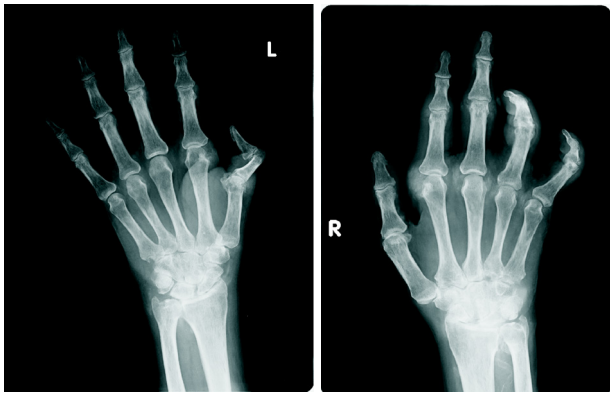

Figure 2 :showing X ray both hands showing soft tissue swelling and destruction of both wrist,left IP thumb,right 4th and 5th PIP joints, calcified tophi seen in right 2nd MCP joint.

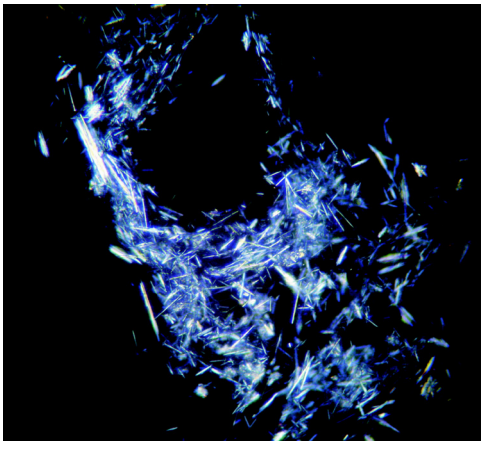

Figure 3 : showing needle shaped monosodium urate crystals under polarized microscopy

DISCUSSION:

Gout is the most common inflammatory arthropathy, reported to affect 2.13% of the population of the United States of America in 2009[1]. Older age, male sex, postmenopausal state and black race are related to a higher risk for development of the disease[2]. Elevation of uric acid levels above the saturation point for urate crystal formation (6.8 mg/dl) usually results from an impaired renal uric acid excretion and although necessary, it is not sufficient to cause gout. Hyperuricemia and gout can be attributed to uric acid elevating drugs, genetic polymorphisms in genes controlling renal urate transport and predisposing dietary factors, such as consumption of red meat, seafood, alcohol and fructose containing soft beverages[3]. Other conditions associated with the disease include insulin resistance, obesity, hypertension, renal insufficiency, congestive heart failure, and organ transplantation[2].

Over time, poorly controlled gout may progress to a chronic phase, characterized by polyarticular attacks, painful symptoms between acute flares and monosodium urate crystal deposition (tophi) in soft tissues or joints[2]. Tophi are typically found on the helix of the ears, on fingers, toes, wrists and knees, on the olecranon bursae, on the Achilles tendons and also rarely on the sclerae, subconjuctivally,[4] and on the cardiac valves[5]. They can cause pain and dysfunction and are rarely associated with ulcerations[6], bone fractures[7], tendon and ligament rupture[8], carpal tunnel[9] and other nerve compression syndromes[10]. Differential diagnosis for subcutaneous or articular nodules includes septic arthritis, synovial cysts, nodal osteoarthritis, rheumatoid arthritis, sarcoidosis, lymphoma or neoplasms[11]. Synovial fluid or tophus aspiration permits diagnosis through demonstration of negatively birefringent monosodium urate crystals[2].

Treatment options for acute gouty attacks include dietary and lifestyle modifications, NSAIDs, colchicine, oral or topical steroids and corticotropin (ACTH). Interleukin-1 (IL-1) antagonists, such as anakinra, a human recombinant IL-1 receptor antagonist and canakinumab, a monoclonal antibody against IL-1â, have also shown promising results in the treatment of refractory cases or cases intolerant to classical therapy[2]. Even without treatment acute attacks usually resolve

spontaneously within seven to 10 days. Normalizing hyperuricemia is of cardinal significance for the control of recurrent attacks and for the regression of tophi. This is achieved with drugs, which either favor uric acid excretion (probenecid), convert uric acid into soluble allantoin (pegloticase), or inhibit uric acid production (allopurinol, febuxostat)[2].

Surgical treatment is seldom required for gout and is usually reserved for cases of recurrent attacks with deformities, severe pain and joint destruction[11]. The main indication for surgery in patients with tophaceous gout is sepsis or infection of ulcerated tophi, followed by mechanical problems, confirmation of diagnosis and pain control[12]. Removal of tophaceous deposits from the hands can be achieved through tenosynovectomy for heavily infiltrated tendons, through a soft-tissue shaving technique for heavy skin infiltration with ulceration and draining fissures[13], or through more complex surgical approaches involving large skin incisions and excision of the tophi[14]. A hydrosurgery system applying a highly pressurized saline stream has also been used with good results for the debridement of tophi[15]. In the early stages, surgical arthroplasty can be carried out, but simple enucleation of the tophi may lead to complications such as skin necrosis, tendon and joint exposures[11]. Amputation is always a valid option for untreatable and infected ulcerations[16].

CONCLUSION

Secondary infection of tophaceous gout are not uncommon can lead to septicemia. Surgical treatment is required for such cases along with medical therapy.

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Audited Account of 30th Annual APICON. Odisha Branch. 2010 held at Bhubaneswar submitted by Organising Secretary

RECEIPT & PAYMENTS ACCOUNT FOR THE YEAR ENDED 31ST MAR.2011

RECEIPT	Amount(Rs.)	PAYMENT	Amount(Rs.)
To Opening Balance :			
Bank	2,000.00	By Seminar	28,205.00
		By Tent & Banner	90,399.00
To Delegate Fees Collection	130,150.00	By By Decoration & Light Sound	50,850.00
To Pharma Collection	983,060.00	By Printing & Stationery Exp.	18,493.00
To Bank Interest	4,444.00	By Postage Stamp Exp.	2,273.00
		By Telephone	4,450.00
		By Souvenir	40,000.00
		By Fooding	314,196.00
		By Travelling	28,792.00
		By Remuneration	16,000.00
		By Room Hire chg.	625.00
		By Payment to Secretary	2,000.00
		By Payment to IMA	300,000.00
		By Closing Balance :	
		Bank	**223,371.00**
	1,119,654.00		**1,119,654.00**

INCOME & EXPENDITURE ACCOUNT FOR THE YEAR ENDED 31ST MAR.2011

Expenditure	Amount(Rs.)	Income	Amount(Rs.)
To Seminar	28,205.00	By Delegate Fees Collection	130,150.00
To Tent & Banner	90,399.00	By Pharma Collection	983,060.00
To Decoration & Light Sound	50,850.00	By Bank Interest	4,444.00
To Printing & Stationery	18,493.00		
To Postage & Stamp	2,273.00		
To Telephone	4,450.00		
To Souvenir	40,000.00		
To Fooding	314,196.00		
To Travelling	28,792.00		
To Remuniration	16,000.00		
To Room Hire chg.	625.00		
To Audit Fees	3,000.00		
To Excess of Income over exp	520,371.00		
	1,117,654.00		**1,117,654.00**

BALANCE SHEET AS ON 31.03.2011

Liabilities		Amount(Rs.)	Assets	Amount(Rs.)
Capital Fund				
Opening Balance :	-			
Add: Excess of Income	520,371.00	520,371.00		
over Exp.			Advance to IMA	300,000.00
Audit Fees Payable		3,000.00	Cash at Bank	223,371.00
		523,371.00		**523,371.00**

RECEIPT & PAYMENTS ACCOUNT FOR THE PERIOD FROM 01.04.2011 TO 31.08.2011

RECEIPT	Amount(Rs.)	PAYMENT	Amount(Rs.)
To Opening Balance :			
Bank	**223,371.00**		
To Pharma Collection	40,000.00	By Printing & Stationery Exp.	984.00
To Bank Interest	3,915.00	By Postage Stamp Exp.	493.00
		By Audit Fees Payable	3,000.00
		By Audit Fees	1,000.00
		By Furniture & Fixture	58,523.00
		By Office Equipment (AC)	32,000.00
		By Api Orissa State	50,000.00
		By Seed money for 30th Annual Meeting	10,000.00
		By Remuneration	6,000.00
		By Payment to IMA	100,000.00
		By Closing Balance :	
		Bank	**5,286.00**
	267,286.00		**267,286.00**

INCOME & EXPENDITURE ACCOUNT FOR THE PERIOD FROM 01.04.2011 TO 31.08.2011

Expenditure	Amount(Rs.)	Income	Amount(Rs.)
To Printing & Stationery	984.00	By Pharma Collection	40,000.00
To Postage & Stamp	493.00	By Bank Interest	3,915.00
To Audit Fees	1,000.00	BY Excess of exp. over income	24,562.00
To API Orissa State	50,000.00		
To Seed money for 30th Annual Meet.	10,000.00		
To Remuniration	6,000.00		
	68,477.00		**68,477.00**

BALANCE SHEET AS ON 31.08.2011

Liabilities		Amount(Rs.)	Assets		Amount(Rs.)
Capital Fund					
Opening Balance :	520,371.00		Fixed Assets		
Less: Excess of exp. over Income	24,562.00	495,809.00	Furniture & Fixture	58,523.00	
			Office Equipment (AC)	32,000.00	90,523.00
			Advance to IMA		400,000.00
			Cash at Bank		5,286.00
		495,809.00			**495,809.00**

JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA ORISSA STATE BRANCH

Manuscript submission : Check List for Contributors

1. Letter of submission.
2. Copyright statement signed by all the authors.
3. Three copies of manuscript with copies of illustrations attached to each.
4. Title page.

   Title of manuscript.

   Full name(s) and affiliations of author(s); institution(s) and city(ies) from which work originated.

   Name, Address, Telephone, Fax numbers and e-mail address of corresponding author.

   Number of pages, number of figures and number of tables.
5. Structured abstract (objectives, methods, results, conclusion) along with title, and key words.
6. Article proper (double spaced on A/4 size paper).
7. Acknowledgements (separate sheet).
8. References (double spaced, separate sheets, Vancouver style).
9. Maximum number of references for Original articles - 20, Short articles-10,

   Case reports-6, Documentation-3, Correspondence-3.
10. Each table on separate sheet.
11. Figures/diagrams on separate sheet.
12. Photographs in envelope appropriately marked.
13. Legends on separate sheet.
14. Covering letter signed by all authors confirming that they have read and approved the contents and also confirming that the manuscript is not submitted or published elsewhere.
15. Statement regarding Ethics Committee Approval and informed consent from subjects.*
16. Floppy diskettes are Compulsory Now*

* This is new addition to the check list, contributors to note.

- Hon Editor.

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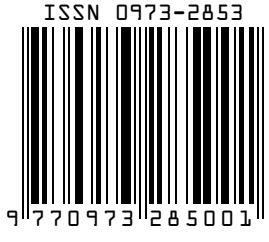

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