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CONTENTS

Editorial

SCRUB TYPHUS IN ODISHA - EMERGING AWARENESS

N. Mohapatra*, M.R. Behera**

Scrub typhus is an acute infectious disease of variable severity, that is caused by the gram-negative obligate intracellular bacterium Orientia (formerly Rickettsia) tsutsugamushi. It is transmitted to humans by the bite of trombiculid mite which usually feed on rats . Man is an accidental host in this zoonotic disease. The term "scrub" is used to refer to the type of vegetation (terrain between woods and clearings) that harbors the vector, and the word "typhus" is derived from the Greek word "typhus",which means "fever with stupor"[1]. Scrub typhus is endemic in the region known as the 'tsutsugamushi triangle' which includes Japan, Taiwan, China and South Korea on the north, India and Nepal on the west and Australia and Indonesia on the south[2]. It was first described from Japan in 1899. In India, the disease had occurred among troops during World War II in Assam and West Bengal, and in the 1965 Indo-Pak war. It was known to occur all over India, including Southern India and Northern India[3,4,5,6]. However, in later years, the disease virtually disappeared, probably because of the widespread use of insecticides to control other vector borne diseases, empiric treatment of febrile illnesses with tetracyclines and chloramphenicol by practitioners and changes in lifestyle.

Although the disease is endemic in our country, it is grossly underdiagnosed owing to the non-specific clinical presentation, lack of access to the specific diagnostic facilities in most areas, and low index of suspicion[7]. In India, cases of scrub typhus have been reported recently from different parts of the country[7-11]. But there have been no reports of the disease from Odisha earlier. In the current issue of the Journal, a case series of scrub typhus has been reported for the first time from Odisha from a tertiary care hospital. This report shows that this disease is widely prevalent in the state and describes the diverse clinical and laboratory manifestations of scrub typhus.

The basic pathologic changes in scrub typhus are focal vasculitis and perivasculitis of the small blood vessels in the various organs, resulting from the multiplication of the organisms in the endothelial cells lining the small blood vessels. After an incubation period that ranges from 6 to 21 days (usually, 10–12 days), the clinical symptoms vary in severity from a mild febrile illness to a severe potentially fatal disease with multi organ dysfunction syndrome(MODS). The typical systemic features include fever, gastrointestinal disturbances, malaise, cough, myalgia, and headache[11]. A maculopapular rash starting on the trunk and spreading to the limbs is seen towards the end of the first week of fever along with regional lymphadenopathy. A significant finding is an eschar at the bite site which is almost diagnostic[2]. An eschar is usually found on Caucasian and East Asian patients but is seen less frequently on South Asians, especially those who are dark skinned[5,6]. It starts as a small papule that enlarges and subsequently undergoes central necrosis to turn black. The common sites of eschar are groin, axilla, waist and other exposed parts of the body. Severe complications of the disease include acute respiratory distress syndrome(ARDS), hepatitis, renal failure, meningoencephalitis, and myocarditis with shock, which may occur in varing proportions of patients. The vast variability and non-specific presentation of this infection makes it difficult to diagnose clinically as it mimics other tropical diseases like malaria, dengue fever, leptospirosis, and community acquired pneumonia.

The mainstay of diagnosis in scrub typhus is serology. The current choice for the serologic diagnosis are IgM ELISA testing or immunofluorescence assay

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(IFA), which are considered the gold standard, but are less frequently available[2]. The cheapest test currently available and used extensively in our country is Weil- Felix test which is highly specific, but lacks sensitivity[4-8,13].

In the current issue of the journal 'Scrub Typhus:An unrecognized disease in Odisha', by S. Sahu et al have reported 26 cases of scrub typhus from Odisha, the first report from the state. All the cases were seen between July to December, indicating increased transmission during rainy season. 50% of the cases identified from urban areas showing that it is no more a disease confined to rural areas. All the patients presented with fever(100%) and respiratory symptoms were seen in 85.5% which was similar to other studies[9,10]. Eschar, which is pathognomonic of scrub typhus, was found in only 5 cases(19.2%),similar to findings by Subhalaxmi et al in 13.1% and Kedareswar et al in 13.3%[9,10]. Respiratory failure was seen in 92.3% cases as compared to 60% in Kedareswar et al. study, as the case series were mostly from the ICU/HDU. Renal failure occurred in 42.3% cases and altered mental status in 15.3%, similar to other reports[8,9,10]. Mortality was 11.6% which is comparable to other Indian studies which ranged from 2% to 33.3%[8,9,10].

Early diagnosis of this disease is important because there is usually an excellent response to treatment and timely anti-microbial therapy (Doxycycline, Azithromycin, Chloramphenicol) may help to prevent complications. In developing countries with limited diagnostic facilities, it is prudent to recommend empiric therapy in patients with undifferentiated febrile illness having evidence of multiple system involvement(2) The mortality from this infection does appear to be decreasing over the last several years. To conclude, scrub typhus is prevalent in Odisha. It should be considered in the differential diagnosis of patients with acute febrile illness with multisystem involvement. High index of suspicion is required amongst the physicians to diagnose this disease. However, developing awareness of this infection amongst clinicians in endemic settings and reliable methods for rapid diagnosis will be the key to early diagnosis and further reducing the mortality caused by this deadly disease.

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Original Article

SCRUB TYPHUS: AN UNRECOGNIZED DISEASE IN ODISHA

S. Sahu*, B. Ray, S. Sinha***, S. Pattanaik***, S. Dash****, Sunita Sahoo*******

ABSTRACT

Aim: *To describe the clinical features, laboratory manifestations, complications in patients diagnosed with scrub typhus at a tertiary care hospital in Bhubaneswar, India.*

Material and Methods: *All cases of acute onset fever diagnosed to have scrub typhus from August 2011 to December 2013 were analysed. Cases of scrub typhus confirmed by the IgM ELISA were studied.* ***Results:*** *26 confirmed cases of scrub typhus were studied over a period of 29 months. Apart from coming from rural areas 50% of cases came from urban areas. Most common symptoms were due to the involvement of respiratory tract in the form of cough and breathlessness in 23(88.5%). Radiological abnormalities on chest x-ray were seen in 16(61.5%). Elevated liver enzymes were found in 14(53.8%) and renal failure was seen in 11(42.3%). Central nervous system involvement in the form of altered sensorium was seen in 4(15.4%) patients. Eshcar was seen in 5(26.9%) and rashes in 7(26.9%) patients. Three (11.5%) patients died in our study.* ***Conclusion:*** *Scrub typhus is present in Odisha and should be suspected in patients with fever and multisystem involvement. The predominant symptoms were cough and breathlessness. The clinical features are similar to scrub typhus occurring in other parts of India. They are as common in urban areas as compared to rural areas. Clinicians should have high suspicion for this disease and confirm the diagnosis by immunological tests. Empirically treatment by Doxycycline may be life saving.* ***Key words :*** *Typhus, scrub typhus.*

INTRODUCTION:

Scrub typhus is an acute febrile illness caused by the intracellular parasite Orienta tsutsugamushi. It is zoonotic disease, transmitted by the bite of trombiculid mite. These mites usually feed on rats. Man is an accidental host, and is infected when an infected mite bites the patient[1]. The infection manifest as fever, headache, myalgia, nausea, vomiting, cough or breathlessness along with multiple organ dysfunction. Scrub typhus has protean manifestations which can mimic conditions like pneumonia, meningoencephalitis, acute hepatitis, acute renal failure, loose motions and occasionally joint pains. Eshcar or rashes may be present, but its absence does not rule out the disease. Pulmonary complication of scrub typhus occurs in 20-70% of patients and is manifested as breathlessness and cough[2]. Scrub typhus, if undiagnosed or diagnosed late, or untreated, may prove fatal. India is an endemic country of scrub typhus and it has been reported from Vellore, Puducherry, Shimla, Jammu, Haryana, Goa, Maharastra, Sikkim, Assam, West Bengal and other parts of India.[3-8] The diagnosis of Scrub Typhus is frequently missed due to its non-specific presentations, limited awareness, lack of clinical suspicion among the doctors and non availability of diagnostic methods. Odisha has not yet reported Scrub Typhus. We present a case series from a tertiary care hospital reporting Scrub Typhus for the first time in Odisha.

MATERIAL AND METHODS:

This is a retrospective observational study of patients with scrub typhus who were admitted between

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August 2011 and December 2013 in our ICU/HDU. Clinical and laboratory features of patients aged more than 15 years, with fever, and confirmed diagnosis of scrub typhus was collected and analysed. Scrub Typhus was confirmed by Scrub Typhus Detect IgM elisa system of InBios International Inc.

Table 1: Baseline Characteristics of the patients

Characteristics of the patient	Number of patients	(%)
Age (mean, SD)	43.30	(16.4)
Males	13	(50%)
Females	13	(50%)
Rural background	13	(50%)
Urban background	13	(50%)

Table 2: Showing the symptoms and signs

Symptoms	Number of patients	(%)
Fever Duration < 7 days	04	(15.3%)
Fever Duration 7-14 days	17	(65.4%)
Fever Duration > 14 days	04	(15.3%)
Fever (mean, SD)	10.11 (3.06) days	
Cough & Breathlessness	23	(88.5%)
Jaundice	12	(46.2%)
Altered Mental Status	04	(15.4%)
Eschar	05	(19.2%)
Rashes	07	(26.9%)

Table 3: Showing the Laboratory abnormalities

Investigation	Number of patients	(%)
Anaemia(Hb<10gm%)	06	(23%)
Leucopenia(<4000/cumm)	02	(7.6%)
Leucocytosis(>12,000/cumm)	13	(50%)
Platelets (< 1 lakh/cumm)	02	(7.6%)
Elevated Serum Aspartate transaminase	14	(53.8%)
Elevated Serum Alanine transaminase	14	(53.8%)
Elevated Serum Creatinine(>2mg%)	11	(42.3%)
Infiltrates on chest radiograph	14	(53.8%)
Pleural Effusion	02	(7.6%)
Myocarditis(global LV dysfunction)	02	(7.6%)
Hypoxia(PaO_2<60mmHg)	24	(92.3%)
Hypercapnia(PCO_2>40mmHg)	07	(26.9%)

Table 4: Treatment and Outcome

	Number of patients	(%)
ICU stay (mean, SD)	4.46(2.78)	
Hospital Stay (mean, SD)	8.42(3.89)	
Apache II Score (mean, SD)	13.57(4.97)	
SOFA Score (mean, SD)	6.33(3.306)	
Mechanical ventilation (Inv & NIV)	16	(61.5%)
NIV	09	(34.6%)
Invasive	07	(26.9%)
Vasopressors during ICU stay	16	(61.5%)
Treatment		
Doxycycline	15	(57.7%)
Doxy+ Azithromycin	11	(42.3%)
Outcome		
Survival	23	(88.5%)
Death	03	(11.5%)

RESULTS:

26 cases were included in the study. They came from all over the state. The baseline characteristics, clinical features, (Fig.1&2) laboratory abnormalities and treatment and outcome are presented in tables 1-4. The mean age of these patients was 43.3 years (SD-16.4, range-15-71 years). There were 13 males (50%) and 13 females (50%). Only 13 patients (50%) were from rural areas. The mean duration of fever on admission was 10.11 (SD-3.06) and majority presented in the second week when complications started. Respiratory symptoms were present in 23 patients (88.5%). On ABG we assessed the blood gas and hypoxia was present in 92.3% (n=24) of cases and hypercapnia in 26.9% (n=7) of cases. Other organ abnormalities like elevated bilirubin and liver enzymes was found in 53.8% (n=14), raised serum creatinine(acute kidney injury) in 42.3% (n=11); three of them requiring hemodialysis. Leukocytosis was present in 50% (n=13), leukopenia in 7.6% (n=2), anaemia in 23% (n=6) and thrombocytopenia in 7.8% (n=2) of cases. Among the skin lesions eschar was found in only 5 cases(19.2%) but rashes were present in 26.9% (n=7) of cases. Chest x-ray showed interstitial and acinar shadows in 53.8% (n=14) and pleural effusion associated with acinar shadow in 2 cases (7.6%). Most of the shadows were bilateral and basal in distribution. (Fig.3) CT thorax showed bilateral acino-nodular shadows.(Fig.4) The mean Apache II score of patients in the first 24 hours of admission was 13.57(SD 4.97) and mean SOFA score was 6.63(SD 3.306). The average stay of patients in ICU was 4.46 (SD 2.78) days and hospital stay was 8.42(SD 3.89) days. Mechanical ventilation was required in 7 cases (26.9%) and non-invasive was required in 9 cases (34.6%). Rest of the cases were managed with oxygen inhalation only. Fourteen cases (53.8%) required vasopressors during their ICU stay ranging from 1-7 days to maintain their blood pressure. Two cases were detected to have LV dysfunction with global hypokinesia suggesting myocarditis. Both of them recovered. One case had vasculitis leading to gangrene of the toes which recovered completely.(Fig.5) All patients were managed with doxycycline but azithromycin was added in eleven cases (42.3%) who were very sick and we wanted to give IV antibiotics. 88.5% of cases (n=23) survived and only 3 patients died (mortality 11.5%).[Table-5&6] All the three deaths were due to cardiovascular cause although they had other organ dysfunction like ARDS and AKI. Their Apache II score were 16, 28 and 20

respectively. Two of them were young (age 21 & 30) and had sudden cardiac arrest on day 6 and day 7 possibly due to myocarditis. The other death was in a 60 year old diabetic who died of unsupportable hypotension on day four.

DISCUSSION:

It is important to rapidly delineate the cause of fever in tropical regions where several infections like dengue fever, malaria, scrub typhus, and community-acquired pneumonia are common. Epidemics of scrub typhus have been reported from north, east and south India[3-8] but there are no case reports of scrub typhus from the state of Odisha. We have been seeing cases with multiorgan dysfunction in the ICU since last few years which do not look like bacterial sepsis. Probably we were missing these cases because of lack of clinical suspicion. We suspected the first case in this series when a young girl presented with respiratory distress, hypoxia and had an eschar in the face and finally developed vasculitis and gangrene in Aug 2011. The second case was diagnosed in Nov 2011. Since July 2013 we had an outbreak and diagnosed 24 cases until Dec 2013.

O.tsutsugamushi is an obligate intracellular bacterium transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*[9]. These larval mites usually feed on the wild rats of the subgenus Rattus. The organism is maintained by transovarian transmission in mites. There are several serotypes of *O.tsutsugamushi.* One-serotype gives only transient cross immunity to another[6]. Man is accidentally infected when he encroaches the mite-infested areas with secondary scrub growth, which grows after the clearance of primary forest. The basic pathologic changes are focal vasculitis and perivasculitis of the small blood vessels in the involved organs, arising from multiplication of the organisms in the endothelial cells lining the small blood vessels[10].

In the present study all the cases were seen during the months of July to December. Scrub vegetation, optimum amount of monthly rainfall, and soil bound moisture are important factors responsible for disease transmission[3]. Consequently, an increase in incidence of cases is seen in the rainy season[11]. As described in literature the disease is common in farmers, persons rearing domestic animals and those living close to bushes and woodpiles[11]. In our study 50% of the cases came from urban areas. Therefore people living in urban areas can also get scrub typhus and it is no more a disease of the rural areas only.

The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash[1]. An eschar at the wound site is the single most useful diagnostic clue and it is very important to perform a thorough physical examination to look for eschar and signs to exclude other causes of fever. Though eschar is pathognomonic of scrub typhus, it was noted only in 5 cases (19.2%) in our patients. Number of eschars reported in other Indian studies by Mathai *et al* (2003), Vivekananda *et al* (2010) and Subbalaxmi *et al*(2014) are also similar to our study. The reason for the less number of eshcar in Indian studies may be due to the high skin colour of the population and due to variation of serotypes among different regions[5]. Maculopapular rash was seen in 7 cases (26.9%) in our series and is comparable to other Indian studies[3,6]. Average duration of fever in our study group was 10.11 days (ranging from 5 to 18 days). Scrub typhus involves multiple organs including the lung, heart, central nervous system (CNS), and is characterised by focal vasculitis or perivasculitis. Table 5 shows the clinical features of our study in comparison with other series. Such microangiopathies may also involve the kidney (acute renal failure), gastrointestinal tract (gastrointestinal bleeding), liver (hepatic dysfunction and hepatomegaly), spleen (splenomegaly), and lymph node (lymphadenopathy)[10].

Respiratory tract involvement is a common manifestation of scrub typhus. Cough and breathlessness were present in majority of our cases. Respiratory failure is a common complication of scrub typhus and was reported in 11% of cases in one large series[12]. In our series 24(92.3%) of our cases had respiratory failure out of which 7 needed invasive ventilation, 9 were managed with noninvasive ventilation and the rest were managed with oxygen only. Chest radiograph abnormalities in the form of reticulo-nodular opacities, air space consolidation, peribronchial infiltration, pulmonary congestion, pulmonary oedema, acute respiratory distress syndrome (ARDS) and pleural effusion were known to occur in scrub typhus[12,13,14].

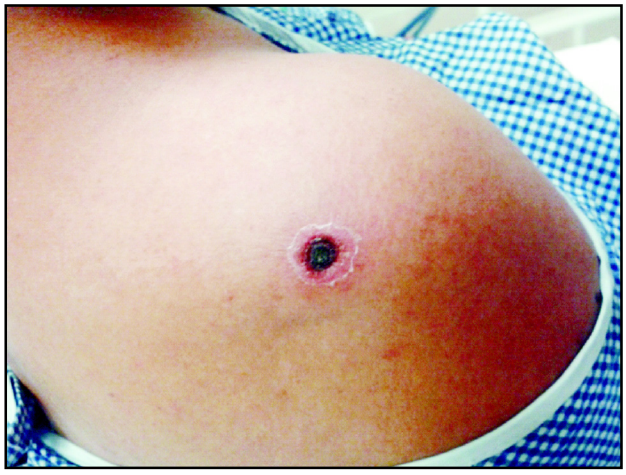

Fig 1. Eschar on Abdomen

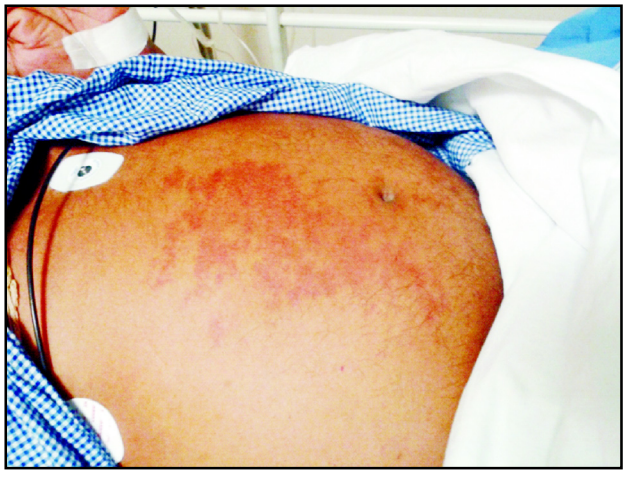

Fig 2. Maculopapular Rashes on the skin of Abdomen.

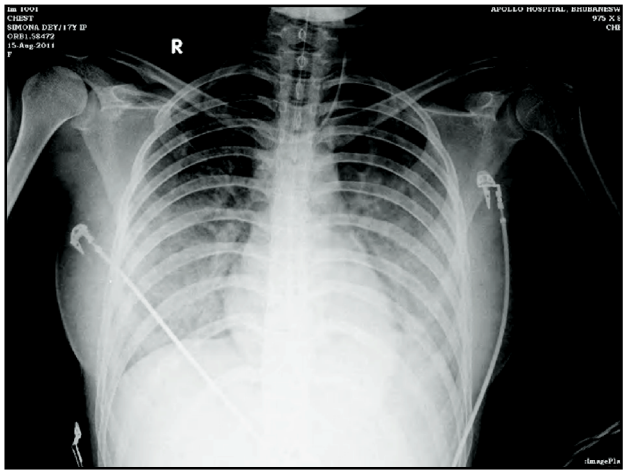

Fig 3. Bilateral Acino-nodular shadows on Chest X-ray.

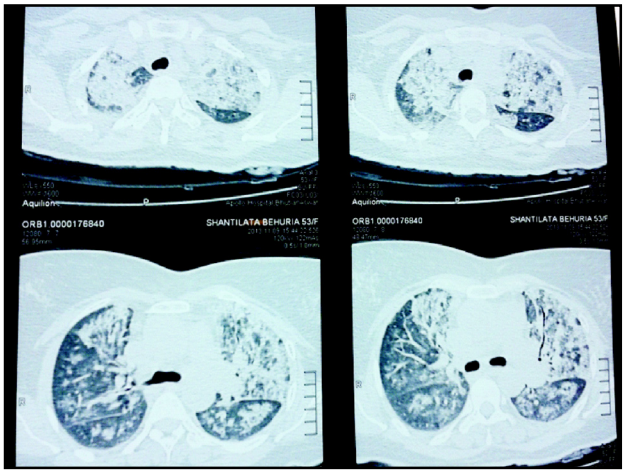

Fig 4. Bilateral Acino-nodular shadows on a CT Thorax.

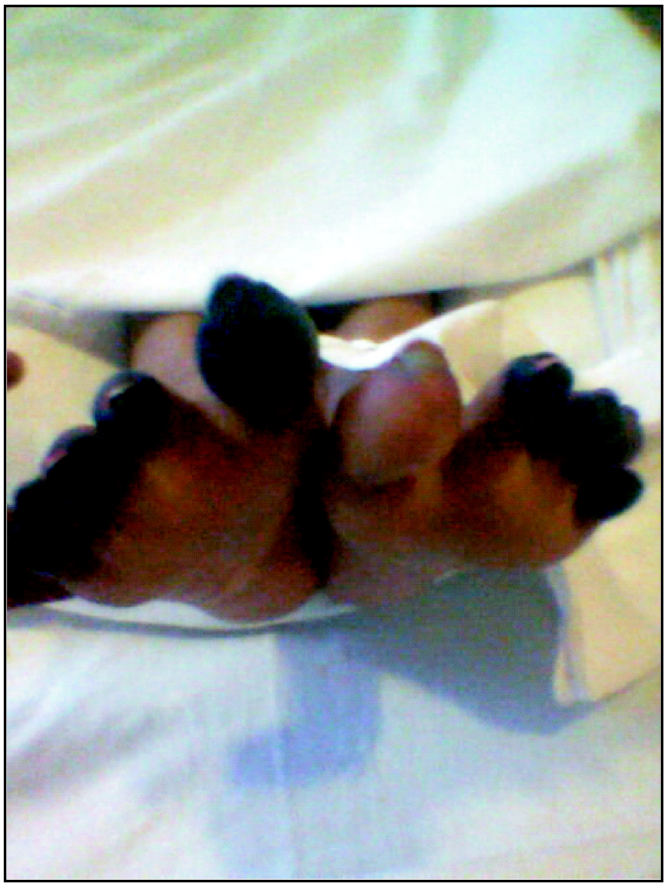

Fig 5. Gangrene of feet due to vasculitis.

Table - 5

Showing Comparison of Clinical Features of scrub typhus from various studies in India

Clinical features	Mathai et al	Mahajan et al	Vivekanandan et al	Kedareshwar et al	Subbalaxmi et al	Sahu et al
Place of study	Vellore 2003	Shimla 2006	Pondicherry 2008	Goa 2010	Andhra Pradesh 2014	Odisha 2014
No.of subjects studied	28	21	50	15	176	26
Fever	27(100%)	21(100%)	50(100%)	15(100%)	176(100%)	26(100%)
Myalgia	14(52%)	38%	19(38%)	12(80%)		
Altered mental status	5(19%)	24%	10(20%)	1(6.7%)	23(13.1%)	04(15.3%)
Headache	9(33%)	20(52%)	92(52.3%)			
Cough	12(44%)	20(40%)	7(46.7%)	94(53.4%)		
Breathlessness	13(26%)	9(60%)	84(47.7%)	26(100%)		
Nausea, vomiting	13(48%)	43%	29(58%)	15(100%)		
Pain abdomen	29%	10(20%)	7(46.7%)			
Diarrhoea	8(16%)	4(26.7%)	28(15.9%)			
Hepatosplenomegaly	43%	24(48%)	13(86.7%)	51(28.9%)		
BP < 90 mmhg	8(16%)	7(46.7%)	16(61.5%)			
Eschar	1(4%)	10%	23(46%)	2(13.3%)	23(13.1%)	05(19.2%)
Maculopapular Rash	22%	10%	07(14%)	07(26.9%)		7 (26.9%)
Leucopenia < 4000/cmm	1(2%)	42(23.9%)	02(7.6%)			2 (7.6%)
Leucocytosis > 11000/cmm	14(54%)	15(30%)	10(66.7%)	18(10.2%)	13(50%)	13 (50%)
Thrombocytopenia < 100000/cmm	9(43%)	5(10.8%)	4(26.7%)	53(30.1%)	02(7.6%)	2 (7.6%)
Hepatitis	22(88%)	47(95.9%)	12(80%)	153(86.9%)	14(53.8%)	14 (53.8%)
Renal failure	8(37%)	6(12%)	5(33.3%)	49(27.8%)	14(53.8%)	11 (42.3%)
Mortality	3(11%)	2(15%)	1(2%)	5(33.3%)	8(4.5%)	03(11.5%)

Table - 6

Table 6: Baseline characteristics and outcomes of patients admitted to ICU with severe scrub typhus

Variable	Numbers	Survivors (*n*=64)	Nonsurvivors (*n*=20)	(n=26)
Baseline characteristics & Outcome	Peter et al, Vellore, 2013			Sahu et al Odisha, 2014
Mean (SD) age, years	84	38.8 (15.2)	44.4 (16.2)	43.3
Number of males	84	37 (57.8)	8 (40)	13(50%)
Duration of symptoms, mean (SD) days	79	8.7 (4.4)	6.7 (3.7)	10.1
Admission creatinine (mg/dl)	84	1.7 (1.2)	2.5 (1.3)	
Shock at presentation	76	29 (49.2)	14 (82.4)	16(61.5%)
Altered mental status at presentation	80	11 (17.2)	6 (37.5)	04(15.3%)
Admission APACHE II score, mean (SD)	73	18.3 (6.6)	26.4 (8.2)	13.5
Admission SOFA score, mean (SD)	74	9.7 (3.4)	12.9 (3.5)	8.4
Mortality (%)	84	64(76.1)	20(23.9)	03(11.5)
Number ventilated (%)	82	46 (74.2)	19 (95)	16(61.5)
Renal failure at admission	84	6 (9.4)	5 (25)	11(42.3)
Need for dialysis during admission	81	4 (6.5)	5 (26.3)	03(11.5)
Presence of eschar, number (%)	80	26 (40.6)	5 (27.)	05(19.2)
Liver dysfunction at admission	84	4 (6.3)	2 (10)	14(53.8)

Fourteen cases (53.8%) had acino-nodular shadows on the CXR and two had pleural effusion in addition to the above lesions. The respiratory manifestations in our series is more than the other series because our series was from the ICU/HDU.

Among the gastrointestinal manifestations, elevated hepatic transaminases are a striking feature in scrub typhus. 53.8% of our patients had elevated bilirubin and liver enzymes which were comparable to other studies[3,6].

Renal failure was present in 42.3% of our patients out of which 3(11.5%) required hemodialysis. Renal failure was seen in 12- 37%[3,6] from different studies from India. Our series had more renal failure which could be due to a different serotype.

Scrub typhus is characterised by fever with altered sensorium. CNS involvement ranges from aseptic meningitis to frank meningoencephalitis[15]. The pathologic changes in the brain are predominantly vascular in nature and actual tissue destruction is rare and they are potentially reversible despite widespread lesions[12]. As reported in other series in literature,[4] (15.3%) of our patients had drowsiness on examination during hospital stay. Seizures were not present in our series.

The existence of myocarditis in scrub typhus is easily ignored, because the symptoms of myocardial involvement are usually subclinical and sometimes may lead to heart failure[16]. We could detect myocarditis in 2 cases and probably missed out in two other cases which died of sudden cardiac arrest.

Among the laboratory abnormalities, most common haematological abnormality noted was leucocytosis (50%) in our series which is more than the other series as ours was a cohort of sicker patients who were admitted to ICU/HDU. Thrombocytopenia and leucopenia were less common.

IgM elisa system was used to diagnose cases of scrub typhus in our patients. This test has a high sensitivity and specificity and a useful and reliable test for early detection of Scrub Typhus[17].

Antibiotics of the tetracycline class (doxycycline in particular) have a high degree of efficacy and low toxicity in treating rickettsial infections, even in children and pregnant women. The treatment of choice for scrub typhus infection is doxycycline 100 mg per dose administered twice daily (orally or intravenously) for adults or 2.2 mg per Kg for children less than 45.5 Kg[18]. This treatment should be started empirically as soon as diagnosis is suspected. Rapid defervescence of fever occurs in 1-2 days with start of treatment. The optimal duration of treatment has not been established, but current recommendation suggest at least 3-7days for life threatening cases to a maximum of 15 days for severe or complicated disease. Alternatively chloramphenicol (500 mg 4 times a day orally for 7 days in adults or 150 mg per kg per day for 5 days in children) in endemic areas has been proven effective in treating scrub typhus and preventing relapse[18]. Rifampicin or azithromycin are effective in doxycycline resistant strains of scrub typhus. All our patients were treated with doxycycline and supportive care. Oral Doxycyline was given for 7 days in mild disease and 14 days for patients with multiorgan disease. Inj Azithromycin was added in 11 cases (42.3%) who were serious.

Scrub typhus is known to produce serious complications and has a mortality rate of 2-33%[3,4,6,8,19]. Deaths are attributable to late presentation, delayed diagnosis and drug resistance[5]. Pandey et al from Himachal Pradesh reported 3 cases of ARDS due to scrub typhus[14]. Tsay et al from Taiwan found 8 cases of ARDS, 3 cases of acute renal failure and one case each of myocarditis and septic shock[16]. Out of 26 patients 23 (88.5%) recovered, three (11.5%) patients died. The main cause of death was sudden cardiac arrest in two cases who we suspect might have had myocarditis which was missed. They also had ARDS and other organ dysfunction. The third case died of multiorgan failure with unsupportable blood pressure on day 4. The mortality in our study is comparable to other Indian studies[3,4,6,8,19]. The delay in diagnosis in the three cases who died was 8, 9 and 10 days.

CONCLUSION:

In conclusion we would state that Scrub Typhus is prevalent in Odisha. It should be considered in the differential diagnosis of patients with acute febrile illness with multisystem involvement. The clinical features are similar to scrub typhus occurring in other parts of India. They are as common in urban areas as compared to rural areas. Clinicians should have high suspicion for

this disease and confirm the diagnosis by immunological tests. Empirically treatment by Doxycycline may be life saving.

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Original Article

RED CELL DISTRIBUTION WIDTH: A PROGNOSTIC MARKER IN SEVERE SEPSIS AND SEPTIC SHOCK.

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ABSTRACT

***Aim**: To investigate the prognostic significance of Red cell distribution width (RDW) in severe sepsis and septic shock. **Materials and Methods**: A multicentric prospective case control study ofpatients with severe sepsis and septic shock admitted to the Intensive Care Unit (ICU) from July 2011 to June 2014. A total of 765 patients were included. They were divided into two groups of patients with normal RDW of less than 14% (Group 1; n=380) and patients with increased RDW of greater than or equal to 14 % (Group 2, n=385). The groups were well matched with respect to demographic and key physiologic variables. All patients with severe sepsis and septic shock received the early goal directed therapy(EGDT). Patients' demographic data, RDW at admission, Sequential Organ Failure Assessment (SOFA) and The Simplified Acute Physiology Score II (SAPS II) were compared between the two groups. The primary outcome was death before hospital discharge or until study day 30 if patients were still in the hospital. Secondary outcomes included the number of ventilator free days and organ failure free days upto day 30. **Results:** A total of 765 patients were included. The overall mortality was 33.9%. The 30 day mortality in Group 1 was 25.7% and that of Group 2 was 42% (P < 0.05); hazard ratio 2.35 ;95% confidence interval (CI), 1.63 – 3.97. There was no statistically significant difference in the secondary outcomes. **Conclusion:** RDW at the time of admission to the ICU is an independent prognostic marker of 30-day mortality in patients with severe sepsis or septic shock. **Key words:** Severe sepsis, septic shock, Red cell distribution width, mortality. **Key Message**: Red cell distribution width (RDW) in severe sepsis and septic shock, is a cost effective, widely available independent prognostic marker of 30-day mortality in severe sepsis and septic shock.*

INTRODUCTION

Sepsis is one of the most elusive syndromes in medicine. Severe sepsis is sepsis plus any one or more organ dysfunction and septic shock is sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia[1].The incidence of severe sepsis depends on how acute organ dysfunction is defined and on whether that dysfunction is attributed to underlying infection. Severe sepsis and septic shock occurs in 2% of hospitalized patients half of which are treated in the intensive care unit representing 10% of all ICU admissions [2]. Pneumonia is the most common cause of severe sepsis and septic shock followed by intra-abdominal and urinary tract infections[2]. Mortally from severe sepsis and septic shock is still close to 30% [3]. The prediction of outcome from severe sepsis and septic shock by simple cost effective markers may encourage more aggressive therapy.

The red cell distribution width (RDW) is a measure of the heterogeneity of the erythrocytes which is calculated by dividing the standard deviation of erythrocyte volume by the mean corpuscular volume (MCV) and multiplying by 100 to express the result as

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a percentage [4]. The normal RDW is < 14%. RDW is part of the complete blood count (CBC) report, which is done routinely during admission in all intensive care unit (ICU) patients.

In combination with mean corpuscular volume (MCV), RDW has been used for differential diagnosis of anemia [5]. However, recently significant association has been found between increased RDW with poor prognosis in patients with congestive heart failure, acute myocardial infarction, pulmonary embolism, pneumonia and critical illness [6-11]. Although the mechanism of elevated RDW in these patients is not known, it has been postulated that systemic inflammation and malnutrition may be associated with increased RDW. Proinflammatory cytokines such as interleukin-6 and tumor necrosis factor could suppress the maturation of red blood cells and decrease the half-life of red blood cells which can result in elevated RDW[12], but the association with mortality still remains unclear.Previous studies on RDW in critically ill patients did not focus on septic patients [13].

The aim of this study was to find the association of increased RDW at the time of admission to theICU with 30-day mortality in patients with severe sepsis and septic shock. Secondary outcomes included the number of ventilator free days and organ failure free days upto day 30.

MATERIALS AND METHODS

This was a multicentric prospective case control study of patients with severe sepsis and septic shock admitted to the Intensive Care Units (ICUs) from July 2011 to June 2014 in two teaching medical college hospitals of Eastern Odisha, India. All patients admitted to the ICUs who had severe sepsis or septic shock were included in the study. Patients on erythropoietin therapy, known history of iron or vitamin B_{12} deficiency, folic acid deficiency or known hemolytic anemia were excluded from the study. A total of 765 patients were included. All patients with severe sepsis and septic shock received the early goal directed therapy (EGDT). They were divided into two groups. Group 1 (N=380) of patients with normal RDW of less than 14%; and Group 2 consisting of patients with increased RDW of greater than or equal to14 % . (N=385). Baseline demographics (age, gender, and race), and history of chronic kidney disease (CKD), were collected. Clinical and laboratory variables obtained during ICU admission included complete blood count (CBC) with RDW, serum levels of sodium, potassium, total calcium, phosphate, urea, creatinine, glucose, albumin and liver function test, serum procalcitonin, chest x-rays, ultrasound of abdomen and thorax, cultures and sensitivity of blood, urine and sputum/tracheal aspirates as needed. Parameters for patients included mean arterial pressure, presence of acute renal failure (ARF) and need for renal replacement therapy, need for mechanical ventilator and ventilator days, duration of ICU and hospital stay (days) were recorded as observational data and other variables useful to calculate The Simplified Acute Physiology Score (SAPS) II [14] and the Sequential Organ Failure Assessment (SOFA) scores [15]. Data on central venous pressure were available for 238 patients in group 1 and 258 in the group 2; data on lactate level, for 374 and 367, respectively; data on serum albumin level, for 221 and 213, data on central venous oxygen saturation, for 238 and 258, respectivelyand data on serum procalcitonin level for 342 and 354 respectively. Length of stay in the ICU was defined as the time from ICU admission to the time of transfer out of the ICU. There were no statistically significant differences between the two groups except with respect to Red cell distribution width ($P < 0.05$) (Table 1). Among preexisting conditions, liver disease was defined as the presence of cirrhosis, portal hypertension, or previous episodes of liver insufficiency; and congestive or ischemic heart disease as New York Heart Association class II. The Simplified Acute Physiology Score (SAPS II)was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness. The Sequential Organ Failure Assessment (SOFA) scoreincludessubscores ranging from 0 to 4 for each of five components (respiratory, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe organ dysfunction. The scoring was modified by decreasing to 65 mm Hg the mean arterial pressure threshold for a cardiovascular subscore of 1, for consistency with the hemodynamic targets as defined according to the EGDT. Organ dysfunctions were defined as a SOFA score of 2 or more on the respiratory component; 2 or more on the

coagulation component; 2 or more on the liver component; 1,2, 3, or 4 on the cardiovascular component; and 2 or more on the renal component.Shock at the time of admission was defined as a score of 3 or 4 on the cardiovascular component of the SOFA. The primary outcome was death before hospital discharge or until study day 30 if patients were still in the hospital. Secondary outcomes included the number of ventilator free days and organ failure free days upto day 30.

The medical ethics committee approved this study.

Statistical analysis: Data from each patient were pooled to create the Database and analyzed with the use of SPSS 20 software (IBM, Armonk, NY). The discriminative powers of admission and highest RDW % values regarding day-30 mortality were evaluated by producing receiver operating curves (ROC). Binary end points were analyzed by means of a Fisher's exact test. Continuous variables were compared with the use of unpaired t-tests, Welch's tests, or Wilcoxon ranksum tests. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from inclusion to death in the two groups was compared with the use of the log-rank test, and the results are presented as Kaplan–Meier curves (Figure 1). Hazard ratios for death from increased RDW were calculated by logistic regression model. All p values were 2-tailed and p values of < 0.05 were considered statistically significant.

RESULTS

A total of 765 patients were included. The overall mortality was 33.9% (n=260). The 30 day mortality in Group 1 was 25.7% (n=98) and that of Group 2 was 42% ((n=162) $P < 0.05$); hazard ratio 2.35; 95% confidence interval(CI), 1.63 – 3.97. There was no statistically significant difference in the secondary outcomes (Table 2 and Figure 1).

DISCUSSION

In this study we find that increased RDW at the time of admission to ICU is an independent prognostic factor for 30-day mortality in patients with severe sepsis and septic shock. Recent studies have found significant association between increased RDW with mortality in patients with general cardiovascular diseases, congestive heart failure, acute myocardial infarction, pulmonary embolism, pneumonia and critical illness[6-11].Subsequent studies have also found increased morbidity in association with increased RDW in patients with heart failure, coronary artery disease and stroke [16,17]. Although previous studies had found association of increased RDW with increased mortality in critically ill patients, these studies had not focused on sepsis.

In an observational study of critically ill patients, the rate of sepsis was higher according to RDW levels, and RDW was associated with significant risk for blood stream infections [13]. Although this study included the patients with sepsis, they evaluated the association of mortality with RDW in all patients who received critical care. In addition, the database that they used did not include physiologic data, and severity score such as the APACHE II score or SAPS II[13]. In the present study, we consecutively included patients with severe sepsis and septic shock in the two ICUs prospectively and divided them into two well matched groups of similar severity of illness as demonstrated in the SOFA and SAPS II score (Table 1.) and having statistically significant difference in RDW at the time of admission. This is the first study in Eastern India to evaluate the association of RDW with outcomes in severe sepsis and septic shock. Similar to our study You Hwan Joet al., (2013) in their retrospective analysisobserved that RDW of non-survivors was higher than that of survivors in severe sepsis and septic shock, and there was a graded association between RDW and 28-day mortality.[18]. Chan Ho Kim et al., (2013) have further found that that an increase in RDW from baseline during the first 72 hours after hospitalization can serve as a strong independent predictor of mortality in patients with severe sepsis or septic shock [19].

The mechanism underlying elevated RDW and increased mortality in severe sepsis and septic shock is uncertain. Severe sepsis and septic shock are associated with inflammation and pro-inflammatory cytokines such as tumor necrosis factor á, interleukin-6, and interleukin-1â could suppress red blood cell maturation and decrease the half-life of red blood cells[12]. Pro-inflammatory cytokines can also down regulate erythropoietin receptors however erythropoietin receptor assay was beyond the scope of the present study.

Table 1.Characteristics of the Patients at Baseline.*

CHARACTERISTIC	GROUP 1 (N=380)	GROUP 2 (N=385)
Age – years (Median)	63	65
Female sex — no. (%)	148(38.9)	151(39.2)
Ideal body weight†	63.8 ± 9.2	61.5 ± 4.6
Reason for ICU admission — no. (%)		
Medical-	305(80.27)	298(77.4)
Elective surgery-	28(7.37)	30(7.79)
Emergency surgery-	47(12.36)	57(14.8)
Preexisting condition — no. (%)‡		
Liver Disease-	5(1.3)	6(1.5)
COPD-	47(12.3)	45(11.6)
Chronic kidney disease-	18(4.7)	13(3.3)
Congestive Heart Failure-	19(5.0)	21(5.5)
Ischemic heart disease-	43(11.3)	47(12.2)
SAPS II score§		
Median (IQR)-	48(37-59)	48(36-60)
Physiological variable		
Heart rate — beats/min	105±22	106±20
Mean arterial pressure — mm Hg	74±16	73±15
Central venous pressure — mm Hg	10.0±4.9	9.8±4.7
Urine output — ml/hr		
Median (IQR)	50(20-90)	50(15-95)
Lactate — mmol/liter		
Median (IQR)	1.3(2.2-4.6)	1.2(1.6-4.3)
Serum albumin — g/liter	24.1±6.3	24.2±6.2
Hemoglobin — g/dl	9.9±2.1	10±2.2
Central venous oxygen saturation —%		
Median (IQR)	73(65-79)	73(68-80)
Serum Procalcitonin—ng/ml		
Median (IQR)	2.75 (2-3.25)	2.75(2.25-3)
SOFA score ¶		
Median (IQR)	8(6-10)	8(5-9)
Organ dysfunction — no. (%)		
1 organ	79(20.8)	81(21.0)
2 organs	152(40.0)	155(40.3)
3 organs	99(26.1)	101(26.6)
4 organs	37(9.7)	42(10.9)
5 organs	12(3.2)	15(3.8)
Shock — no. (%)**	147(38.7)	152(39.4)
Mechanical ventilation — no. (%)	130(34.2)	137(35.6)
Red cell distribution width		
Median (IQR)	11 (9-13.5)	18(14-20)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except with respect to Red cell distribution width ($P < 0.05$). COPD denotes chronic obstructive pulmonary disease , IQR denotes Interquartile range and ICU intensive care unit. † The ideal body weight (IBW) in (kg); Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet. Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.‡ Refer study protocol § Refer study protocol ¶ Refer study protocol. ** Refer study protocol.

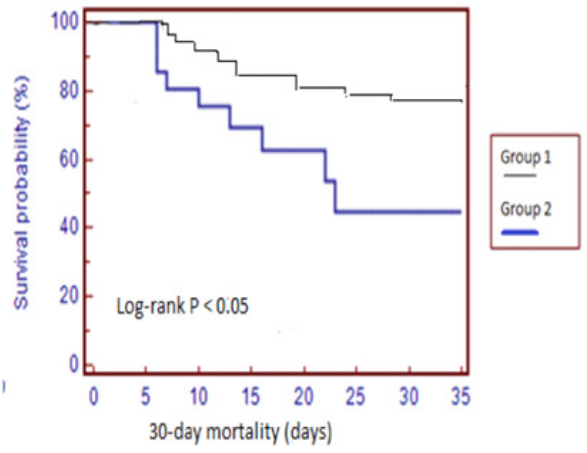

Figure 1. Kaplan-Meier plots for cumulative 30-days.

In addition to inflammation, oxidative stress and neurohormonal responses in sepsis might contribute to reduce the half-life of red blood cell and induce accelerated red blood cell production[20]. Hence, both inflammation and oxidative stress can increase RDW. Ineffective erythropoiesis is also associated with malnutrition and renal dysfunction leading to increased RDW[21].

We have done procalcitonin (PCT) in more than 90% cases and there is no statistically significant difference in the PCT levels in the two groups (Table 1). Other inflammatory markers such as tumor necrosis factor á, interleukin-6, and interleukin-1â needed to be done to establish the inflammation hypothesis. Also there was no significant difference in the renal dysfunction status in the two groups (Table 1). Taken together the pro-inflammatory state, oxidative stress, renal dysfunction and malnutrition may all be

Table 2.Main Outcome Variables.*

VARIABLE	GROUP 1 (N=380)	GROUP 2 (N=385)	DIFFERENCE 95% (CI)	P VALUE
Death in ICU/Hospital to day 30 — no. (%)†	98(25.7)	162(42)	2.3(1.6 to 2.9)	< 0.05
Ventilator-free days to day 30 — no.	5.1±10.8	15.1±11.0	0.0 (- 1.6 to 1.5)	0.85
ICU-free days to day 30 — no.	14.3±10.1	14.4±10.3	-0.2 (- 1.6 to 1.3)	0.79
Organ-failure–free days to day 30 — no. ‡				
Free of cardiovascular failure	8.5±4.8	8.7±4.9	- 0.2 (- 0.9 to 0.5)	0.61
Free of coagulation abnormality	10.7±5.1	11.1±4.8	- 0.3 (- 1.1 to 0.4)	0.39
Free of hepatic failure	10.8±5.0	11.0±4.3	- 1.0 (- 1.2 to 0.4)	0.37
Free of renal failure	10.1±5.3	10.5±4.7	- 0.9 (- 1.7 to 0.2)	0.10

* Plus–minus values are means ±SD. CI denotes confidence interval.† This outcome includes all deaths after randomization in any heath care facility before the patient was discharged home until study day 30. Study participants who were still in a health care facility at study day 31 were considered to be alive for this outcome.‡ Ventilator-free days and organ failures as defined in the study protocol.

contributing to the increased mortality associated with increased RWD in patients with severe sepsis and septic shock. Also increased RDW is a marker rather than a cause of increased mortality in patients with severe sepsis or septic shock**.**

CONCLUSION

RDW at the time of admission to the ICU is an independent prognostic marker of 30-day mortality in patients with severe sepsis or septic shock. RDW being a part of the CBC at the time of ICU admission, does not incur any additional expenses and canencourage a more aggressive therapy in severe sepsis or septic shock presenting initially with an increased RDW.

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BEST PAPERS OF 2014

The following original article and case report are selected as best papers of 2014 by the following referees and are to be awarded on 8th November, 34th APICON Odisha Branch, 2014 at Berhampur.

Refrees : Prof. P.K. Dash (Cuttack), Prof. R.N. Sahoo (Cuttack), Prof. Sarat Mohanty (Berhampur)

Original Article

Title : Study of heavy metals in drinking water of Cases of chronic kidney disease

Authors : *D. Bhanja, K.N. Padhiary, M. Murmu, A. Kar*

Case Report :

Title : Dichlorovos induced delayed polyneuropathy with bilateral foot drop : An unusual presentation of organophosphorous poisoning

Authors : *P.K. Mohanty, L.K. Dash, M. R. Mohapatra, R.K. Singh*

Original Article

CLINICO – HAEMATOLOGICAL ANALYSIS OF PANCYTOPENIA IN ADULTS

A. Dash*, S. Sethy, P.K. Padhi***, R.K. Jena******

ABSTRACT

Objective: *To study the spectrum of clinical presentation in pancytopenia.To correlate haematological parameters with clinical findings in differentiating causes of pancytopenia.* ***Materials And Methods;*** *The present study was carried out in the PG Department of Medicine, SCB Medical College, Cuttack during the period of September 2012 to September 2013. 80 Patients with pancytopenia were studied.* ***Results;*** *Out of 80 cases, 44 (55%) had hypocellular bonemarrow followed by 29 cases of hypercellular marrow (36.25%) and rest 8.75% had normocellular marrow.Males (60%) were affected more than females (40%). Aplastic anaemia was found to be the major cause of pancytopenia. Majority of cases of aplastic anaemia were of unknown origin.* ***Conclusion;*** *Pancytopenia is a common haematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anaemia,prolonged fever and tendency to bleed. Peripheral blood findings and bonemarrow study play an important role in the diagnosis of pancytopenia.* ***Keywords :*** *Pancytopenia, Aplastic anaemia*

INTRODUCTION

Pancytopenia is the simultaneous presence of anaemia, leukopenia, thrombocytopenia.[1]Pancytopenia therefore exists in the adult when the haemoglobin level is <13.5g/dl in males or 11.5g/dl in females, the leucocyte count is <4 $x10^9$ /l and the platelet count is <$100x10^9$/l.[1] Presenting symptoms are attributable to anaemia or thrombocytopenia. Leukopenia is an uncommon cause of the initial presentation but can become the most serious threat in life. Anaemia leads to fatigue, dyspnoea and cardiac symptoms. Thrombocytopenia leads to bruising, mucosal bleeding and neutropenia to sharply increased susceptibility to infection.[1]

MATERIALS AND METHODS

The study was undertaken in the PG Department of Medicine of SCB Medical College, Cuttack, during the period of September 2012 to September 2013. All newly diagnosed adult patients with pancytopenia were included in the study. Patients receiving myelotoxic chemotherapy and radiation therapy in the past six months were excluded.Patients who were already diagnosed to be case of bonemarrow failure syndrome elsewhere and were on follow up were excluded from the study. Detailed history taking and clinical examination were done in all the cases.Investigations included Hb, RBC count, WBC count, TPC, reticulocyte count, haematocrit, red cell indices,peripheral smear study, bonemarrow study. Iron profile and serum vitamin-B12 were also performed when required.

RESULTS

Out of total 80 cases studied,48 were males and 32 were females.47.5 % 0f total cases belonged to the age group of 15-30 years.All of the 80 cases taken were anaemic.90% of them presented with generalised weakness.49 patients(61.25%) presented with fever.32

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patients (40%) presented with bleeding manifestations and 17 patients(21.25%) had dyspnoea. Aplastic anaemia was the most common (45%) cause of pancytopenia among both males and females. Megaloblastic anaemia, acute leukemia, MDS, hypersplenism, HIV and multiple myeloma were more common in males. Systemic lupus erythematosus(SLE) as a cause of pancytopenia was seen in females. Aetiological profile of pancytopenia is shown in Table-1. 52.6% of aplastic anaemia (20cases) had petechiae. 50% of patients of acute leukaemia also had petechiae. Sternal tenderness was present in 10 cases of acute leukaemia.Lymphadenopathy was seen in 50% cases of acute leukaemia. Hepatosplenomegaly was significantly associated with disorders other than aplastic anemia. The profile of clinical features is shown in Table-2. Mean haemoglobin value, mean leucocyte count was lowest in patients with myelodysplastic syndrome(MDS). The mean platelet count was lowest in patients with aplastic anaemia.Anisocytosis(66.25%) was more common than normocytic blood picture among all cases.In patients of aplastic anaemia,normocytic normochromic blood picture was the commonest (61%) peripheral blood findings. Bone marrow examination revealed 44 cases (55%) had hypocellular bone marrow followed by 29 (36.25%) cases of hypercellular marrow and 7 (8.75%) cases had normocellular marrow. (Table-3)

DISCUSSION

Age and sex distribution were comparable with other studies of pancytopenia. Common age group affected was first to third decade in the studies done by Kishore et al**,** Khunger et al, Niazi et al[2,3,4]. In the present study, 15-30 age group was the most commonly affected. Present study also showed male preponderance with M:F ratio of 1.5:1 which was comparable to Santra G et al[5].

Physical findings included fever in 49 (61%), pallor in 80 (100%), hepatomegaly(40%), splenomegaly(32.5%), sternal tenderness 14 (17%), petechiae/purpura 32 (40%) and lymphadenopathy in 9 (11.25%) cases. The findings of our study is comparable to observations of Santra G et al[5] who noted hepatomegaly in 24.32%, splenomegaly in 44.4% and lymphadenopathy in 6.31% cases as common clinical manifestations[5]. Presence of hepatosplenomegaly was found significantly in cases with megaloblastic anaemia (60%) similar to khunger et al[3]. Hepatosplenomegaly was also found in acute leukemia(60%), MDS(75%) and all cases of hypersplenism which was in striking contrast to cases with aplastic anaemia in which only 14% had hepatomegaly. Presence of petechiae was significantly seen in cases with hypoplastic anaemia(56%), acute leukemia(50%) and MDS(50%). Lymphadenopathy was found in about 50% cases of acute leukaemia and the cases with disseminated tuberculosis(TB) and HIV. Sternal tenderness was found in 71% of acute leukemia comparable to Khunger et al[3].

Aniosopoikilocytosis was the predominant finding in megaloblastic anaemia, leukemia, MDS, hypersplenism, malaria, SLE, TB.The morphological findings of hypersegmented neutrophils and macroovalocytes in the peripheral smears may preclude the need for a bone marrow study in patients with clinical pictures of megaloblastic anamia.This was also observed by Tilak et al and Khunger et al[3,5]**.** This demonstrates the value of peripheral smear in the differential diagnosis of pancytopenia.

In the present study, 44 cases (55%) had hypocellular marrow followed by hypercellular (36.25%) and normocellular marrow (8.75%). Presence of hypocellularity in bone marrow was found in all cases of hypoplastic anaemia and cases with disseminated TB, SLE and HIV while 21% cases of acute leukemia also had reduced bonemarrow cellularity. Aplastic anaemia was the common cause both in males and females. No particular cause could be found for bone marrow aplasia and has been attributed to unknown environmental factors. J Y Mary in their study on epidemiology of aplastic anaemia in France reported that 74% of aplastic anaemia cases were idiopathic and only 13% were due to drug induced aplasia,which was similar to our findings[8]. Surapo Issaragrasil et al had also similar findings regarding cause of aplastic anaemia[9].

Table 1

AETIOLOGICAL PROFILE OF PANCYTOPENIA

Diagnosis	Male	Female	Total (%)
Aplastic anemia	23	13	36 (45%)
Megaloblastic anemia	10	7	17 (21%)
Acute leukemia	8	6	14 (17.5%)
MDS	3	1	4 (5%)
Hypersplenism	2	0	2 (2.5%)
Malaria	0	2	2 (2.5%)
SLE	0	2	2 (2.5%)
HIV	1	0	1 (1.25%)
Disseminated TB	0	1	1 (1.25%)
Multiple myeloma	1	0	1 (1.25%)
Total	48	32	80 (100%)

Table 2

CLINICAL SIGNS AMONG DIFFERENT AETIOLOGIES

DIAGNOSIS	HEPATOMEGALY	SPLENOMEGALY	LYMPHADENOPATHY	STERNAL TENDERNESS	PETECHIAE
APLASTIC anemia	5	0	0	0	20
Megaloblastic anemia	10	9	0	2	0
Acute leukemia	8	8	7	10	7
MDS	3	3	0	0	2
hypersplenism	1	2	0	0	1
malaria	2	2	0	0	0
SLE	0	1	0	0	1
HIV	1	0	1	1	1
Disseminated TB	1	1	1	1	0
MM	1	0	0	0	0

TABLE 3
BONE MARROW CELLULARITY IN CASES OF PANCYTOPENIA

Sl.no	etiology	hypercellular	normocellular	hypocellular
1	Aplastic anemia	0	0	36
2	Megaloblastic anemia	14	3	0
3	Acute leukemia	9	2	3
4	MDS	2	1	1
5	Hypersplenism	2	0	0
6	Malaria	1	1	0
7	SLE	0	0	2
8	Disseminated TB	0	0	1
9	HIV/AIDS	0	0	1
10	Multiple myeloma	1	0	0
	total	29	7	44

The second most common cause of pancytopenia was megaloblastic anaemia(21.25%) followed by acute leukaemia (17.5%). Other causes in our study included MDS, hypersplenism,malaria,SLE,HIV,disseminated TB and multiple myeloma.

Similar observation were made by Kumar et al from India who showed that aplastic anaemia was the commonest cause of pancytopenia[10].

However, in the studies made by Kishore Khodke,Vijai Tilak, J M Khunger from India and Savage et al, megaloblastic anaemia was found to be the most common cause followed by aplastic anaemia[2,3,6,7]. Hence future studies are required to know the true incidence of various etiologies of pancytopenia in this part of the world.

CONCLUSION

Pancytopenia is a common haematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anaemia,prolonged fever and tendency to bleed.The physical findings and peripheral blood picture provide valuable information in the work of cytopenic patients.Bonemarrow examination is an important diagnostic tool which helps to evaluate various causes of cytopenia. In the present study over a period of one year,eighty cases of pancytopenia were studied.Aplastic anaemia was the major cause followed by megaloblastic anaemia, acute leukemia,MDS,malaria,SLE,HIVand disseminated TB.

More studies with more number of cases need to be done which could reveal something more in this aspect.

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Original Article

EVALUATION OF CARDIOLOGICAL MANIFESTATIONS IN PATIENTS WITH SNAKE BITE

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ABSTRACT

Cardiovascular manifestations in snake bite have not been studied much. So this study has been conducted to find out the various cardiological changes occurring in case of snake bite patients and to compare the cardiological manifestations among neurotoxic vasculotoxic and non envenomed groups. It was found that significant changes occurred in clinical findings, ECG and cardiac enzymes. So these parameters may be used as tools for monitoring myocardial damage in cases of snake bites. ***Keywords :*** *Snake bite, cardiological manifestation.*

INTRODUCTION

Snake bite is a major public health problem throughout the world especially in tropical and subtropical countries. Snake venom is probably the oldest known poison to mankind and has been described in oldest medical writings and myths. In tropical countries, snake bite is an occupational disease of herders, hunters and farmers.[1] Encroachment of snake habitats by people has led to increase in incidence of snake bites. Recent estimates indicate between 1.2 million and 5.5 million snakebites worldwide each year, with 421,000-1,841,000 envenomation and 20,000–94,000 deaths.[2] Various studies have shown nearly 15,000 to 20,000 people die of snake envenomation in India. Snake bite accounts for 2.8 to 5.3% hospital deaths in various states in India.[3] The high mortality in India is due to climatic factors, rural preponderance of population and their agricultural dependence. It is estimated that 2500 to 6000 cases of snakebite occurs in Odisha and out of them, 400 to 900cases die[4,5]. Odisha is a state with majority of population living in rural areas. There is a high incidence of snake bites, but many of them go unreported or under-investigated.

Snake venom contains endothelins and safratoxins which have coronary vasoconstrictor effect[6]. Myocardial infarction following viper bite can be due to a) Direct toxic effect on myocardium b) Coagulation abnormalities or vasospasm induced by endothelins and haemorrhagins. c) Hypovolemic shock due to bleeding.d) Hyperviscosity secondary to hypovolemia induced haemoconcentration.e) Anxiety f) Anaphylactic shock[6]. Cobra cardio toxins depolarize the cardiac cell membrane which leads to systolic arrest[7].

The exact prevalence of the cardiac involvement in various types of snake bites has not yet been studied in Odisha. Hence the current study was undertaken to find the clinical, electrocardiographic, enzymatic and echocardiographic changes in various types of snake bites and to compare the difference in cardiological manifestations in neurotoxic, vasculotoxic, non envenomed snake bite cases.

MATERIALS AND METHODS:

It is a hospital based longitudinal, descriptive study.

Selection Of Patients: 50 consecutive patients first admitted to the Department of Medicine S.C.B Medical College Cuttack with definite history of snake bite who came to the hospital within first 24 hours of bite during the period September 2013 – September 2014 were taken up for the study.

Exclusion Criteria Previous history of documented heart disease (Rheumatic Heart Disease, Acute Myocardial Infarction, Dilated Cardiomyopathy,

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myocarditis, Congenital Heart Disease etc), diabetes mellitus, hypertension, renal disease, myopathy or intake of drugs like steroids, statins, fibrates, etc

Method Of Study:

Relevant clinical history followed by detailed clinical and laboratory evaluation of the patients was done by the same investigator.

Following signs of envenomation were considered for the study purpose.

Vasculotoxic signs: Presence of any of the following signs like local swelling, bleeding from site of wound, bleeding from systemic sites, nausea and vomiting, sweating, haemoglobinuria , abnormal 20 minute whole blood clotting and retraction time and renal failure was considered to be a case of vasculotoxic snake bite.

Neurotoxic signs: Presence of any of the following signs like ptosis, extra ocular muscle weakness, dysphagia, respiratory paralysis, convulsion, coma, myalgia, abdominal pain were considered to be case of neurotoxic snake bite.

Blood samples were collected on the first day of admission .CK-MB, TroponinT levels were estimated by Electro-chemiluminiscence method (Cobas E411 Immunology Analyzer, manufacturer Roche Diagnostics, Switzerland). ECG recording was done 6 hourly on the first day, second day and third day and abnormal E.C.G noted. 2D Echocardiography was done in all patients. The data was entered in Microsoft excel and analyzed using SPSS software version 16. Results displayed with the help of suitable tables.

RESULTS:

Out of 50 snake bite patients, 26 were males and 24 were females. The mean age among females was 38.04 ±14.4 years and that of males was 45±10.7 years. Most (74%) of the cases were admitted in the months of July, August, and September. Most of the snake bites were nocturnal. Among all the snake bite cases, neurotoxic(N), vasculotoxic(V), and non-envenomed(NE) bites comprised of 30% (15/50), 54%(27/50) and 16%(8/50) respectively.

The following clinical cardiological findings were observed such as hypertension in 14 % (7/50), tachycardia 34 % (17/50), bradycardia 6% (3/50) and shock 13%(3/50). No significant difference was found among neurotoxic, vasculotoxic and non envenomed groups [TABLE 1].

Electrocardiographic changes observed were T wave inversion in 22% (11/50), ST depression 4%(2/50) , Tall T 2%(1/50) , Sinus tachycardia 34%(17/50) and Sinus bradycardia in 6%(3/50). No significant difference was observed among neurotoxic, vasculotoxic, and non envenomed groups [TABLE 2].

CK MB was raised in 40% (6/15), 74.1% (20/27), 0% of the neurotoxic (N) , vasculotoxic (V) and non – envenomed(NE) patients respectively. This differential increase in CK MB was significant (p=0.001). Similarly, Troponin T was raised in 33.3% (5/15), 63% (17/27), 0% of N, V, NE patients respectively [p= 0.004][TABLE 3].

The median and interquartile range ($Q_1 - Q_3$) for CK MB in N, V, and NE groups were 16(20-40), 44(20-70) and 11(8.5-13.5) IU/L respectively. The median ($Q_1 - Q_3$) Troponin T were 8.4(6.4-28), 26(10-100) and 8.5(6.34 – 11.7) pg/dl respectively for the above three groups.[TABLE 4]

The 2D Echocardiographic findings in all the snake bite patients were found to be normal.

DISCUSSION

According to our study, conducted in a tertiary level hospital in Cuttack, where patients come from various districts of Odisha, majority of bites were in rainy season where as Gupta et al in Jammu reported that majority of the bites occurred in summer and rainy season[8]. Out of 50 snake bites, majority were by vasculotoxic snakes (54%) followed by neurotoxic (30%) and non envenomed (16%) snakes which is in accordance to the findings of Lee et al, Gupta et al and Akbar et al[8,9,10]. Most of the bites were nocturnal.

The common clinical cardiological findings observed were tachycardia, bradycardia, hypertension and shock out of which tachycardia(34%) was most prevalent which was in accordance with Warrel et al who noted tachycardia in 43% cases of E.carinatus bites and Nayak et al who found tachycardia in 36.7% cases, bradycardia in 10% ,hypertension in 6.7% and hypotension in 16.7%[8,11].

TABLE 1: COMPARISION OF CLINICAL CARDIOLOGICAL FINDINGS IN SNAKE BITE AMONG NEUROTOXIC (N), VASCULOTOXIC (V), NON-ENVENOMED GROUP (NE)

Clinical finding	N(n=15)	V(n=27)	NE(n=8)	P VALUE *
Hypertension	1(6.7%)	6(22.2%)	0(0%)	0.175
Tachycardia	8(53.3%)	6(22.2%)	3(37.5%)	0.122
Bradycardia	2(13.3%)	1(3.7%)	0(0%)	0.334
Shock	3(20%)	0	0	0.024
No finding	5(33.3%)	17(63%)	5(62.5%)	0.158

*Pearson Chi- Square Test

TABLE 2: COMPARISION OF ELECTROCARDIOGRAPHIC FINDINGS IN AMONG NEUROTOXIC (N), VASCULOTOXIC (V), NON-ENVENOMED GROUP (NE) SNAKE BITE CASES

ELECTROCARDIOGRAPHIC FINDINGS	N(n=15)	V(n=27)	NE(n=8)	P VALUE*
T WAVE INVERSION	3(29.6%)	8(29.6%)	0(0%)	0.201
ST DEPRESSION	0(0%)	2(7.4%)	0(0%)	0.412
TALL T WAVES	0	1(3.7%)	0(0%)	0.334
SINUS TACHYCARDIA	8(53.3%)	6(22.2%)	3(37.5%)	0.122
SINUS BRADYCARDIA	0	1(3.7%)	0	0.334
NORMAL	5(33.3%)	17(63%)	5(62.5%)	0.158

*Pearson Chi- Square Test

TABLE 3: COMPARISION OF RAISED LEVELS OF CARDIAC ENZYMES IN NEUROTOXIC (N), VASCULOTOXIC (V), NON-ENVENOMED (NE) GROUPS OF SNAKE BITES

ENZYMES	N(n=15)	V(n=27)	NE(n=8)	P VALUE*
CK-MB(IU/L)	6(40%)	20(74.1%)	0(0%)	0.001
TROPONIN T(pg/dl)	5(33.3%)	17(63%)	0(0%)	0.004

*Pearson Chi- Square Test

TABLE 4: COMPARISION OF CARDIAC ENZYMES IN SNAKE BITE AMON NEUROTOXIC (N), VASCULOTOXIC (V), NON-ENVENOMED GROUP (NE)

CARDIAC ENZYMES	N(n=15) Median (Q1-Q3)	V(n=27) Median (Q1-Q3)	NE(n=8) Median (Q1-Q3)	P VALUE*
CK-MB(IU/L)	16(20-40)	44(20-70)	11(8.5-13.5)	<0.001
TROPONIN T(pg/ml)	8.4(6.4-28)	26(10-100)	8.5(6.34-11.7)	<0.037

*Kruskal –Wallis Test

The ECG changes found were Sinus tachycardia, Sinus bradycardia, T wave inversion, ST depression, Tall T waves, commonest being Sinus tachycardia(34%). Nayak et al had documented ECG abnormalities which included Sinus tachycardia and arrhythmia, bradycardia, Tall T-waves, non specific T-wave abnormalities and Atrio-ventricular blocks[7]. However, Agarwal et al, in a retrospective series of 55 patients of elapid snake bites, found no clinically significant cardiac involvement[12]. According to them tachycardia and bradycardia in their study may be due to autonomic nervous system dysfunction[12].

There was no significant difference in between neurotoxic, vasculotoxic and non envenomed groups as far as clinical and electrocardiographic findings were concerned.

In the current study there was significant difference in the rise of cardiac enzymes such as CK MB and Troponin T among neurotoxic, vasculotoxic and non envenomed groups. The vasculotoxic group had maximum rise in cardiac enzymes followed by the neurotoxic group. The findings were in accordance with Cupo et al who observed that the CPK-MB values are raised in patients with snake envenomation and Lan Hai et al who found raised cardiac enzymes in 87.8% of 124 cases cobra bite and 79.4% of 86 cases bite by Trimeresurus stejnegeri[13,14].

CONCLUSION

The present study of Odisha showed cardiological involvement in various types of snake bites like earlier studies. Cardiac involvement should be kept in mind especially in severely envenomed patients. ECG and cardiac enzymes may be used as tools for monitoring myocardial damage in snake bites.

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Original Article

SIGNIFICANCE OF INSULIN RESISTANCE IN NON DIABETIC SUBJECTS WITH ACUTE MYOCARDIAL INFARCTION AND ITS RELATIONSHIP WITH ACUTE PHASE REACTANTS

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ABSTRACT

Aim: *The current study was undertaken to assess the prevalence of insulin resistance in non diabetic subjects with acute myocardial infarction, to study the relationship between insulin resistance and acute phase reactants in patients with acute myocardial infarction and to ascertain its prognostic significance.* ***Materials:*** *100 consecutive non diabetic subjects with acute myocardial infarction were included in the study. A detailed physical examination and estimation of FBS, 2h PPBS, Fasting serum insulin, hsCRP, Lipid profile was done at admission and then after 3months of follow up. Insulin resistance was calculted by HOMA IR and HOMA B method.* ***Result:*** *In the present study, overall prevalence of insulin resistance was 63% (males = 63.4% females = 60.8%). hsCRP was, mildly elevated in 87.4% [hsCRP=3.187± 1.4109(mg/l)]insulin resistant subjects and 86.5% normal subjects.[hsCRP= 3.950 ± 1.390(mg/L)]. At admission the mean hsCRP in the study group(n=100) was 3.8665± 0.135 and after a Period of 3 months it decreased to 2.109± 0.914. At the end of 3 months hsCRP levels in the group with insulin resistance was 2.394 ± 0.869 mg/L and in the group with no insulin resistance was 1.712 ± 0.871 mg/l (p=0.016) Overall prevalence of metabolic syndrome in the study population was 24%. . Multivessel disease was present in 50% patients with insulin resistance and 21.7% patients without insulin resistance. Mortality rate was slightly higher in patients with insulin resistance at 3.2%.* ***Conclusion****: There was high prevalence of insulin resistance in non diabetic patients with AMI. Insulin resistance and acute phase reactants like hsCRP can predict the outcome and risk of future cardiovascular events in CAD patients.* ***Key words:*** *insulin resistance, acute phase reactants, coronary artery disease,acute myocardial infarction*

INTRODUCTION

The glycometabolic state of non diabetic patients at hospital admission for Acute Myocardial Infarction and their mortality rate is inter related. The risk of new onset CVD in patients with metabolic syndrome in absence of Diabetes is 1.5 to 3 fold.[1,2] In recent years the question as to whether insulin resistance is involved in pathogenesis of CVD has persisted.

Its validity was supported by finding that insulin possesses a variety of anti atherogenic effects which might be blunted by insulin resistance, and that insulin resistance is related to several non traditional risk factors for CVD, including markers of coagulation, systemic inflammation, sub clinical vascular disease, oxidative stress, or disregulated adipokine signalling. There is growing evidence that relationship between atherosclerosis, inflammation, and insulin resistance is not merely correlative but causative.An accumulating evidence shows that markers of inflammation are correlated with CAD risk.[3,4,5]

Inflammation is present during all the stages of atherosclerosis and is intimately linked to atherosclerotic plaque rupture. When CRP is secreted from cells

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within intima, it can activate local endothelial cells and induce a prothrombotic state. CRP adds prognostic information at all levels of traditional risk factors as indentified by Framingham Heart Study. It strongly and independently predicts the risk of acute myocardial infarction.[6] Insulin Resistance is defined as resistance to metabolic effects of insulin, including suppressive effects, of insulin on endogenous glucose production, stimulatory effects of insulin on peripheral (especially skeletal muscle) glucose uptake, glycogen synthesis and inhibitory effects of insulin on adipose tissue.[7] Its presence is associated with clustering of cardiovascular risk factors including diabetes mellitus, hypertention, raised VLDL, triglycerides, and low plasma HDL cholesterol.[7]

In addition to clustering with conventional risk factors, more recent evidence indicates that IR is linked with 'non traditional' CAD risk factors and proartherosclerotic inflammatory state.

MATERIALS AND METHODS

100 Non diabetic patients with Acute myocardial infarction were taken up as cases.Patients excluded from study were those with Diabetes mellitus, acute infections and comorbid conditions like, hypertension chronic renal failure, cirrhosis of liver, malignancy.AMI was diagnosed by Criteria For Acute, Evolving, And Recent AMI: (Universal definition of myocardial infarction)[16] Type2 DM was diagnosed based on criteria given by American Diabetes Association. Insulin resistance was calculated by HOMA IR and HOMA B methods .HOMA IR >2 was used to define insulin resistance[11,13]. An hsCRP level more than 3mg/L. was considered high in accordance with AHC/CDC scientific statement summary[17]. WHR and BMI were defined according to criteria given by NCEP:ATP III 2001 and IDF criteria for metabolic syndrome.[12] WHR of more 0.9 in females and 1.0 in males was considered abnormal.[12]

STATISTICS

The data was analysed using SPSS software version (16:SPSS Inc, Chicago IL). Students t-Test was done to compare numerical varaibles in the two groups.

RESULT

A total of 100 subjects were included in our study, out of which 77 were males and 23 were females. The baseline parameters of the patient is shown in Table-1. The age distribution of the study population did not show a wide range of variation and the mean age of the study population was 62.4± 10.014 years. Maximum number of cases were in the age group between 60-69 years which included 44% of the subjects (41.5% males and 52.22% females. The prevalence of insulin resistance in males was 63.4% and in females was 60.8%. The overall prevalence of insulin resistance was 63%. Most the patients showing insulin resistance were in age group of 60-69 which included 40.8% male and 57.2% females. Mean fasting serum insulin level in the group with HOMA IR > 2 was 16.457 ± 9.851(µIu/ml). In the group with HOMA IR <2 the mean fasting serum insulin was 4.573 ± 1.972(µIu/ml). (p<.ooo1). The value of HOMA B in the insulin resistant subjects was 184±72.671. In normal population it was 132.276±54.568(p value<0.0002.The difference was statistically significant (p <0.0001). Prevalence of dyslipidemia in the group showing insulin resistance was 65% and in the group without insulin resistance , it was 32%. The prevalence of metabolic syndrome was 24% Family history was present in 2% insulin resistant patients (Fig.1). The hsCRP was elevated in 87.4% of subjects with insulin resistance and 86.5% of normal subjects. The hsCRP levels in patients with insulin resistance was 3.187±1.4109(mg/l). In patients without insulin resistance the hsCRP value was slightly higher at 3.950±1.390(mg/L) (p value is 0.6485).

A total of 45 study subjects were followed up after a period of 3 months. (Table-2) At admission the mean hsCRP was 3.8665±135mg/L. After a period of 3 months it decreased to 2.109±0.914mg/L. The decrease was statistically significant(<0.0001). At the end of 3 months hsCRP levels in the group with insulin resistance was 2.394 ±0.869 mg/L and in the group with no insulin resistance was 1.712±0.871mg/L(p=<0.016), the fall being greater in normal subjects. Coronary Angiography was done in 67 patients, 44 of which had insulin resistance. Multivessel disease was present in 50% patients with insulin resistance. In normal study population prevalence of multivessel disease was 21.7%.

TABLE 1

BASELINE PARAMETERS OF STUDY POPULATION

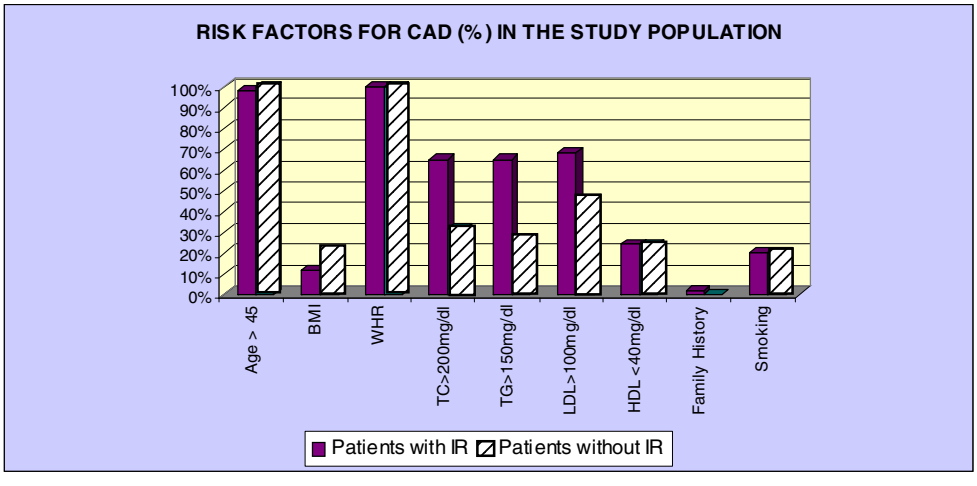
Parameters	Patients With IR	Patient without IR	P-Value
Age	61.813 ±10.176	60.081±8.021	
Male : Female	3.5 : 1	3.1 : 1	
FBS mg/dl	91.350 ± 14.944	95.510± 19.498	0.1880
PGBS mg/dl	104.433 ± 28.368	105.285 ± 28.650	0.7447
HbA1C	5.094± 0.831	5.157 ± 1.083	0.8854
HOMA IR	3.890 ± 2.170	1.0037 ± 0.428	<0.0001
HOMA B	184.856 ± 72.671	132.276± 54.638	<0.0002
TC mg/dl	227.471 ± 76.843	179.510 ± 61.201	0.6770
Tg mg/dl.	184.856 ± 72.671	132.276 ± 54.638	0.5110
HDL mg/dl	47.573 ± 16.566	44.511 ± 13.289	0.5221
LDL mg/dl)	106.378 ± 31.878	96.134 ± 34.815	0.6112
hsCRP (mg/l	3.187 ± 1.4109	3.950 ± 1.390	0.6485

TABLE 2

BIOCHEMICAL PARAMETERS AFTER A FOLLOW UP OF THREE MONTHS

Parameters	Patients With IR	Patient without IR	Pvalue
BMI	22.672 ± 5.320	21.464 ± 5.791	<0.364
Fasting Serum Insulin	16.029 ± 4.483	6.400 ± 1.297	<0.0001
FBS (mg/dl)	90.500 ± 3.901	94.945 ± 4.582	<0.1780
PGBS (mg/dl)	98.458 ± 5.381	99.945 ± 5.011	<0.7447
hs-CRP (mg/l)	2.394±0.869	1.712±0.871	<0.016
HOMA IR	3.562 ± 0.9415	1.495 ± 0.291	<0.0001
HOMA B	218.141 ± 78.847	96.141 ± 7.307	<0.002

Figure - 1



DISCUSSION

Insulin resistance is increasingly recognized as a chronic,low-level, inflammatory state. Hyperinsulinemia and insulin action were initially proposed as the common preceding factors of hypertension, low high-density lipoprotein cholesterol, hypertriglyceridemia, abdominal obesity, and altered glucose tolerance, linking all these abnormalities to the development of coronary heart disease. A total of 100 subjects were included in our study, out of which 77 were male and 23 were female. The age distribution of the study population did not show a wide range of variation and the mean age of the study population was 62.4± 10.014 years. . In a study by Choi K.M et al(2005) the mean age of study subjects was 58.4%±6.0 years out of which 73.3% were male[10]. In another study done by Das S et al(2007) the mean age of normoglycemic CAD patients was 57±7.34 years and the male : female ratio was 18:2.[8]

The prevalence of insulin resistance in males was 63.4% and in females was slightly lower at 60.8%. The overall prevalence of insulin resistance was 63%.The Homeostasis assessment model(HOMA) developed by Matthew and coworkers was used in our study[13]. Recently HOMA method has been revalidated as a reliable method to assess insulin resistance, as HOMA-IR score has been shown to closely mirror the insulin resistance values obtained by the euglycemic glucose clamp technique in the assessment of insulin sensitivity. The HOMA method utilizes single fasting plasma value of glucose and corresponding fasting plasma insulin levels[15]. In our study HOMA IR>2 was taken as insulin resistance. Although a HOMA IR score of 1 is ideal ,the normal value of insulin resistance as assessed by HOMA-IR in our population is less than 2 (Das .S et aI.,2007) [11] . Bonora et al also found a mean HOMA IR score of 2.06±0.14 in non diabetic population [9,15]. The value of HOMA B in the insulin resistant subjects was 184±72.671. In normal population it was 132.276±54.568(p value<0.0002). In normal population beta-cell function is assumed to be 100. (Mathew DR et aI., 1985)[13]. In our study beta cell dysfunction was present in the subjects showing insulin resistance and difference in beta cell functions of the two groups was statistically significant.

Analysis of BMI and WHR ratio in the current study revealed that prevalence of central obesity was 100%. We observed that our patients had lower BMI but higher WHR as compared to their western counterparts. Indian population differs from Caucasians and Afroamericans in their body composition, they don't have generalized obesity but tend to have higher intra-abdominal fat mass and excess truncal subcutaneous fat[1,2]. Mean BMI of male and female patients showing insulin resistance was 23.183±1.746 & 23.058±2.063 respectively. In the group without insulin resistance the mean BMI in male and female patients was 22.531±2.034 & 22.291±1.910 respectively. This is consistent with earlier findings of Das S et al 2007 [8].

Although central obesity was high in 100% patients, there was statistically significant difference in WHR of group. In insulin resistant group the WHR of male patients was 1.2905 ± 0.175, and in the group without insulin resistant the WHR of male patients was 1.0139 ± 0.0219. The difference was statistically significant ($p < 0.0001$). Similar patterns were observed in the female patients also. The WHR of female patients with insulin resistant was 1.254 ± 0.953, and in the normal group of female patients WHR was 0.930 ± 0.032. Again the difference was significant ($p < 0.0001$). Relative increases in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in these populations compared with African-American men in whom subcutaneous fat predominates. It is also possible that visceral fat is a marker for, but not the source of, excess postprandial FFAs and IR in obesity and metabolic syndrome[4]. The percentage of dyslipidemia was higher in the group showing insulin resistance. The overall prevalence of dyslipidemia in the group showing insulin resistance was 65% and in the group without insulin resistance, it was 32%. Bonora et al in 2003 showed that the incidence of dyslipidemia in normoglycemic subjects with insulin resistance was 66%.[15]

In the current study we observed that even after excluding hypertension and diabetes mellitus, several risk factors for CAD as defined by NCEP ATPIII

criteria[12] were present in our study group. 100% of our patients had central obesity.However the percentage of dyslipidemia was higher in the group showing in IR. 20% subjects in both the groups were smokers.The prevalence of metabolic syndrome was 24% Family history was present in 2% insulin resistant patients . In our study apart from insulin resistance and elevated hsCRP predominant risk factors for CAD were advanced age, hypertriglyceridemia and central obesity. This data is comparable with findings of Joshi et al 2003[14]. In the study by Das S et al 2007 the prevalence of metabolic syndrome in nondiabetic CAD was found to be 34%[8]. The AHA/CDC Scientific Statement Summary(Circulation 2003) considers hsCRP as a global indicator of future cardio vascular events in adults without any previous history of cardiovascular disease (CVD), with acceptable precision levels down to or below 0.3[17] mg/L .hsCRP enhances risk assessment and therapeutic outcomes in primary CVD prevention. In our study though hsCRP levels were not significantly high, mild elevation was present in 87.4% subjects with insulin resistance {hsCRP=3.187±1.4109(mg/l)}and 86.5% of normal subjects{hsCRP=3.950±1.390(mg/L). The difference was statistically insignificant (p value is 0.6485).

It was observed that the incidence of Anterior wall AMI was highest at 46% followed by, Inferior wall AMI which was present in 45% cases. NSTEMI was present in 6% cases. Incidence of Lateral wall AMI was 3%. However a different trend was observed in patients showing insulin resistance.In these subjects incidence of Inferior Wall AMI highest at was 57.5% followed by Anterior Wall AMI at 36.5% . Incidence of NSTEMI and Lateral Wall AMI was observed to be 4%. Three patients included in the study succumbed to complication of acute myocardial infarction. Mortality rate was slightly higher in patients with insulin resistance at 3.2%. It was 2.8% in patients without insulin resistance. Angiography was done in 67 patients, 44 0f which had insulin resistance. Multivessel disease was present in 50% patients with insulin resistance. In normal study population prevalence of multivessel disease was 21.7%. In the study done by Das.S et in 2007 et al prevalence of multivessel disease in the normoglycemic CAD population was 44%[8].

A total of 45 study subjects were followed up after a period of 3 months. During this period no new cardiovascular event or deaths were reported. At admission the mean hsCRP was 3.8665±135mg/L. After a Period of 3 months it decreased to 2.109±0.914mg/L. The decrease was statistically significant(<0.0001).The findings were at par with the study done by Choi K.M.et al which shows that the hsCRP levels and IL-6 concentration decreased significantly($p<0.0001$), however Insulin resistance and serum adiponectin did not change significantly[10]. The fall in hsCRP levels was more marked in patients without insulin resistance and the difference was statistically significant.($p<0.016$) indicating that in patients with insulin resistance persistant low grade inflammation is present.

CONCLUSION

The conclusions drawn from our study reveal that there was high prevalence of insulin resistance , even in non diabetic patients with CAD and theses patients had significantly higher WHR and central obesity despite having normal BMI. The pattern of rise in acute phase reactants reactants was similar in patients showing insulin resistance as well as those with no insulin resistance. However the hsCRP levels remained significantly high at the end of three months in insulin resistant subjects pointing towards a persistence of low grade chronic inflammatory state. We also observed higher prevalence of multivessel CAD and a slightly higher mortality rate in insulin resistant patients. Insulin resistance and acute phase reactants like hsCRP can predict the outcome and risk of future cardiovascular events in CAD patients, however longer term studies are needed for this purpose. Insulin resistance, central obesity, and associated metabolic abnormalities might underlie high rate of CAD in Indian population.

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Original Article

THE PROGNOSTIC VALUE OF N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF AN ACUTE CORONARY SYNDROME AND NO ST-SEGMENT ELEVATION

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ABSTRACT

Background *: Patients with symptoms suggestive of an acute coronary syndrome and no ST-segment elevation constitute a large and heterogeneous population. Early risk stratification has been based on clinical background factors, electrocardiography (ECG) and biochemical markers of myocardial damage. The neurohormonal activation has, so far, received less attention. The objective of the study was to evaluate the prognostic value of single measurement of N-terminal pro brain natriuretic peptide (NT-proBNP) in NSTEACS (Non ST-Elevation Acute Coronary Syndrome) patients.* ***Methods :*** *The NT-proBNP was analyzed on admission in 25 patients admitted because of symptoms suggestive of an acute coronary syndrome and no ST-segment elevation .Patients were followed for 120 days concerning death from any cause or new onset of congestive heart failure, or recurrent myocardial infarction.* ***Results :*** *The 25th, 50th, 75th percentile values of NT-proBNP were 105.0, 258.0 and 1149.5 pg/ml respectively. NT-proBNP level in patients who developed complications in the form of heart failure, recurrent infarction or death during 120 days follow up was found to be much higher than in patients who did not develop any complication. The comparision of median NT-proBNP levels in the above groups was statistically significant (p=0.0016).* ***Conclusions :*** *A single measurement of NT-proBNP on admission will substantially improve the early risk stratification of patients with symptoms suggestive of an acute coronary syndrome and no ST-segment elevation. A combination of clinical background factors, ECG, troponin T and NT-proBNP obtained on admission will provide a highly discerning tool for risk stratification and further clinical decisions.* ***Keyword :*** *NT-proBNP, Acute Coronary Syndrome, Ischemic Heart disease.*

INTRODUCTION

During the last decade, Brain Natriuretic Peptide (BNP) has been recognized as a useful marker for the detection of acute and chronic left ventricular dysfunction. BNP is released by the ventricles as a neurohormonal response to increased wall stress due to pressure and volume overload[1]. The BNP is produced as a prohormone, pro-BNP, which on secretion is proteolytically split into BNP and the N-terminal pro-brain natriuretic peptide (NT-proBNP)[2]. A close correlation exists between these peptide levels. However, in patients with left ventricular dysfunction, the proportional and absolute increase of NT-proBNP exceeds that of BNP, suggesting that NT-proBNP may be a more sensitive marker of LV dysfunction[3].

Acute regional left ventricular dysfunction is a hallmark of sudden and prolonged myocardial ischemia, and is one of the first step in the ischemic cascade that leads to cell necrosis. Thus BNP might be released by ventricular myocardium in the settings of acute coronary occlusion and prolonged cardiac ischemia[1].

BNP is released during ischemia provoked by exercise testing and after acute myocardial infarction. When measured at the time of presentation of acute

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coronary syndrome, N-terminal fragment of pro-BNP is strongly associated with the short term and long term risk of death and congestive heart failure[4-8].

Patients presenting with chest pain or other symptoms suggestive of an acute coronary syndrome amount today to about 20% of all visits to the medical emergency department. Of the two-thirds who will be admitted, about 90% will have an electrocardiogram (ECG) nondiagnostic of acute myocardial infarction (AMI) and, thereby, constitute a heterogeneous group concerning both the underlying pathophysiology and future risk of cardiac events. An early risk stratification of these patients is important for several reasons. Those identified as being high-risk patients might need a more intense pharmacologic treatment and be considered for intervention early. Patients with a low risk, in contrast, may benefit more from conservative management with a low risk of side effects. Moreover, considerable economic gains may be achieved by early identification of patients who are at sufficiently low risk for early transfer to a lower level of care and early discharge. Early risk stratification has been based on clinical background factors, electrocardiography and biochemical markers of myocardial damage. The neurohormonal activation has, so far, received less attention[3].

Recently, it has been documented that a single measurement of NT-proBNP obtained in first few days of onset of symptoms provided important prognostic information in patients with non-ST segment elevation AMI or unstable angina pectoris. What is more enlightening, is the fact that NT-proBNP has been proved to be an independent predictor of outcome of acute coronary syndrome[3].

Since almost all the studies have been carried out in the developed countries and because of marked paucity of Indian studies, this study was undertaken . We estimated the level of NT-proBNP at the time of admission in patients with symptoms suggestive of an acute coronary syndrome and ECG showing no ST-segment elevation and followed-up the selected patients for a period of 120 days. The endpoint in follow-up was death from any cause or new onset of congestive heart failure, or recurrent myocardial infarction.

MATERIALS AND METHODS

Patient selection : Patients admitted with history of chest pain and other symptoms suggestive of an acute coronary syndrome admitted to the Department of Medicine and Cardiology, S.C.B. Medical College, Cuttack during the period of July 2008 to December 2009 were taken as subjects. Unstable angina was defined as angina pectoris or equivalent ischemic discomfort with at least one of the three features –(a) occured at rest (or with minimal exertion), usually lasting >20 mins(if not interrupted by nitroglycerin administration) (b)was severe and of new onset (i.e. within 1 month) and occured with a crescendo pattern. The diagnosis of NSTEMI was made when a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected by Troponin I >0.11mg/l.ECG findings was suggestive of UA / NSTEMI (i.e. ECG was considred abnormal) when with the above clinical findings ECG shows ST depression > 0.05 mV, T wave inversion > 0.3mV, LBBB, Bifascicular Block.

Age and sex matched controls were taken up in this study for comparison. These were both healthy volunteers as well as other patients admitted to medicine ward with unrelated illnesses. The following patients were excluded from the study : (a) presence of ST-segment elevation on admission ECG (b)age > 80 years (c)renal dysfunction (Creatinine level >2mg/dl) (d)acute pulmonary edema (e)coronary revascularization during last 6 months. Examination during admission included medical history, clinical examination, routine blood chemistry, Chest X-Ray, ECG, Echocardiography, coronary angiography (where feasible),Troponin-I, and NT-proBNP. All the patients were followed up for a period of 120 days.The study end points were death from any cause or new onset of Congestive Heart Failure or recurrent myocardial infarction. Recurrent infarction was considred when alongwith ischemic chest pain there was new ST-segment elevation or appearance of new Q-waves on the ECG or re-elevation of cardiac biomarkers. Follow-up was performed by out patient visit and / or by telephone interview.

ECG was done by a standard 12 lead ECG machine. In our study all patients were subjected to M-mode as well as colour Doppler echocardiography. Coronary angiography was performed using Judkins catheter following a standard technique. An expert interventional cardiologist reviewed the angiogram with no knowledge of the biomarker levels and the patient outcome. Angiographically severe lesions were defined as the presence of stenosis >50% in vessles with a diameter <2mm. Extension of coronary disease was classified according to the standard way into single, double and triple vessel disease and / or left main disease.

Laboratory analysis

NT-proBNP concentration was measured by Enzyme-linked fluroscent Assay (VIDAS Automated quantitative test). The analyte range was 20-25, 000 pg/ml. The recommended decision thresholds as per the manufacturer (Bio Merieux-France) literature were 125 pg/ml for patients <75years old and 450 pg/ml for patients >75years old. However the cut-off points were based on study on patients with or without congestive heart failure. The assay principle combined a one-step immunoassay sandwich method with a final fluorescent detection . Troponin-I concentration was measured by Enzyme-linked fluorescent Assay (VIDAS Automated Quantitative Test). The analyte range was 0.01 to 30 mg/L.

Statistical Analysis

All results for continuous variables were expressed as means ± SD(standard deviation).However, since the distribution of NT-proBNP was skewed, therefore median values were also considered. Difference between mean values were evaluated with unpaired T-test. To compare the patient characteristics defined by the groups with low and high levels of NT-proBNP, we used the Fishers exact test. Correlation coefficients reported between continuous variables were based on Pearson correlation coefficient. A p value <0.05 was considered statistically significant. The data analyses were performed using the SPSSS system 16.0 (Statistical Package for the Social Sciences, Chicago) and GraphPad Instat 3.

TABLE - 1

	Male (n= 19)	Females (n= 6)	T otal(%) (n= 25)
Age groups (in years)			
< 50	4	1	5(20%)
50-59	8	2	10(40%)
60-69	5	2	7(28%)
70-79	2	1	3(12%)
Lipid abnormalities			
Raised cholesterol (≥200mg/ dl)	6	1	7(28%)
Raised TG (? 150mg/ dl)	8	4	12(48%)
Raised LDL-C (> 100mg/ dl)	9	5	14(56%)
Low HDL-C (< 40mg/ dl)	4	1	5(20%)
Complications			
Heart failure	3	2	5(20%)
Recurrent Infarction	2	0	2(8%)
Death	0	1	1(4%)

RESULTS

In the present study, out of 25 cases of UA / NSTEMI, 19 (76%) were males and 6 (24%) were females.Maximum no. of cases were in the age group of 50–59 yrs (Table-1). Among the two groups of ACS patients selected from the study, largest group was NSTEMI consisting of 21 (84%) cases. In the UA group there were 4 (16%) cases. Among the patients of UA / NSTEMI studied, raised cholesterol level was

seen in 7 cases (28%), raised triglyceride level in 12 cases (48%), raised LDL-C in 14 cases (56%), low HDL–C in 5 cases (20%) respectively. These were the predominant lipid abnormalities observed. However there was considerable overlapping and quite a few patients had more than one lipid abnormality (Table-1).

TABLE-2

Risk factor	Males (n=19)	Females (n=6)	Total (n=25)	Mean NT-ProBNP (pg/ ml)	*p* value
Hypertension	4	3	7(28%)	1367.29	0.37
Diabetes Mellitus	7	1	8(32%)	1093.63	0.708
Smoking	11	0	11(44%)	885.18	0.92

In the case group the mean value of serum NT-proBNP in males was 710.96 pg /ml whereas in females it was 1589.3 pg/ml. In the control group the mean value of serum NT-proBNP in males was 47.63 pg /ml whereas in females it was 37.00 pg/ml. The overall mean serum NT-proBNP level in the case group was 921.77 pg/ml whereas the overall mean serum NT-proBNP level among the controls was 45.50pg/ml. The observed difference between the case group and control group was statistically significant (p = 0.008). Among the various risk factors present in the cases, it was observed that smoking was the most common risk factor (11 cases, 44%) followed by Diabetes Mellitus (8 cases, 32%) and Hypertension (7 cases, 28%). Some of the patients had more than one risk factor. The NT-proBNP level among patients with risk factors was higher than the patients without risk factor. However, the association of NT-proBNP level with either of the risk factors was statistically not significant (Table-2). 72% of cases had no complications while 28% of cases had complication in the form of heart failure, recurrent infarction and death. Out of 25 cases (19 males and 6 females), 5 males (26.32%) and 2 females (33.33%) developed one or more complications. Most common complication observed in either sex was heart failure. There were 2 cases of recurrent infarction and one patient died in the study who presented with heart failure(Table-1).

It was observed that in patients with NSTEACS, NT-proBNP level was inversely related (moderate correlation) with the ejection fraction and the result was statistically significant. On, the whole, in patients of NSTEACS who had high NT-proBNP level, ejection fraction was found to be low(Table-3). Out of 18 cases that underwent Angiography, majority (9 cases, 50%) had SVD and 5 cases (27.78%) had DVD followed by TVD in 4 cases (22.22%). The LAD was the most common artery to be involved in 14 cases (77.78%). The RCA was the next most common artery to be involved in 9 (50%) cases. It was followed by LCX artery which was involved in 8 (44.44%) cases.

TABLE - 3

TABLE-4

	Serum NT proBNP Level(pg/ ml)	
Baseline characters	**≤ 258**	**> 258**
Median Age(yrs)	54	59
Males(n=19)	11(57.90%)	8(42.11%)
Females(n=6)	2(33.33%)	4(66.67%)
Diabetes Mellitus(n=8)	5(62.5%)	3(37.50%)
Hypertension(n=7)	3(42.86%)	4(57.14%)
Smoking(n=11)	5(45.45%)	6(54.55%)
Trop-I > 0.11µg/ L (n=21)	9(42.86%)	12(57.14%)
Complications(n=8)		
Heart failure(n=5)	0	5(71.43%)
Recurrent infarction (n=2)	0	2(28.57%)
Death(n=1)	0	1(14.29%)

The 25th, 50th, 75th percentile values of NT-proBNP was 105.0, 258.0 and 1149.5 pg/ml respectively. Taking the median value (258.0 pg/ml) the baseline characteristics were compared. The patients who had NT-proBNP level more than 258 pg/ml were older, of female gender, had hypertension, had smoking history, positive Trop-I level , had higher complications in the form of heart failure, recurrent infarction, and death(Table-4). Patients who had NT-proBNP level > 258 pg/ml had an index diagnosis of NSTEMI. Patients who had NT-proBNP level ≤ 258 pg/ml had an index diagnosis of Unstable Angina. However the observed difference was statistically not significant. Patients having NT-proBNP level ≤ 258 pg/ml had DVD /TVD than SVD in coronary angiography and had significantly lower ejection fraction compared to those who had lower NT-proBNP levels.(Fig.2) NT-proBNP level in patients who developed complications in the form of heart failure, recurrent infarction and death during 120 days follow-up was found to be much higher than in patients who did not develop any complication.(Fig.2) The comparision of median NT-proBNP levels in the above group was statistically significant. (Table 5).

Table - 5

Correlating factors	NT-proBNP Level ≤ 258pg/ ml	NT pro-BNP Level >258pg/ ml	*Fisher's Exact test*
UA(n=4)	4(16%)	0	0.09
NSTEMI (n=21)	9(36%)	12(48%)	
Angio SVD (n=9)	9(50%)	0	0.0023
Angio DVD/ TVD (n=9)	2(11.11%)	7(38.89%)	
EF<57% (n=12)	3(12%)	9(36%)	0.0169
EF≥57% (n=13)	10(40%)	3(12%)	
Heart failure Present (n=5)	0	5(20%)	0.015
Heart failure Absent (n=20)	13(52%)	7(28%)	
Overall complication Present(n=7)	0	7(28%)	0.0016
Overall complication Absent(n=18)	13(52%)	5(20%)	

Fig. 1

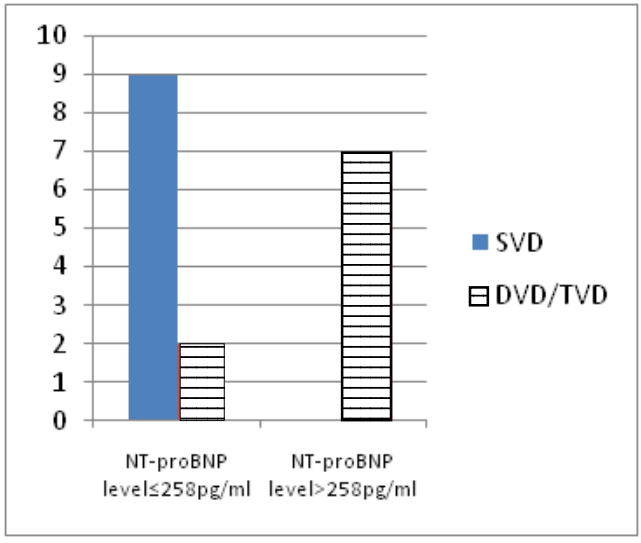

Fig.1 : Comparison of median NTproBNP level between patients having SVD & DVD/TVD in angiography.

Fig. 2

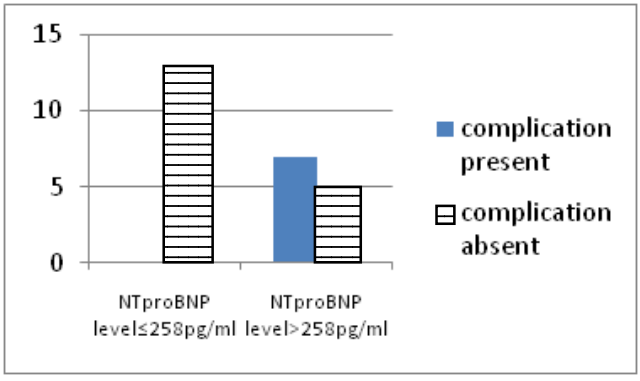

Fig.2 : Comparison of median NTproBNP level with overall complications.

DISCUSSION

In the present study, 25 cases of Unstable Angina (UA)/Non ST Elevation Myocardial Infarction (NSTEMI) and 10 healthy controls were taken. The median age of cases in the group where NT-proBNP ≤ 258 pg/ml was 54 yrs, while in the group where NT-proBNP >258 pg/ml the median age of cases was 59 yrs. Thus, higher baseline levels of NT proBNP was directly associated with age i.e. patients with NTproBNP > 258pg/ml were older (median age 59 yrs). These finding were consistent with earlier studies which also

reported that higher level of BNP was seen in older patients [9-11] . Out of a total number of 6 female patients, 4(66.67%) had NT-proBNP levels >258.0 pg/ml, while only on 8 males (42.11%) out of a total 19 males had supramedian NT-proBNP levels. Thus, higher NT-proBNP levels were seen in the female gender. Similar observation was seen by James SK et al in the GUSTO-IV substudy [12]. The overall mean serum NT-proBNP level was significantly higher in NSTEACS patients compared to controls. From Table – 2, it was clear that though NT-proBNP level was higher among hypertensives, diabetics and smokers, still, the association was not significant. The present study was the first one to demonstrate that a single measurement of NT-proBNP, obtained on admission, provides important prognostic information in patients with symptom suggestive of an acute coronary syndrome but with an ECG without ST-segment elevation. NT-proBNP level in patients who developed complications in the form of heart failure, recurrent infarction or death during 120 days follow up was found to be much higher than in patients who did not develop any complication (Table –5). The comparision of median NT-proBNP levels in the above groups was statistically significant. Only 1 patient died during follow up. This data apparently indicates low mortality compared to other studies. However when converted to percentage, it was 4% which was similar to the study by Galvani M. et al and Blazing MA et al in which it was 6.4% and 5.11% [13-14]. So, the above fallacy could be due to small study population. It was observed that in patients with NSTEACS, NT-proBNP level was inversely related with ejection fraction and that patients with double / triple vessel disease had higher NT-proBNP levels while patients with single vessel disease had significantly lower NT-proBNP levels. At least two possible mechanisms can explain the relation between NT-proBNP level and prognosis in the present population. First, an elevated NT-proBNP may reflect a permanent LV dysfunction established prior to or during the current episode of instability, which is an important predictor of outcome in patients with acute coronary syndromes [15]. Second, it can also reflect a temporary LV dysfunction secondary to transient ischemic episodes jeopardizing a large part of the myocardium. Previous studies have demonstrated elevation of BNP shortly after percutaneous coronary intervention [16]. Thus, an elevated NTproBNP does not necessarily reflect a neurohormonal activation or cell leakage in response to myocardial necrosis. Elevated NT-proBNP levels had a close relation with the number of vessels involved [17]. Even in patients with normal LV function, the level of NT-proBNP mantains the same relation with the extension of CAD[18]. Thus a mechanism other than LV dysfunction might be responsible for the adverse outcome in patients with NSTEACS and high levels of NT-proBNP . Toth et al[19] have found evidence that tissue hypoxia alone triggers release of BNP in absence of LV dysfunction. These results were confirmed by a recent physiological study showing that ventricular BNP gene expression is up-regulated by myocardial hypoxia resulting in augmented plasma concentrations of BNP and NT-proBNP[20]. The association of elevations of BNP with a greater severity and extent of ischemia may explain, atleast in part, the adverse clinical outcomes of such elevation. To be useful, a clinical risk indicator should not only identify patients with increased risk, but also patients who benefit from a certain treatment, and thereby be able to guide treatment. Troponin and ECG changes have previously been shown to identify patients with a high risk of subsequent cardiac events and who benefit most from intensive antithrombotic treatment and early revascularization[21-24]. A previous study[25] showed that treatment of heart failure guided by NT-proBNP concentrations resulted in a better outcome than treatment guided by clinical assessment. It is therefore tempting to suggest that patients with elevated NT-proBNP will benefit from an early aggressive treatment with neurohormonal antagonism (such as angiotensin-converting enzyme inhibitors and beta-blockade) and early revascularization in addition to an intense antithrombotic treatment. However, this needs to be evaluated in future studies. Conversely, patients with a low level of NT-proBNP on admission and a low risk of subsequent events will probably benefit most from a conservative management with a low risk of side effects.

CONCLUSION

The early risk stratification of patients with symptoms suggestive of an acute coronary syndrome and an ECG without ST-segment elevation had been based on clinical background factors, the acute clinical presentation, ECG measurement and biochemical markers of myocardial damage. The neurohormonal activation had, so far, received less attention. This study showed that a single measurement of NT-proBNP on

admission provided independent prognostic value in the Unstable Angina/Non-ST Elevation Myocardial Infarction patients. However, more studies are necessary to identify parameters that could be used in combination with natriuretic peptides to guide clinical decision making and treatment.

Acknowledgement

We would like to express our gratitude to all the patients who participated in our clinical trials.

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Original Article

CLINICAL PROFILE OF OPPORTUNISTIC INFECTIONS IN HIV SEROPOSITIVE PATIENTS ATTENDING M.K.C.G MEDICAL COLLEGE & HOSPITAL & ART CENTER, BERHAMPUR

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ABSTRACT

Background: *According to Odisha state HIV statistics, 43% of all PLHAs are from Ganjam district alone. Ganjam has been identified as one of the 14 most critical districts affected by HIV in the country. We decided to focus on opportunistic infection (OIs) in HIV patients on Southern Odisha since they contribute to the mortality and morbidity.* ***Method:*** *It's a cross sectional, hospital based study with 100 patients with HIV infections as per NACO guidelines with features of OIs.* ***Results****: Out of 100 patients 74 was male(74%), and 26 female(26%) 58 % (n=58) of them were in 30-39yrs age group and 29 %(n=29) in 20-29yrs. Majority of cases were labourers (43%) & less educated (n=55). Symptoms included loss of appetite (76%) n=76, fever (73%) n=73, cough (55%) n=55 & diarrhoea 15 %(n= 15). The respiratory system was most frequently involved by opportunistic infections and accounted for 56% (n=56) of the total cases and clinically consolidation/crepitation was the most frequent presentation accounting for 78.57% (n=44). Tuberculosis was the most common OI(53%) with combined pulmonary and extra pulmonary in 56.60%(n=30),tubercular meningitis and tubercular lymphadenopathy each accounting for 32.43%(n=12) amounted majority, with pleural effusion 16.21%(n=6). Median CD4+T cell count was 217.72 in TB. Candidiasis is second most common OI with 49 %(n=49), median CD4 count being 190.07. Other OIs observed were pneumocystosis 16% (n=16), cryptococcosis 4% (n=4)* ***Conclusion:*** *Most common OI in the study was tuberculosis (extra pulmonary TB meningitis & TB lymphadenitis) followed by Candidiasis, Pneumocystosis and Cryptococcosis.* ***Key words****: Opportunistic Infection, TB, HIV, AIDS.*

INTRODUCTION

AIDS, Acquired immune deficiency syndrome is a fatal illness caused by retrovirus, HIV. It slowly breaks down body's immunity there by making body vulnerable to various opportunistic infections.

In 2003 alone there were at least 5 million new cases of infection worldwide and three million deaths from AIDS, making it the fourth leading cause of death world wide.[1,2,3] The current estimate of the number of cases of HIV infection worldwide is 34 million(± 50% know their HIV status). People eligible for HIV treatment are 14.8 million, 8 millions are already on HIV treatment,2.5 millions are new HIV infection and 1.7 millions HIV related deaths as per UNAIDS 2012 Global Report[6].

Based on HIV Sentinel surveillance 2008-2009, it is estimated that 23.9 lakhs people are infected with HIV of which 39% are females. The four high prevalence states are Andhra pradesh-5 lakhs, Maharashtra- 4.2 lakhs, Karnataka - 2.5 lakhs, Tamilnadu - 1.5 lakhs, and accounts for 55% of all HIV infections of country[4].

Odisha state (eastern India) with its population crossing 4.19 crore has an estimated 71,813 PLHAs with an adult prevalence of 0.29%[3].

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The population of Odisha state is about 3.46% of the population of India, and there are an estimated 9% new infections in 2009[3,4].

Ganjam district with its population of more than 3.5 million is spread over a geographical area of 8070 square kilometer. According to Odisha state HIV statistics, 43% of all PLHAs are from Ganjam district alone. From a total of 640 districts in India, Ganjam has been identified as one of the 14 most critical districts affected by HIV in the country. There are more than 0.1 million migrants and 90% of these migrate to high HIV destination areas (Surat district in Gujurat, Mumbai and Thane district in Maharashtra(OSACS) .

According to latest data dated as on 30/09/ 2013 from Berhampur ART centre, the number of PLHIV registered in HIV care- 9894 and number of PLHIV ever started on ART- 3985.

HIV infection is characterized by an insidious deterioration of the immune system. There is quantitative and proportional decrease in CD+4-T cell over a period of years with development of AIDS.The degree of immunodeficiency associated with HIV infection as defined by the onset of opportunistic infection closely correlate with CD4+T cell count. HIV infection is complicated by various opportunistic infections like Tuberculosis, PCP, cryptococcosis, toxoplasmosis, Candida etc. These influence morbidity and mortality[5]

Being one of the top critical districts in India, and directly under scanner of NACO, morbidity and mortality are increasing in HIV. Opportunistic infections (OIs) are gaining its importance in becoming the predominant cause of mortality even with wide spread use of ART therapy and with prophylaxis to these infection. Many infections mimic similar clinical presentation and pose diagnostic challenge.

With such significance, studies regarding Opportunistic infections (OIs) are lacking especially in its critical district like Ganjam, Odisha. With this background, the present study was undertaken to find the clinical profile of opportunistic infection in HIV disease.

MATERIAL & METHODS

It was an observational, analytical and prospective study. The study included all HIV infected patients with OIs admitted to the Department of Medicine, M.K.C.G Medical College and Hospital, Brahmapur from 2011 to 2013. Patients with known HIV positive status having OIs or patients with different OIs admitted to the hospital and later found to have HIV positive status were included in the study.

Diagnosis of HIV infection was done at ICTC (Integrated Counseling and Testing Centre) as per the NACO guidelines by three different methods *Dot blot (comb AIDs), Immunochromatographic test (Pareekshak) and Immunoblot (Pareekshak).* Those having reactive test results at other laboratories were sent to the ICTC for confirmation. Informed consent was taken in each case as per NACO ethical guidelines. Children below the age of 15 years were excluded from this study.[6,7]

Detailed history, clinical examination and investigations were done as necessary like CD4+T cell count, CBC, ESR, Blood culture, Arterial Blood Gas analysis, HBsAg, Anti-HCV antibody, Urine routine and culture, Stool routine and culture, Mantoux Test, Sputum examination, CT scan Brain, CT Thorax, MRI Brain, MRI Spine, Fundoscopy, Peritoneal fluid/Pleural fluid/CSF analysis, CSF for Indian Ink staining, CSF PCR, FNAC of lymphnode, ELISA for Toxoplasma IgG & IgM, Latex Agglutination for Cryptococcal antigen, Oral Scraping for Microscopy of fungal element, UGI endoscopy. CD4+T cell count was done by *Partec CD4 flow cytometer using flow cytometry.* [8,9,10,11]

RESULTS

100 adult HIV infected patients with opportunistic infections were included in the study. There was higher proportion of males, n= 74 (74%) as compared to females, n=26 (26%). The male to female ratio was 2.84:1. The maximum number of patients who had opportunistic infections were in the age group of 30- 39 yrs, n=58 (58%), followed by the age group 20-29 yrs, n=21 (21%). No patients were found in the age group above 60 yrs

Most of the patients with opportunistic infections were labourers (43%), n=43, followed by housewives (18%) n=18. Drivers accounted for 15% (n=15) of the total cases. The incidence of opportunistic infections was significantly high (55%), n=55, in patients who were less educated, that is below tenth standard. whereas it was mere 11 %(n=11) in those who were highly educated.

The most common symptoms at presentation were loss of appetite (76%) n=76, fever (73%) n=73(p=<0%01), weight loss (71%) n=71, cough (55%) n=55, whereas diarrhea was seen in only 15 %(n= 15) of the cases (Table-1)

TABLE-1

Symptoms	No. of Cases	Percentage
Fever	73	73%
Weight loss	71	71%
Diarrhoea	15	15%
Cough	55	55%
Loss of appetite	76	76%
Dysphagia	48	48%
Dyspnoea	47	47%
Tachypnoea	23	23%
Genital lesions	10	10%
Body swelling	12	12%
Rash	0	0%
Headache	29	29%
Convulsions	10	10%
Abdominal pain	15	15%
AbdominalDistension	3	3%
Chest pain	26	26%
Visual blurring	16	16%
Vomiting	33	33%
Altered sensorium	14	14%

Those patients who were febrile at presentation had history of fever mostly of more than 1 month duration (69 %) n= 69 and only 4 %(n= 4) of the total cases accounted for fever of less than 1 month duration.

The respiratory system was the most frequent system involved by opportunistic infections and accounted for 56% (n=56) of the total cases and clinically consolidation/crepitation was the most frequent presentation accounting for 78.57% (n=44) of the total respiratory cases. This was followed in sequence by central nervous system involvement (16%) n= 16, cardiovascular system (06%) n=06 genitals (10%) n=10, skin (13%) n=13, and abdomen in 05 %(n=05) of the total cases (Table-2)

TABLE-2

Systems	No. of Cases	Percentage
Respiratory (n=56)		
Consolidation/Infiltration	44	78.57
Pleural Effusion	06	10.71
Fibrosis	05	08.92
Cavity	01	01.78
Cardiovascular (n=6)		
Distant Heart Sounds	05	83.33
Gallop Rhythm	01	16.66
Skin(n=13)		
Tinea	00	0%
Herpes Zoster	04	30.76
Molluscum	06	46.15
Scabies	01	07.69
Seborrhoeic Dermatitis	02	15.38
Genitals (n=10)		
Vesicles	01	10%
Ulcers	00	0%
Papules	06	60%
Warts	00	0%
Vulvovaginal Thrush	03	30%

Table 2 (continued)

Systems	No. of Cases	Percentage
Abdomen (n=5)		
Free Fluid	02	40%
Doughy	00	00%
Palpable Lump	03	60%
Central Nervous System (n=16)		
Meningitis	14	87.50
Focal Deficit	02	12.50

Table - 3

Manifestations	No. of Cases	Opportunistic Infection	percentage	p-value
Pneumonia	44(78.57%)	Tuberculosis (n= 26) Pneumocystis (n=16) Pneumococci (n= 2)	59.09% 36.36% 4.55%	**<0.0001**
Pleural effusion	06(10.71%)	Tuberculosis (n=06)	100%	
Cavity	01(1.78%)	Tuberculosis (n=01)	100%	
Fibrosis	05(8.92%)	Tuberculosis (n=05)	100%	

The most common manifestation of opportunistic infections in respiratory system was pneumonia accounting for 44 cases of which tuberculosis(n=26) was the most frequent opportunistic pathogen accounting for 59.09% of cases and Pneumocystis in 36.36%(n=16). All the cases of pleural effusion, fibrosis and cavity were attributable to tuberculosis. Patients presenting with pneumonia as a part of opportunistic infection had tuberculosis as most frequent infection as compared to others (p=<0.0001) with statistical significance. (Table-3)

The profile of tuberculosis (out of 53 cases) depicts that the most frequent manifestation of tuberculosis was combined pulmonary and extra pulmonary and accounted for 56.60 % (n=30) of the total cases, only pulmonary in 16 (30%) cases, extra pulmonary 7 (13%) cases and was statistically significant (p=<0.0001). (Table-4)

The most frequent Extra pulmonary Tuberculosis was tubercular lymphadenitis and TB meningitis accounting for 32.43% (n=12) each as shown in figure 1. The remaining were pleural effusion (16.21%) n=06, pericardial effusion (13.52%) n=05 and by ascitis (5.40%) n=02. (Fig.1)

The table-5 shows that the mean CD 4 + cell count in tuberculosis was 217. 72 / microL and in Candidiasis 190.07/ microL, and In cryptococcosis 72.89/microL, in pneumocystosis is 145.73/microL

DISCUSSION

During the 2 yrs study among 100 hospitalized HIV patients, 74% were male and 26% female which is comparable with other studies conducted by Chakravarty.J.et al (80.8% male) and Kumarsamy.N.et al (68% male)[13,16].

Most of the patient belonged to the age group 30-39 yrs. (58%) as compared to Chakrabory.N.et al (55% were in 31-44 yrs.) and Singh.A.et al (54% were in 31-40 yrs.)[17,18].

Majority of the patients were labourer which is comparable to that reported by Chakravarty.J.et al (Majority were migrant worker). This was due to illiteracy and low level of awareness about transmission of HIV amongst them[13].

At the time of hospitalization majority of patient presented with more than one symptom like fever, loss of appetite, weight loss, which is similar to study by Sharma Sk et al where the most common presentations

Table 4 [TUBERCULOSIS (n= 53)]

Clinical profile	No. of Cases	Percentage	P-valve
Only pulmonary	16	30.18%	<0.0001
Extrapulmonary	07	13.20%	
Both	30	56.60%	

Figure - 1

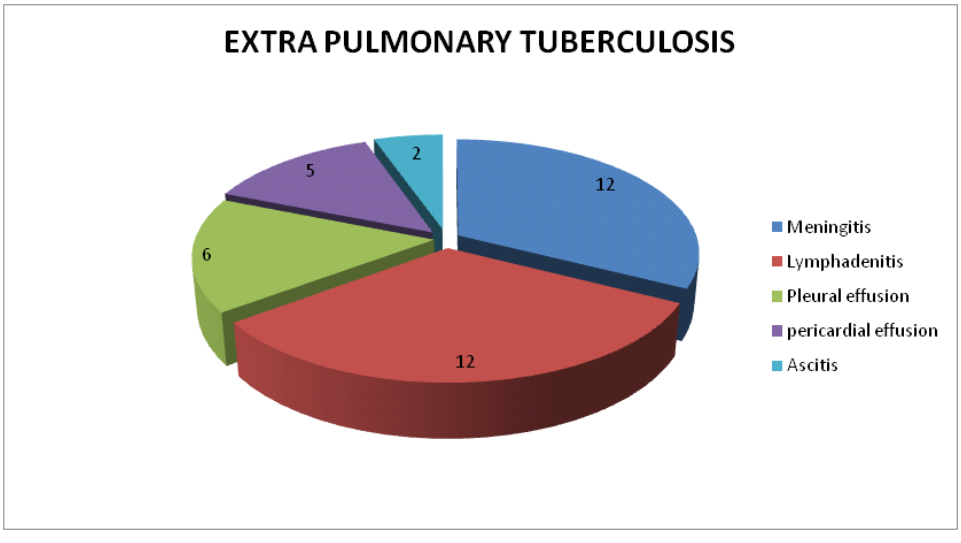
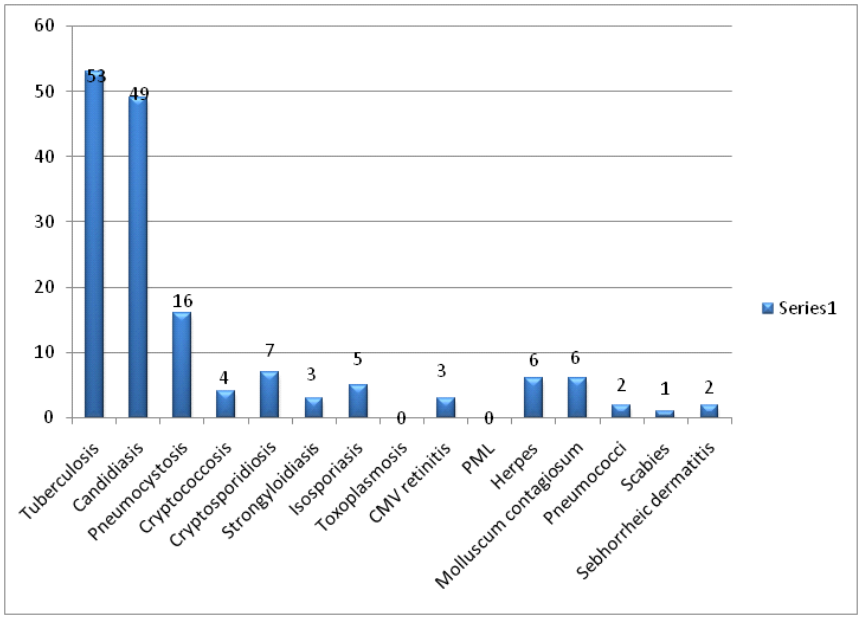


FIGURE-2: FREQUENCY OF VARIOUS OPPORTUNISTIC INFECTIONS



Tuberculosis was the most frequent opportunistic infections accounting for 53 %(n= 53) of all opportunistic infections, followed by Candidiasis in 49% (n=49) of cases. (Fig.2)

Table-5: Mean CD4+ T cell in various opportunistic infections

Opportunistic infections	Mean CD4+ cell count
Tuberculosis	217.72/ micro L
Candidiasis	190.07/ micro L
Cryptococcosis	072.89/ micro L
Pneumocystosis	145.73/ micro L
Cryptosporidiosis	212/ micro L
Isosporiasis	241.80/ micro L
Strongyloidiasis	274/ micro L
Cytomegalosis	019.66 / micro L

were fever (71%) and weight loss (65%). But the study by Chakravarty J et al[13] were different in which majority patient had diarrhoea (43.9%) and cough (40.3%)[13,15].

A significant number of cases (42%) belonged to the CD4T tell count range of 100-200/µl with a median CD4T count of 183. But the study by Chakraborty.N.et al shows 36.8% belonged to CD4 range of 100-200/µl with lower median CD4 count i.e. 120/µl[17].

The study by Chakravarty.J.et al showed a different scenario, in which the mean CD4 count in male was 179±9.3/µl where as CD4 count in female was 32328.26/µl. In another study by Sharma.Sl.et a it was observed that 82.6% had CD4 count <200 from which 46% had CD4 count <50/µl[13,15].

The most common OI was tuberculosis (51%) with combined pulmonary and extrapulmoary as most frequent presentation. Among extrapulmonary, Tubercular meringitrs and lymphadenopahty shared equal presentation. The second most common OI was candidiasis (49%), with most cases suffering from oral candidiasis which was seen to occur at higher CD4 count that tuberculosis.

The OIs found in descending order of their prevalence with Cryptosporidiosis, PCP, Cryptococcal meningitis etc. The prevalence of different OIs varies in different studies like Vajapyee. M.et al, Sing A et al[14,18].

The mean CD4 count for different OIs in this study was observed to be 172/µl for candidiasis, 218/µl for tuberculosis and 142/µl for cryptosporidiosis. But this observation was different than the study conducted by Vajpayee.M.et al where the median CD4 count for candidiasis was 189/µl, tuberculosis was 189. In the

present study the CD4 count is found to be below 100/ µl in cases cryptococcal meringitis.

CONCLUSION

1. The incidence of opportunistic infection was higher in male as compared to females. HIV with opportunistic infections is the disease of youth and is prevalent in those who are sexually active. In our set up the most frequent opportunistic infections are tuberculosis and Candidiasis. There is a direct correlation between the values of CD4 count and the severity of the opportunistic infections, hence indicating the level of immunity and the severity of the disease. The clinician should take every possible effort for the work up of fever, to establish the diagnosis of tuberculosis, which happens to be the most common OI in our study.

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Original Article

A STUDY ON HYPONATREMIA IN STROKE

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ABSTRACT

Background and Aims: *Hyponatremia is the most common electrolyte disorder in critically ill neurological patients. Studies of hyponatremia in stroke across the globe are sparse and hence this study was undertaken with an aim to determine the incidence and cause of hyponatremia in hospitalised patients admitted with stroke and to know the significance of hyponatremia in relation to the outcome of stroke.* ***Materials and Methods:*** *NCCT brain was used to confirm stroke. Serum and urine sodium were determined by ion selective electrode method. Serum and urine osmolality were determined by osmometer. Volume status was measured by central venous catheter.* ***Results:*** *The incidence of hyponatremia in stroke in our study was 19%. The incidence of hyponatremia in ischemic stroke was 9.38% compared to hemorrhagic stroke which was 36.11% [p value – 0.0026]. SIADH comprised of 84.21% of hyponatremia cases and CSW accounted for 15.79%. The mortality rate in hyponatremia patients with stroke was 31.58%, which was significantly more compared to 11.11% among normonatremic patients.* ***Conclusion:*** *The incidence of hyponatremia in stroke in our study was 19% which was more in hemorrhagic stroke when compared to ischemic stroke. SIADH accounted for 84.21% of hyponatremia cases in stroke and CSW made up the rest. The mortality rate was higher in patients of type 2 DM, moderate and severe hyponatremia.* ***Key Words:****Stroke, Hyponatremia, SIADH and Cerebral Salt wasting.*

INTRODUCTION

The WHO defines stroke as "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[1]

Hyponatremia is the commonest electrolyte disorder in the setting of acute neurological diseases. Hyponatremia is defined as serum sodium level less than 135meq/l. The syndrome of inappropriate antidiuretic hormone secretion [SIADH] and cerebral salt wasting [CSW] are the two potential causes of hyponatremia in stroke. Distinguishing between these two causes can be challenging because there is considerable overlap in the clinical presentation. The primary distinction lies in the assessment of the effective arterial blood volume [EABV].

SIADH is characterised by hyponatremia in the setting of inappropriately concentrated urine, increased urine sodium concentration and evidence of normal or slightly increased intravascular volume. By contrast, in CSW there is evidence of contracted extracellular fluid [ECF] volume caused by excessive renal sodium excretion, resulting from a centrally mediated process.

Making an accurate diagnosis is important because the treatment of each condition is different. Vigorous salt replacement is required in CSW, whereas

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fluid restriction is the treatment of choice in SIADH.

MATERIALS AND METHODS

This was a cross sectional study undertaken among 100 stroke patients admitted to M.K.C.G Medical College and Hospital, Berhampur over a period of two years from July 2011 to June 2013.

The inclusion criteria were patients with stroke diagnosed clinically and documented by non-contrast CT scan of brain and serum sodium levels less than 135meq\l. The exclusion criteria were patients with pseudohyponatremia like hypertriglyceridemia, hyperproteinemia and hyperglycemia and patients with hypothyroidism, glucocorticoid or mineralocorticoid deficiency, those suffering from diarrhoea, heart failure, cirrhosis, nephrotic syndrome, renal failure, AIDS,pulmonary diseases like pneumonia, tuberculosis, cystic fibrosis, bronchiectasis, status asthamaticus and carcinoma, psychogenic polydipsia, central nervous system [CNS] infections or who had underwent CNS surgeries in recent past and patients on hyponatremic drugs like antiepileptics, antipsychotics, cyclophosphamide, chlorpropamide, AVP analogues, oxcarbamazepine, clofibrate and clozapine. Few patients with hyponatremia who were on diuretics for hypertension too were excluded.

The routine investigations done were hemoglobin, total count, differential count, total platelet count, peripheral smear, erythrocyte sedimentation rate, serum urea and creatinine, serum sodium and potassium, liver function test, blood sugar, lipid profile, human immunodeficiency virus testing, urine routine, NCCT brain, ECG and chest x-ray.

The specific investigations done were urine sodium, urine and serum osmolality, serum uric acid, hematocrit and CVP. Other investigations like thyroid function, cortisol levels and abdominal sonography were performed depending on the clinical suspicion.

The diagnostic criteria of syndrome of inappropriate secretion of antidiuretic hormone [SIADH] are as follows. Main criteria are 1.Serum sodium less than 135meq/l. 2.Effective decrease of extracellular fluid osmolality [serum osmolality less than 275mosm/kg H_2O]. 3.Very concentrated urine [urinary osmolality more than 100mosm/kg H_2O with normal renal function] for any level of hypo-osmolality. 4.Clinical signs of euvolemia, defined as lack of signs of hypovolemia [postural hypotension, tachycardia, dry mucous membranes, decreased skin turgidity] or hypervolemia [raised jugular venous pulse or pulmonary rales]. 5.Elevated urinary sodium excretion of more than 20meq/l with normal intake of sodium and water. 6. Absence of other possible causes of euvolemic hypo-osmolality: hypothyroidism, hypocortisolism or use of diuretics.

CSW is similar to SIADH with respect to hyponatremia, decreased serum osmolality, increased urine sodium excretion and urine osmolality and is differentiated from SIADH by presence of signs of hypovolemia and decreased effective arterial blood volume as evidenced by increased hematocrit and blood urea nitrogen and decreased central venous pressure below 6cm of water.

Descriptive statistical analysis was carried. Results on continuous measurements were presented as Mean ± SD [Min-Max] and results on categorical measurements were presented as number [%]. Fisher's exact test and Pearson's chi square test for independence and trend by contingency tables had been used to find the significance of study parameters on categorical scale between groups. P value less than 0.05 was considered significant.

Patients admitted with stroke were first subjected to NCCT brain. Serum and urine sodium were estimatedby ion selective electrode method, serum urea by enzymatic analysis using urease - glutamate dehydrogenase reagent, serum creatinine by jaffe rate method [kinetic alkaline picrate], blood glucose by glucose oxidase peroxidase method, serum and urine osmolality by automated osmometer using freezing point depression technique and volume status was measured by central venous pressure monitoring.

RESULTS

Among 100 cases of stroke, 60 [60%] were males and 40 [40%] were females. The male to female ratio was 1.5:1.

The mean age of patients with stroke was 62.52 ± 8.10. The age varied from 33 to 78 years. The mean

age of male patients was 61.93 ± 9.17 years, varying from 33 to 78 years and that of female patients was 63.40 ± 6.15 years varying from 50 to 76 years.

Among 100 cases of stroke, 64 [64%] were due to infarction and 36 [36%] due to hemorrhage. Among 64 cases of infarction, MCA territory infarcts comprised of 36 cases [36%], PCA territory infarcts comprised of 16 cases [16%], ACA territory infarcts comprised of 2 cases [2%] and 10 cases [10%] had normal NCCT scan. Among 36 cases with hemorrhagic stroke, capsuloganglionic hemorrhage comprised of 26 cases [26%], thalamic haemorrhage comprised of 7 cases [7%] and brainstem/cerebellar haemorrhage comprised of 3 cases [3%].

The incidence of hyponatremia in stroke in our study was 19% [19 out of 100 stroke cases]. Among hyponatremic patients, 1 case [5.26%] had mild hyponatremia with serum sodium between 131-134meq/l, 12 cases [63.16%] had moderate hyponatremia with serum sodium between 121-130meq/l and 6 cases [31.58%] had severe hyponatremia with serum sodium ≤ 120meq/l. There was no significant gender difference neither in incidence of hyponatremia in stroke nor among different severities of hyponatremia.

Hyponatremia in stroke included 12 males [63.16%] and 7 females [36.84%]. The mean age of patients with hyponatremia was 65.37 ± 6.06 years, ranging from 55 to 76 years. The mean sodium level in hyponatremia patients was 119.11meq/l ± 10.31meq/l and values ranged from 96 to 131meq/l. Hyponatremia in stroke was more common among patients with aged between 66-70 years. The results are shown in Table-1.

Among 64 cases of infarction, 6 cases [9.38%] including 4 males and 2 females had hyponatremia and out of 36 hemorrhagic stroke cases, 13 cases [36.11%] including 8 males and 5 females had hyponatremia. There was no significant gender difference in incidence of hyponatremia in hemorrhagic and ischemic stroke but incidence of hyponatremia among hemorrhagic patients was significantly more compared to ischemic stroke [P value – 0.0026].

SIADH comprised of 16 out of 19 cases [84.21%] of hyponatremia, of which 10 cases [52.63%] were of moderate hyponatremia and 6 cases [31.58%] were of severe hyponatremia. CSW comprised of 3 out of 19 cases [15.79%] of hyponatremia, of which 2 cases [10.53%] were of moderate hyponatremia and 1 case [5.26%] was of mild hyponatremia. The incidence of SIADH among patients with moderate hyponatremia in stroke patients was significantly more [P value – 0.0395] compared to CSW. (Table 2)

The common risk factors hypertension and type 2 diabetes mellitus in stroke were studied. Among 19 cases of hyponatremia in stroke, 68.42% cases were hypertensive, 42.11% cases were diabetic, 26.32% cases were both hypertensive and diabetic and 15.79% cases had no risk factors. Among 81 normonatremic patients in stroke, 53.09% cases had hypertension, 35.80% cases had type 2 diabetes mellitus, 19.75% cases had both hypertension and type 2 diabetes mellitus and 27.16% cases had no risk factors. There was no significant association of risk factors with incidence of hyponatremia in stroke.

The overall in-hospital mortality rate in stroke patients was 15% [15 out of 100 cases]. The death rate in hyponatremia patients with stroke was 31.58% [6 out of 19 cases]. The death rate in patients of normonatremia in stroke was 11.11% [9 out of 81 cases]. The in-hospital mortality in patients of hyponatremia in stroke was very significantly associated with moderate hyponatremia [P value – 0.0095] and severe hyponatremia[P value – 0.0029]. The death rates in patients of stroke with hyponatremia and normonatremia in relation to various attributes are shown in table 3.

DISCUSSION

The incidence of hyponatremia in stroke in the study was 19%. Among hyponatremic patients, 5.26% cases had mild hyponatremia, 63.16% cases had moderate hyponatremia with and 31.58% had severe hyponatremia. Incidence of hyponatremia in stroke was higher among patients aged between 66-70 years.

In the study by Wen-Yi Huang et al, the incidence of hyponatremia was 11.6%, mean patient age was 69.48 ± 11.62 years and there was no difference in age or gender between the hyponatremic and normonatremic groups.[2] In the study by Rodriques B et al, the incidence of hyponatremia among stroke

Table 1

Hyponatremia among Different Age Groups

Age Group	Hyponatremia					
	Mild		Moderate		Severe	
	No.	%	No.	%	No.	%
51-55	1	5.26	0	0	0	0
56-60	0	0	3	15.79	0	0
61-65	0	0	2	10.53	2	10.53
66-70	0	0	4	21.05	3	15.79
71-75	0	0	2	10.53	1	5.26
76-80	0	0	1	5.26	0	0
Total	1	5.26	12	63.16	6	31.58

Table 2

Causes of Hyponatremia in Stroke – SIADH and CSW

Severity of Hyponatremia	Cases Of Hyponatremia			
	SIADH		CSW	
	No.	%	No.	%
Mild	0	0	1	5.26
Moderate	10	52.63	2	10.53
Severe	6	31.58	0	0
Total	16	84.21	3	15.79
P value - 0.0395*				

Table 3

Outcome in Relation to Various Attributes

Various Attributes	Outcome				Total	P value
	Hyponatremia		Normonatremia			
	Death	Discharge	Death	Discharge		
Mild hyponatremia	0 [0%]	1 [100%]	0 [0%]	0 [0%]	1 [100%]	**1.0000^{ns}**
Moderate hyponatremia	1 [8.33%]	11 [91.67%]	0 [0%]	0 [0%]	12 [100%]	**0.0095****
Severe hyponatremia	5 [83.33%]	1 [16.67%]	0 [0%]	0 [0%]	6 [100%]	**0.0029****
SIADH	6 [37.5%]	10 [62.5%]	0 [0%]	0 [0%]	16 [100%]	**0.5170^{ns}**
CSW	0 [0%]	3 [100%]	0 [0%]	0 [0%]	3 [100%]	**0.5170^{ns}**
Age Group 66-70 Years	4 [57.14%]	3 [42.86%]	2 [11.76%]	15 [88.24%]	24 [100%]	**0.1287^{ns}**

patients was 16%.[3] In one Indian study by Satish Gupta et al, the incidence of hyponatremia was 35%.[4]

The incidence of hyponatremia in ischemic stroke was 9.38% and that in hemorrhagic stroke was 36.11%. Incidence of hyponatremia among hemorrhagic stroke patients was significantly more compared to ischemic stroke [p value – 0.0026].

In a Japanese study by Yoshio Miyasaka et al, the incidence of SIADH among stroke patients was 7.6%. The incidence of SIADH varied significantly according to the type of CVA, being lower in cases with cerebral infarction 1.9%, than in cases with cerebral hemorrhage 12.9%. The incidence of SIADH in patients with thalamic hemorrhage 26.7% was much higher than in patients with putaminal hemorrhage 7.7%.[5]

SIADH comprised of 84.21% of hyponatremia cases in our study andCSW comprised of 15.79%. The incidence of SIADH among moderate hyponatremia patients was more compared to CSW [p value – 0.0395]. In the study by Satish Gupta et al 67% patients had SIADH and 33% patients had CSW.[4]

The overall in-hospital mortality rate in stroke patients in our study was 15%. The death rate in hyponatremia patients with stroke was 31.58%. The death rate in patients of normonatremia in stroke was 11.11%. The in-hospital mortality in patients of hyponatremia in stroke was more with moderate [p value – 0.0095] and severe hyponatremia[p value – 0.0029].

Our study findings are similar to other few studies available on this topic. Rodriques B et al showed hyponatremia was associated with higher mortality in hospital [p = 0.039] and at 3-month [p = 0.001] and 12-month follow-ups [p = 0.001]. Complications during admission were similar between groups except for urinary infection [p = 0.008].[3]Satish Gupta et al showed 44.19% of patients with stroke with hyponatremia died[p< 0.001].[4]

Wen-Yi Huang et al showed that the prevalence of diabetes mellitus and chronic renal insufficiency was significantly higher among hyponatremic patients [p< 0.001] and that the survival rate was significantly lower in hyponatremic patients than in normonatremic patients [p value < 0.001].[2]

Study by Wannamethee et al showed that all-cause and non-cardiovascular mortality were significantly increased at serum sodium levels < 138mmol/l in stroke patients, but the study included all types of stroke [including hemorrhage] and was performed only in middle-aged male patients.[6]

Recent hyponatremia treatment guidelines state the following: "hyponatremia remains incompletely understood because of its association with a plethora of underlying disease states, and its multiple etiologies with differing pathophysiologic mechanisms".[7,8]

The limitations in our study was that other risk factors like smoking, dyslipidemia were not evaluated for casual role in hyponatremia in stroke, the discharged patients were not followed up to notice if hyponatremia increased mortality during next 3 years, sub arachnoid hemorrhage patients in whom hyponatremia is expected in higher frequency were not included in our study because of few cases and urgent referral in most for surgery precluding evaluation in our hospital and whether there was any risk of recurrent stroke in patients initially presenting with hyponatremia.

CONCLUSION

The incidence of hyponatremia among stroke patients in our study was 19% and most of them were in the age group of 66 – 70 years with no significant sex difference**.** The incidence of hyponatremia was significantly higher in hemorrhagic stroke [36.11%] compared to ischemic stroke [9.38%]. SIADH accounted for a majority of 84.21% of hyponatremia cases in stroke and CSW made up the rest. The overall in-hospital mortality rate in stroke patients was 15%. The mortality rate of patients with hyponatremia in stroke was 31.58%, compared to 11.11% among normonatremic patients. Hyponatremia contributed significantly to the mortality in stroke patients.

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Original Article

ROLE OF SODIUM BICARBONATE AS AN ALKALISER IN MANAGEMENT OF ORGANOPHOSPHORUS PESTICIDE POISONING

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ABSTRACT

Objective: *To determine the efficacy of sodium bicarbonate as an alkaliser and to evaluate its role (positive/negative/neutral) in the management of OP poisoning.* ***Method:*** *A total of 52 patients (26 cases and 26 controls) of OP poisoning were taken up for study during the period September 2012 to September 2014. Cases were given sodium bicarbonate in addition to conventional treatment for OP poisoning, controls received only conventional treatment. Initial severity was assessed using poisoning severity score. pH was assessed at the time of admission and on day 3 and day5. Moderate to severe poisoning were admitted to ICU.* ***Result:*** *Both cases and controls presented with metabolic acidosis at the time of admission. The mean rise of pH on day 3 was 7.44 in cases (7.22 in controls) and on day 5 was 7.52 in cases (7.33 in controls). Rise of pH > 7.5 was seen in 76.92% of cases and only 34.61% of controls. The mortality rate did not differ among cases and controls, but there was significant reduction in ICU stay (120.65±35.16 hours), ventilator use (83.2±19.79 hours), secondary complications, total dose of atropine (387.69 ± 123.06 mg) and total period of hospitalisation(186.96± 18.34 hrs) in cases as compared to controls.* ***Conclusion:*** *Addition of sodium bicarbonate although did not alter mortality, but there is significant reduction in ICU requirement, ventilator requirement, secondary complications and thereby decreasing the total duration of ICU stay, ventilator stay and duration of hospitalisation, thereby reducing morbidity and cost of therapy.* ***Keywords:*** *Organophosphorus poisoning, sodium bicarbonate, metabolic acidosis, poisoning severity score.*

INTRODUCTION

Poisoning with 0rganophosphorus pesticides (OP) is an important cause of morbidity & mortality, particularly in developing countries. OP are used in developed & developing countries to improve crop yield, control disease vectors (such as Mosquitoes) & for household use. OP are among the most toxic & common pesticides associated with poisoning (Eddlestone 2000). Hundreds of thousands of people die each year around the world from OP poisoning, the majority in developing countries from intentional or occupational exposures. Out of all poisons the commonest poison in India is OP, as India is an agriculture based economy & it is easily available highly toxic pesticide. The case fatality for pesticide self poisoning is as high as 10 to 20 % depending on the type of OP & route of exposure.[1] OP compound inhibit acetylcholinesterase & butyrylcholinesterase enzymes resulting in overstimulation at cholinergic synapses. Management of OP poisoning depends on the severity of symptoms, supportive care, appropriate

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decontamination & management of symptoms with Antidotes(Atropine, Oximes & Benzodiazepines) remain the treatment priority.[2] In severe poisoning, patients require advanced cardiorespiratory management, close observation & careful titration of antidotes. Despite widespread clinical use, there is no good quality evidence that Oximes are effective in reducing morbidity & mortality in human. The case fatality for intentional self poisoning is around 10 to 20% even when the standard Antidotes (Atropine , Oximes & Benzodiazepines) are used.[5,6] The lack of confidence in Oximes & the high case fatality from OP self poisoning has encouraged clinicians to find alternative antidotes like Sodium bicarbonate($NaHCO_3$).[7]

Acidosis is a prominent clinical manifestation with significant OP poisoning[8]. Asari et al noted rapid onset metabolic acidosis associated with profound hypotension in 4 cases of Organophosphate poisoning.[9] Alkalinisation is not widely used for the treatment of OP poisoning .In some centres however $NaHCO_3$ is commonly used for severe poisoning (Balali-Mood2003, Wong2000 & Vucinic 2008)[10]. $NaHCO_3$ is readily accessible & relatively cheap so is likely to be used first line to induce alkalosis clinically. The beneficial effect of $NaHCO_3$ relate to bicarbonate induced pH changes rather than the sodium component. Darren M Roberts & Nick Buckley suggested benefit of alkalinisation in OP poisoning (2010). They conducted two small randomised controlled trials, one with higher dose of $NaHCO_3$ & the other with lower dose $NaHCO_3$. In the higher dose study, the Relative Risk of death in patients receiving $NaHCO_3$ compared to controls was 0.52(<1). Higher dose $NaHCO_3$ which maintain target arterial pH of 7.5(7.45-7.55) showed slight benefit from using it in conjunction with standard treatment for OP poisoning.[11] In two case controlled series clinical benefits of sodium bicarbonate were suggested including an earlier discharge and/or lower total atropine dose, but no change in mortality (Balali Mood 2003, Vucinic 2008).[10]

Sodium bicarbonate has also been shown to decrease mortality in animals poisoned by OP experimentally (Cordoba 1983, Jeevarathinam 1988, Wong 2000,Stefanovic 2006). Clinical use in humans has supported these benefits in uncontrolled case series (Wong 1996,Wong 2000).[12]

The mechanism of action of sodium bicarbonate in the treatment of OP poisoning has not been established. The following mechanisms have, however been proposed, based on in vitro, animal & human studies.

Enhanced pesticide clearance from the body through nonenzymatic and/or enzymatic hydrolysis (Broomfield 2000), volume expansion with improved tissue perfusion (Mountain 1998), improved efficacy of oximes (Jeevarathinam 1988), direct effect on neuromuscular function (Beekley 2003), bicarbonate induced release of lactate in to the circulation (Hollidge-Horvat 2000).

MATERIALS & METHODS :

In our study 52 patients (26 cases & 26 controls) with history & biochemical or clinical features of acute OP poisoning admitted to Dept of Internal Medicine, VSS Medical College, Burla between September 2012 to September 2014 were taken into study. All patients above 15 yrs of age of both sexes showing clear evidence of consumption of organophosphorus compounds were included. Person who cannot name the poison or who cannot show the container having poison, those who have consumed poison other than OP,or those who have consumed alcohol along with OP were excluded from this study. Patients having comorbid conditions like diabetes mellitus and hypertension were also excluded.

The patients were divided into two groups Group A(cases) & Group B(controls). Group B(controls) received Atropine as incremental doses that is, 2mg(2ml) iv repeating doses every 5 min interval, doubling the dose each time to the point of atropinisation

occurs, followed by 15% of atropine recquired for atropinisation every hour by iv infusion. Injection Oxime was given 6gm in NS daily in divided doses as slow continuous infusion for 1 week. Group A (cases) received incremental doses of atropine followed by continuous infusion of atropine & NaHCO3 along with Oxime. Higher doses of NaHCO3, 5 mEq/kg over 1 hour followed by an infusion of 5-6 mEq/kg over next 23 hrs. The infusion was repeated every day until recovery or death to maintain target arterial pH of 7.5(7.45- 7.55)[13]. The doses are adjusted according to clinical features, all patients received standard medical care for OP poisoning. All patients with moderate to severe poisoning were admitted in ICU and treated accordingly.

Investigations: Routine investigations, ABG was done to measure serum bicarbonate & pH at the time of admission & at certain intervals by Blood Gas Analyser. Plasma cholinesterase was estimated at the time of admission.

Assessment of Response : The severity will be assessed using PSS(poisoning severity score) at the time of admission. The outcome was to be assessed in terms of intermediate syndrome, incidence of pneumonia, convulsion, ventilation period, ICU stay, total period of hospitalisation and mortality.

The data were analysed in terms of t test and chi square test, for determination of p value using standard statistical methods.

Table - 1

pH status at the time of Admission

pH	CASE(26)	%	Contro (26)	%	TOTAL(52)	%
7.25-7.32 (MILD)	6	23.07%	5	19.23%	11	21.15%
7.15-7.24 (MODERATE)	16	61.53%	15	57.69%	31	59.61%
<7.15 (SEVERE)	4	15.38%	6	23.07%	10	19.23%

Table - 2

HCO3 status at the time of Admission

HCO3	CASE (26)	%	Control (26)	%	TOTAL(52)	%
15-20mEq/l (MILD)	6	23.07%	5	19.23%	11	21.15%
10-14mEq/L (MODERATE)	16	61.53%	15	57.69%	31	59.61%
<10mEq/L (SEVERE)	4	15.38%	6	23.07%	10	19.23%

TABLE-3

Status of pH in cases after giving continuous infusion of Sodium bicarbonate

	Ph < 7.5	Ph > 7.5	P value
CASE(N=26)	6 23.07%	20 76.92%	< 0.05
CONTROL(N=26)	17 65.38%	9 34.61%	

TABLE-4

Mean rise of pH from the time of admission to day 5

SUBJECTS	DAY 1	DAY 3	DAY 5
CASE(N=26)	7.20	7.44	7.52
CONTROL(N=26)	7.19	7.22	7.33

Table - 5

Outcome of patients in relation to PSS scoring

PSS	Case(26)		Control (26)		TOTAL(52)	
	Discharge (22)	Death (4)	Discharge (20)	Death (6)	Discharge(42)	Death (10)
MILD	6	0	5	0	11	0
MODERATE	16	0	15	0	31	0
SEVERE	0	4	0	6	0	10

TABLE-6
SECONDARY OUTCOME

	CASE(N=26)	CONTROL(N=26)	P VALUE
Mean duration of ICU stay	120.65 ± 35.16 hrs	177.14 ± 34.22 hrs	< 0.001
Mean duration under Ventilator	83.2 ± 19.79 hrs	133.81 ± 67.175 hrs	0.0057
Mean duration of hospital stay	186.96 ± 18.38 hrs	256.88 ± 16.97	< 0.001
Convulsion	2(7.69 %)	15(57.69%)	< 0.05
Intermediate syndrome	2(7.69 %)	7(26.92%)	>0.1
Pneumonia	3(11.53%)	15(57.69%)	< 0.05
Total dose of Atropine required (Mean)	387.69 + 123.03 mg	1037.06 + 183.84 mg	< 0.001

OBSERVATIONS:

In our study, out of 52 patients (26 cases and 26 controls) males predominate in both cases and controls (65.38% in cases and 69.23 and % in controls) followed by females (34.61% in males and 30.76 % in controls). Most common age group is 15-30 yrs (61.53% in cases and 65.38% in controls) followed by 31-45 yrs (19.23% in both cases and controls) and least in age group > 45 yrs (19.23% in cases and 15.38 % in controls). Mean age of presentation is 30.076 yrs in cases and 31.961 yrs in controls.

Most common OP compound is Chlorpyriphos + Cypermethrin (23.07% in both cases and controls) ,followed by Cypermethrin (23.07% in cases and 19.23% in controls) followed by Malathion(19.23% in cases) and Endosulphan (19.23% in controls). Most of the patients at the time of admission belongs to Moderate poisoning, according to Poison severity score (61.53% in cases and 57.69% in controls). Most common symptoms were salivation (69.23%), altered sensorium (61.53%), tachypnoea (53.84%). The common signs were constricted pupil (84.61%), pulmonary crepitations (61.53%). Most of the patients at the time of admission showed moderate metabolic acidosis (61.53% in cases and 57.69% in controls, p

value < 0.05) Table -1. Majority had HCO3 level between 10-14 mEq/l (61.53% in cases and 57.69% in controls p value < 0.05) Table-2. After NaHCO3 infusion, most of the cases showed significant rise of pH(Table-3). The mean value of pH at the time of admission were nearly same in both the groups (7.20 in cases and 7.19 in controls) but the subsequent mean rise of pH on day 3(7.44 in cases vs 7.22 in controls) and on day 5(7.52 in cases vs 7.33 in controls) were higher in cases as compared to controls, which was statistically significant (Table-4)

The rate of survival and mortality in cases were 84.61% and 15.38% respectively. In controls the rate of survival and mortality were 76.92% and 23.07% respectively. According to Poison severity score those who are categorised as Mild showed 0% mortality in both cases and controls, those with severe showed 100% mortality in both cases and controls, .(Table-5).

Our study showed that majority of secondary consequences were less in the cases.(Table-6)

DISCUSSION :. In our study out of 52 patients most were males (65.38% in cases and 69.23% in controls) as compared to females (34.61% in cases vs 30.76% in controls) which was in contrast to previous study by Das S.N. et al in Odisha and Balani et al that reported female preponderance[14,15]. Most common age group was 15-30 yrs (61.53% in cases and 65.38% in controls), so younger age group were more prone for OP poisoning. Chlorpyriphos + Cypermethrin was the commonest OP compound responsible for poisoning in both cases(23.07%) and controls(23.07%) which was followed by Chlorpyriphos, Malathion , Dimethoate and Endosulphan. Most of the patients belonged to Moderate poisoning in both cases (61.53%) and in controls (57.69%). Based on symptoms both cases and controls have similar presentation, Salivation was most common symptom (69.23% in cases and 65.38% in controls) followed by altered sensorium (61.53% in both 84% in cases and 50% in controls) and tachypnoea (53.84% in cases and 50% in controls). Such observations were more or less universal in most series. Among the signs constricted pupil is the major sign (84.61% in cases and 76.92% in controls) followed by moist mouth (76.92% in cases and controls) and crepitations (61.53% in cases and 57.96% in controls). Moderate metabolic acidosis was seen in both cases (61.53%) and controls (57.69%) at the time of admission which is similar to study done by Liu 2008 and Roberts 2005[8]. Most of the cases showed significant rise in pH >7.5(7.5-7.55) after continuous infusion of NaHCO3 (76.92%in cases vs 34.61 % in controls) which is similar to study done by Darren .M Roberts and Nick Buckley[11]. The mean value of pH at the time of admission were nearly same in cases and controls (7.20 in cases and 7.19 in controls) but the subsequent mean rise of pH on day 3(7.44 in cases vs 7.22 in controls) and on day 5(7.52 in cases vs 7.33 in controls) were higher in cases as compared to controls.

There was no significant difference in mortality between cases and controls. However there is significant decrease in ICU requirement, ventilator requirement, decrease in incidence of pneumonia and convulsion, decrease in mean duration of ICU stay and under Ventilator stay and duration of hospitalisation thereby reducing morbidity and cost of therapy. All these effects were statistically significant. Such observations have also been made by Balali-Mood et al 2005 which supports our study[13].

CONCLUSION:

Addition of sodium bicarbonate in patients of OP poisoning by continuous infusion although did not alter mortality, but there is significant reduction in ICU requirement, ventilator requirement, decrease in incidence of pneumonia and convulsion thereby decreasing the mean duration of ICU stay, ventilator stay and duration of hospitalisation, thereby reducing morbidity and cost of therapy . So addition of Sodium bicarbonate in patients of OP poisoning is beneficial.

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Original Article

STUDY OF SERUM AND URINARY LEVEL OF CALCIUM AND PHOSPHATE IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Aims And Objective- *Diabetes Mellitus is a pan metabolic disorder which affects many people in the world and they suffer from a number of disorders including bone disease. The study aimed to evaluate the effect of hyperglycemia accompanying diabetes mellitus on the serum and urinary level of calcium and phosphate.* ***Material & Methods*** *- A case control study was conducted with recruitment of a total of 100 research subjects aged 21-80 years in the study period of Sept 2012 to sept 2014. Participants were divided into two groups-50 patients which includes diabetes mellitus detected for first time and those having diabetes mellitus with poor glycemic control and another 50 non-diabetic healthy individuals as control. Blood samples were collected after overnight fasting and analysed for blood sugar, serum calcium and phosphate .Urine sample were also collected for estimation of urinary calcium and phosphate. These 50 diabetic cases were assessed for serum and urinary calcium and phosphate again after 6 wks of euglycemia.* ***Results-*** *Out of 50 diabetic patients(35male and 15female) enrolled in the study, there were significant decrease in the serum Ca and po_4 level between diabetics as compared to non-diabetic subjects. Female diabetics showed a greater reduction in serum Ca & po4 as compared to male diabetics. After follow up there was improvement in serum Ca & po_4 level which were more significant in female diabetics. There was increased urinary excretion of Ca & po_4 under poor glycemic control during admission. Six weeks after euglycemia there was decreased excretion of Ca and po_4 which was more significant in female diabetics.* ***Conclusion-*** *Our results revealed that urinary excretion of calcium and phosphorous decreased relatively when the patients were in glycemic control. The enhanced urinary loss of calcium and phosphorous was related to urinary glucose excretion. The calciuria and phosphaturia was reduced in parallel with the improvement in glycemic control. The lower serum Ca and po_4 level on admission were due to the urinary loss of calcium and phosphrous. Poorly controlled diabetics are more prone to suffer from complications of calcium and phosphate loss like nephrolithiasis, osteoporosis with pathological fractures.* ***Key Words-*** *Diabetes mellitus, Serum calcium, Serum phosphate, Urine calcium, Urine phosphate*

INTRODUCTION

Diabetes mellitus is an ice berg disease. It is a growing public health problem. It is the most common endocrine disease in the world today. Diabetes mellitus is a syndrome of disordered metabolism with inappropriate hyperglycemia due either to an absolute deficiency of insulin secretion or a reduction in the biologic action of insulin or both. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ system.

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Global prevalence of Diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025[1]. According to a Journal of Danish Medical Bulletin, decreased bone mineral contents have been observed in several study of type1 diabetes in comparison with age and sex matched control subjects[2]. In type2 diabetic patient's contradictory results have been obtained. This is due to ceased beta cell function with high insulin doses and poor glucose regulation. In a subgroup of patients having all these risk factors bone mineral content was decreased by some 20% as compared with patients without any risk factors. Bone mineral homeostasis is characterised by increased urinary excretion of bone minerals (calcium, phosphate and magnesium) related to degree of hyperglycemia and insulin doses, by decreased serum concentration of ionized calcium and by increased to normal concentration of phosphate.

Studies have shown patients with poorly controlled Type-2 DM have a higher bone mass[3]. However the influence of changes in glycemic control on bone turnover is not known. To clarify whether metabolic improvement of poorly controlled NIDDM affects bone turnover, marker for glucose, mineral and bone metabolism were assessed. Metabolic improvement caused a reduction in urinary calcium and phosphate and an increase in serum phosphate without change in serum calcium. A recent study also showed that hyperglycemia promotes a significant decline in serum phosphorous without changes in serum calcium[4]. Low serum levels of phosphate are related to the risk of insulin resistance in a healthy population. With chronic hypophosphatemia, the disturbance in post-receptor level indicates insulin resistance. The low phosphate level was responsible for several other defects in diabetics.

AIMS AND OBJECTIVE-

The present study was undertaken with an aim to evaluate the effect of hyperglycemia accompanying diabetes mellitus on the serum and urinary level of calcium and phosphate.

MATERIALS AND METHODS-

A case control study was conducted with recruitment of a total of 100 research subjects aged 21-80, those admitted or attending the OPD Department of internal medicine in the study period of September 2012 to September 2014. Participants were divided into two groups-50 patients of which included diabetes mellitus detected for first time and those having diabetes mellitus with poor glycemic control and another 50 non diabetic healthy individuals as controls. Blood samples were collected after overnight fasting and analysed for blood sugar, serum calcium and phosphate. Urine samples were also collected for estimation of urinary calcium and phosphate. These 50 diabetic cases were assessed for serum and urinary calcium and phosphate again after 6 weeks of euglycemia.

Patients who had diabetic complications like ketoacidosis, hypoglycemic coma and other diseases that interfere with calcium and phosphate metabolism like gastrointestinal, hepatic disease, other endocrine diseases, chronic renal disease and overt bone diseases were excluded from this study.

RESULTS

Out of 50 diabetic patients(35male and 15 female) enrolled in the study, there was significant change in the serum calcium level between diabetic and non-diabetic subjects with mean 8.67±0.07 mg/dl and 9.3 mg/dl respectively.

In table 8 it is shown that female diabetic cases were having increased urinary excretion of phophate (mean=55.64±2.63mg%) as compared to male diabetics(mean=43.9±11.31mg%). But after follow up female diabetics showed a significant decrease in phosphate excretion (mean=35.14±2.82mg%) with a p value <0.001.

TABLE 1
LEVEL OF SERUM CALCIUM IN THE STUDY GROUP

Serum Ca(mg/dl)	Control	Cases on admission	Cases after follow up	P value
<9mg/dl	9	33	20	<0.001
9-10.5mg/dl	41	17	30	
Mean±SD	9.3	8.67±0.07	9.006±0.21	

After follow up there was significant improvement in the Serum Calcium level from 8.67±0.07 mg/dl to 9.006±0.21 mg/dl with a p value <0.001(table1)

TABLE 2- LEVEL OF SERUM CALCIUM IN THE GENDER GROUP

Serum Ca	Control	Cases on admission	Cases after follow up	P value
Male	9.36±0.21	8.84±0.07	9.02±0.21	0.117
Female	9.2	8.26±0.77	8.96±0.14	0.00022

There was significant improvement in the serum Calcium level in female diabetic cases after follow up as compared to male diabetic cases(table2).

Serum level of phosphate were lower among diabetics with poor glycemic control (mean=3.26±1.27mg/dl) in comparison to control group (mean=4.16mg/dl) which showed a significant association(p value=0.001) as shown in Table 3.

TABLE 3 - LEVEL OF SERUM PHOSPHATE IN STUDY GROUP

Serum po4	Control	Cases on admission	Cases after follow up	P value
<3.5mg/dl	7	35	14	<0.001
3.5-5.5mg/dl	43	15	36	
Mean±SD	4.16	3.26±1.27	3.73±0.98	

TABLE 4 - LEVEL OF SERUM PHOSPHATE IN GENDER GROUP

Serum po4	Control	Cases on admission	Cases after follow up	P value
Male	4.2	3.514±1.27	3.80±0.98	0.074
Female	4.26±0.28	2.68±0.49	3.57±0.49	<0.001

As shown in the table 4, female diabetic were having much lower level of serum phosphate (2.68±0.49)as compared to diabetic male(3.524±1.27).But after follow up there were significant improvement in serum phosphate level in female patients as compared to male diabetics with p value 0.001.

There was increased urinary excretion of calcium(mean=34.32±11.31mg%) under poor glycemic control during admission than that of healthy controls (mean=13.73±9.89mg%).But after follow up there was decrease in urinary excretion of Calcium (mean=27.924±9.05mg%) as shown in Table 5 .

TABLE -5 URINARY CALCIUM IN THE STUDY GROUP

Urine calcium	Control	Cases during admission/During OPD basis	Cases after followup	P value
<20mg%	48	5	10	< 0.01
>20mg%	2	45	40	
Mean±SD	13.73±9.89	34.32±11.31	27.924±9.05	

TABLE 6- URINARY CALCIUM IN THE GENDER GROUP

Urine Ca	Control	Cases on admission	Cases after follow up	P value
Male	13.28±6.8	33.08±11.31	28.84±9.05	0.09
Female	12±9.97	37.2±7.77	25.76±14.49	<0.001

In the above table 6 it was shown that female diabetic cases were having increased urinary calcium excretion as compared to male diabetic cases but after follow up there were significant decrease in the urinary calcium level (mean=25.76±14.49mg%) in female diabetics as compared to male diabetics (mean=28.84±9.05mg%)

Similarly there were increased phosphate excretion in diabetic case (mean=47.428±11.31mg%)as compared to controls. After follow up there were significant decrease in phosphaturia (mean=37.514±9.89mg%) (Table-7)

TABLE 7- URINARY PHOSPHATE LEVEL IN THE STUDY GROUP

Urine po4	Control	Cases during admission/OPD basis	Cases after followup	P value <0.05
<27mg%	8	2	7	
27-54mg%	42	29	40	
>54mg%	0	19	3	
Mean±SD	33.26±6.22	47.428±11.31	37.514±9.89	

TABLE 8- URINARY PHOSPHATE LEVEL IN THE GENDER GROUP

Urine po4	Control	Cases on admission	Cases after follow up	P value
Male	32.14±0.35	43.90±11.31	38.53±9.89	0.039
Female	34.94±6.22	55.64±2.33	35.14±2.82	<0.001

DISCUSSION

In the present study we compared several parameters of bone and mineral metabolism in patients with poorly controlled diabetes to those after they achieved improved glycemic control. It is well established that inadequate management and control of hyperglycemia predispose diabetic patients to number of complications. The aim of this study was to compare between serum and urinary level of calcium and phosphate in uncontrolled diabetics and 6wks after correction of hyperglycemia.

In this study, level of serum calcium decreased in patients compared to control with significant effect of hyperglycemia accompanying diabetes[5]. Female diabetics were having much lower serum Calcium level than male diabetics. This may be due to post menopausal osteoporosis. Level of serum phosphate was lower in diabetics in comparison to healthy subjects; this may indicate possible negative feedback effects of hyperglycemia on serum phosphorous[6]. A possible factor contributing these results is that all patients involved in this study were under almost full or at least partial control so that the effect of chronic hyperglycemia is relatively cancelled. Another possibility is that dietary sources of calcium (cheese ,milk, dairy product) are relatively available even for those with limited income ,this in turn could compensate for any deficiency associated with diabetes, so this possibility could be augmented by the fact that a statistical significant difference in phosphorous level between patients and controls.

One of the most common clinical situation in which hypophosphatemia has been found, is poorly controlled diabetes. On initial presentation, total body phosphate stores are usually markedly depleted, but the plasma phosphate concentration may be reduced mildly or moderately. This is due to shift in phosphate from intracellular to extracellular compartment. The

negative phosphate balance is the result of many factors, including decreased dietary intake, but more important is a large increase in urinary phosphate excretion caused by the osmotic diuresis induced by glucose[7].

The enhanced urinary loss of calcium and phosphate related to urinary glucose excretion became reduced in parallel with improvement in glycemic control. The precise cause of hypercalciuria in diabetes is not known. This probably results from a reduction in the tubular reabsorption of calcium and phosphate[8]. In diabetic patients its shown that calcium absorption is independant of alteration in glucose concentration where as in idiopathic hypercalciuria calcium reabsorption is dependent on glucose[9].

CONCLUSION

Hyperglycemia exaggerates urinary loss of calcium and phosphorous in patients with diabetes. Hyperphosphaturia decreases serum phosphorous. Excess urinary calcium seems to be derived from bone. The present results indicate that glycemic control alter calcium and phosphate handling and bone turnover in patients with diabetes. Hence they are more prone to suffer from related complications like nephrolithiasis and pathological fractures.

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Original Article

CLINICAL PROFILE OF DENGUE FEVER IN ADULT PATIENTS IN SOUTHERN ODISHA

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ABSTRACT

Introduction: *Dengue epidemics were reported throughout India, particularly in the last decade. This retrospective study was conducted in a tertiary teaching hospital in Southern Odisha to determine the clinical profile of dengue patients.* ***Materials and Methods:*** *144 patients who were positive for dengue(NS-1, IgM,IgG) by dengue card test was observed. The cases were classified using newer WHO dengue classification(2009) and their clinical signs, laboratory data and outcome were noted. All patients were treated according to WHO protocol.* ***Result:*** *127 patients were classified as non severe dengue{dengue±warning signs}and 17 patients were classified as severe dengue. 57% were males and 43% were females. Male to Female ratio was 1.3 : 1. Mean age was 29 ± 11 yrs. The presenting symptoms were fever(100%), headache (70%), myalgia (76%), nausea/vomiting(63%), arthralgia(52%), rashes(55%), abdominal pain/tenderness(38%), restlessness/lethargy(31%), altered bowel movements(22%), retro-orbital pain(19%), persistent vomiting(15%). Spontaneous bleeding manifestations was present in 13% of patients, gastrointestinal tract being the most common site. The major physical findings included hepatomegaly(17%) and spleenomegaly(6%). The commonest laboratory abnormalities were leucopenia(13%) ,leucocytosis(8%), thrombocytopenia (42%), increased haematocrit (26%), raised SGOT (35%) and raised SGPT (33%).Radiological findings include right sided pleural effusion(15%), left sided pleural effusion(8%) and bilateral pleural effusion(6%), ascites (18%), hepatomegaly (18%),and splenomegaly (10%). Mortality rate is 0.007%.* ***Conclusion:*** *Certain symptoms like hematemesis, malena and findings like increased hematocrit, thrombocytopenia, raised liver enzymes, bilateral pleural effusion and ascites point towards severe dengue. Dengue is a treatable disease requiring close watching for warning signs and frequent monitoring of hematocrit and platelet count along with proper management with IV fluids.* ***Keywords:*** *Dengue Fever, Dengue haemorrhagic fever, Dengue shock syndrome, clinical profile.*

INTRODUCTION

Dengue infection is one of the commonest mosquito borne acute febrile viral haemorrhagic illness. Dengue epidemics were reported throughout the world, but most frequently from the regions of South East Asia. Most of the studies regarding dengue infection/ virus, epidemiological, clinical and management pattern were studied in the region of South East Asia.

Dengue infection presents with varied clinical manifestations ranging from asymptomatic or simple viral illness to severe dengue. Dengue infection has the potential to cause severe bleeding, shock and death. So early diagnosis and recognition of complication is cornerstone in management. Even though dengue infection admissions are common in pediatric age group, adult patient's admissions have also increased in recent years. However, the data about dengue infection among adults are limited. This study was done to get additional data's on dengue infection among adults from Southern Odisha, which is from the regions of South East Asia.

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This study was done in M K C G Medical College, Berhampur which is highly endemic for communicable infectious diseases. This study deals with clinical and laboratory profile of dengue infection among adults from Southern Odisha.

MATERIALS AND METHODS

This study was done in adult (>14 yrs) patients admitted to General Medicine ward of M K C G Medical College Hospital, Berhampur from October 2011 – June 2013. All patients with clinical features of Dengue infection and positive for Dengue Card Test were taken up for the study. Their clinical profile, laboratory parameters and outcome were recorded.

All the patients were evaluated for

Clinical Features like :

Fever, headache, retro orbital pain (ROP), myalgia and arthralgia, abdominal pain, nausea/ vomiting, diarrhea/ constipation, sleeplessness/lethargy, persistant vomiting, conjunctival injection, hepatospleenomegaly, rashes, bleeding manifestations, plasma leakage manifestations

Laboratory parameters evaluated where complete blood count, renal function – Urea, Creatinine, Na^+, K^+, Blood sugar, Liver Function Test, Chest X-ray (PA) view, Ultra-Sound of Abdomen, Dengue Test (Rapid Card Test).

Statistical Analysis

The relationship between the frequencies of clinical parameter of Non severe dengue {dengue fever with and without warning symptoms} and severe dengue were analyzed after construction of 2x2 table and applying the Statistical Test of significance using Fisher's Exact test.

Exclusion criteria

Patients with Malaria, Enteric fever, Leptospirosis and Pneumonia were excluded by doing appropriate investigations.

Dengue patients were classified into two groups-

Non severe Dengue and Severe Dengue according to WHO TDR[1]. Non severe Dengue includes those dengue patients with and without warning symptoms.

Following WHO criteria was adopted to classify dengue:

DENGUE WITHOUT WARNING SIGNS - PROBABLE DENGUE

Live in/travel to dengue endemic area. Fever and 2 of following criteria : Nausea / Vomiting, Rash, Aches and pains, Tourniquet test positive, Leucopenia. Any warning signs.

DENGUE WITH WARNING SIGNS

Abdominal pain or tenderness, Persistent vomiting, Clinical fluid accumulation. Mucosal bleed, Lethargy; restlessness, Liver enlargement >2cm. Laboratory: Increase in HCT concurrent with rapid decrease of platelet count.

SEVERE DENGUE

1. Severe plasma leakage leading to:
   - Shock (DSS)
   - Fluid accumulation with respiratory distress
2. Severe bleeding as evaluated by clinician
3. Severe organ involvement
   - Liver: AST or ALT>=1000
   - CNS: Impaired consciousness
   - Heart and other organs

RESULTS

Totally 144 patients were included in the study. 127 (88.2%) patients were classified as Non-severe Dengue and 17 (11.8%) patients are classified as having Severe Dengue. Out of the 127 Non severe Dengue patients, 68 (53.5%) patients were classified as Dengue without warning signs and 59 (46.5%) were classified as Dengue with warning signs. Out of the total 144 patients, 82 (57%) were male patients and 62 (43%) were females. Male to female ratio was 1.3:1. Mean age was dengue patients is 29 + 11 years. Of the total Dengue cases 75% of the cases occurred in the month between September and November.

Table 1
CLINICAL SYMPTOMS

SYMPTOMS	Total (n=144)	Non severe dengue (n=127)	Severe dengue (n=17)	P value
Head ache	101 (70%)	85 (67%)	16 (94%)	0.0229*
Myalgia	110 (76%)	103 (81%)	07 (41%)	0.0014**
Arthralgia	75 (52%)	57 (53%)	08 (47%)	0.7973
Retro orbital pain	27 (19%)	23 (18%)	04 (23%)	0.5263
Nausea vomiting	90 (63%)	74 (58%)	16 (94%)	0.0030**
Abdominal pain/tenderness	54 (38%)	42 (33%)	12 (70%)	0.0060**
Altered bowel movements	31 (22%)	27 (17%)	04 (24%)	0.7623
Persistent vomiting	21 (15%)	17 (13%)	04 (24%)	0.2760
Restlessness/lethargy	34 (31%)	34 (27%)	10 (58%)	0.0111*
Rashes	79 (55%)	68 (54%)	11 (65%)	0.3069

*****statistically significant, **very significant

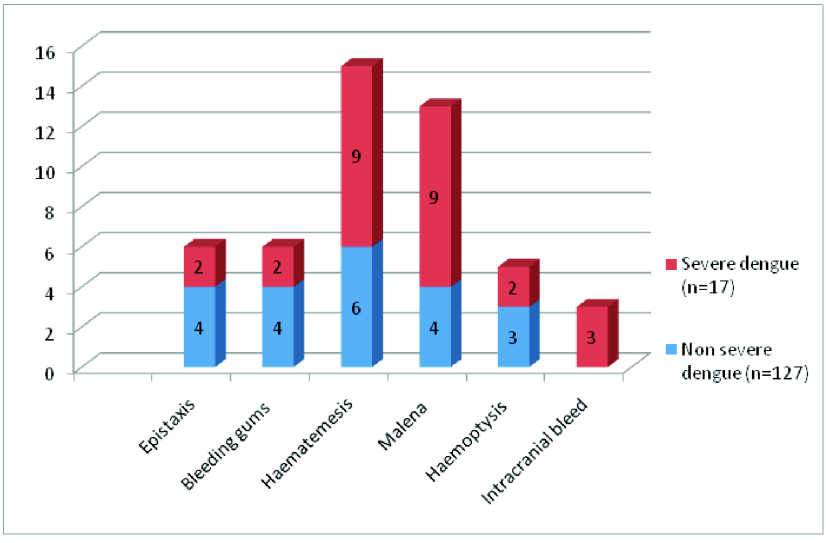
Table 2
LEUCOCYTE , PLATELET COUNT AND HEMATOCRIT

LEUCOCYTE COUNT	Total (n=144)	Non severe dengue (n=127)	Severe dengue (n=17)	P value
Leucopenia TC < 4000	19 (13%)	15 (12%)	04 (23%)	0.2430
Leucocytosis TC > 11000	11 (8%)	09 (7%)	02 (12%)	0.6197
Normal Leucocyte Count	114 (79%)	103 (81%)	11 (65%)	0.1011
Platelets count < 100000	60 (42%)	43 (34%)	17 (100%)	0.0001***
Haematocrit >45%	38 (26%)	28 (22%)	10 (59%)	0.0270*

Table 3
PLATELET COUNT DISTRIBUTION

PLATELET COUNT DISTRIBUTION
81,000 – 1,00,000
61,000 – 80,000
41,000 – 60,000
21,000 – 40,000
11,000 – 20,000
<10,000

FIGURE 1 : SPONTANEOUS BLEEDING MANIFESTATIONS



In the rapid card test for Dengue, number of patients who showed NS_1 Ag positive were 82 (57%) patients. 97 (67%) patients were IgM positive, 68 (47%) patients were IgG positive, 44 (30%) patients were positive for both IgM and IgG. 86 (60%) patients had primary infection while 68 (40%) had Secondary infection. In severe dengue , 04 patients had primary infection and 13patients had secondary infection

Fever occurred in all patients. Mean duration of fever was 5.1 + 1.6 days. High grade fever was present in 86(60%) patients and low grade fever is present in 68(80%). Mean duration of fever in non severe dengue patients was 4.9 days and in severe dengue patients was 6.4 days. Headache (70%), Myalgia (76%), Nausea/vomiting (63%), arthralgia (52%), rashes (55%) were the common symptoms. Headache, myalgia, nausea/vomiting, abdominal pain/ tenderness, restlessness/ lethargy were statistically significant symptoms. (Table-1). Conjunctival congestion was found in 54 (38%) of the patients. Hepatomegaly and spleenomegaly was found in 24 (17%) and 8 (6%) cases respectively. Total no. of patients with spontaneous bleeding manifestations were 19 (13%). In that, hemetemesis 15 (78%) and malena 13 (68%) were the most common bleeding manifestations. (Fig.1)

Complete blood count was almost normal in all the patients except for variation in WBC count and platelet count. Leucopenia (TLC < 4000/cmm) was found in 13% of patients. About 42% (60) of the patients had platelet count less than 1,00,000 /mm^3. Mean platelet count in thrombocytopenia patients was 47816/mm^3. Mean platelet count in severe dengue patients was 19588/mm^3. Thrombocytopenia was found in 60 (42%) of the patients. This was found to be highly statistically significant. Increased haematocrit (>45%) was found in 26% of the patients. (Table 2 & 3).

Liver function test are abnormal in 55 patients. Bilirubin was found to be raised in 13 patients.Mean bilirubin in patients who had abnormal LFT was 1.16 mg/dl. Mean SGOT is 113 IU. Mean SGPT was 95 IU. Mean bilirubin in severe dengue patients was 1.55 mg/dl. Mean SGOT was 140 IU. Mean SGPT was 120 IU. Renal function tests were abnormal in 3 (0.02%) patients. Pleural Effusion was present in 28% (41) of the patients. In that right sided pleural effusion was found in 21 patients, left side in 11 and bilateral in 9 no. of patients. Out of 144 patients 26 (18%) of the patients had ascites. 53% of the severe dengue patients had ascites and this was found to be highly statistically significant. 26 (18%) patients had hepatomegaly and 14 (10%) had splenomegaly.

IV fluids was given to 53% of the patients.Vasopressors was given to 6 (4%) patients. Blood transfusion was given to 5 (3%) patients and Platelet transfusion to 7 (5%) patients. Of all the dengue patients treated, one patient died of intractable shock. Case fatality rate was 0.007%.

DISCUSSION

This study describes the clinical profile, laboratory features, radiological findings and outcome of dengue fever in adult patients.

In this study totally 144 patients were included. In that 127 (88%) were classified as non- severe dengue (Dengue ± warning signs) and 17 (12%) were classified as severe dengue. This is in contrast to the Abhinav jain et al where only 3% patients had severe dengue[2].

Dengue infection commonly occurred in males (56%). Other studies like Malavige et al reported 58% males, NP Singh et al reported 75% males, Janak Kishore et al reported 66% males. This study also showed male preponderance and this is due to the male outdoor activity compared to that of female which might have caused more mosquito bites[3,4,5].

Mean age in this study 29 + 11 yrs, M:F ratio was 1.4:1 and age distribution was 13-40 yrs. Age distribution, mean age, male:female ratio are comparable to that of other studies. Mean age, age distribution, M:F ratio in Malavige et al study was 26.6 yrs, 13-56 yrs, 1.4:1 and in NP Singh et al study was 26 + 10 yrs, 12-29 yrs, 3:1 and Janak Kishore et al study was 30 + 14 yrs, 15-30 yrs, 2:1 respectively[3,4,5].

Malavige et al study and Adriana O et al study showed that primary infection occurred in 34% of the patients whereas in the present study primary infection reported in 60% of patients[3,7].

Fever has been documented in 100% of all the adult dengue studies including the present study. The mean duration of fever in the present study was 5.1 + 1.6 days, whereas in Malavige et al was 4.7 days and Janak Kishore et al was 5.9 days and NP Singh et al was 4.5 ± 1 days[3,4,5].

The common clinical manifestations in the present study is similar to that of other adult dengue studies. In the present study, Headache (70%), Myalgia (76%) Arthralgia (52%), Nausea / vomiting (63%) and the Rashes (53%) were the common symptoms. This findings were in accordance with that of the study conducted by Malavige et al where Headache (66%), Myalgia (76%), Arthralgia (57%), Nausea/ vomiting (63%) and NP Singh et al where Headache (61.6%), Myalgia (57.8%), Nausea/ vomiting (50%) were reported[3,4].

An increased incidence of gastro-intestinal symptoms is noted in this study. In this study about 38% had abdominal pain in contrast to 20% reported by Seema Awashi et al and 15% reported by Malavige et al and 21% reported by NP Singh et al[3,4,8]. This symptom is also highly statistically significant in severe dengue patients. This symptom was predominantly noted in the early leak phase and is attributed to hepatomegaly and serosal inflammation.

12% of the patients presented with spontaneous bleeding and is similar to that described by Seema Awashi et al (8%), Kabra SK et al (8%)[8,9]. But increased incidence of bleeding manifestations were reported Malavige et al (39%) and NP Singh et al (40%)[3-4]. The gastrointestinal tract was the predominant site of bleeding observed in the present study and is comparable to other series reported by Sharma et al from india and Chairulfatah et al from indonesia[10-11]. Hematemesis (31%) and Melena (30%) were the common bleeding manifestations.

Hepatomegaly was described as a common clinical presentation by WHO and also studies conducted by Malavige et al[3] (45%) and Pradeep et al (45%)[3]. In the present study it is reported in 17% of patients but this is statistically significant in severe dengue patients. Spleenomegaly was present in a very low percentage of patients and is similar to other reports in india.

Thrombocytopenia is a common finding in dengue infection and is reported in 42% of the patients in the present study. This is very less when compared

to that reported by Seema Awashi et al (84%), Malavige et al (74%) and Janak Kishore et al (70%)[3,5,8]. The degree of thrombocytopenia is related to the severity of infection and in the present study it is present in all severe dengue patients and is highly statistically significant finding.

Increased hematocrit is related to increased severity and is due to increased vascular permeability which is the basic pathophysiology in dengue. In the present study, higher hematocrit was related to more severe infection and the difference was statistically significant. The incidence in this study 26% is similar to studies like Malavige et al (26%) and Rachel Daniel et al (27.9%)[3,12].

Leucopenia (TC<4000) was found to be present in 13% of the patients and leucocytosis was present in 11% of the patients in present study. But increased incidence of leucopenia has been reported by Abhinav jain et al (64%), Malavige et al (31%) and Firdous Jahan et al (32.5%)[2,3,13].

Liver function tests were abnormal in 39% of the patients, particularly elevated transaminases in the present study. This is due to virus induced damage to the hepatocytes, hypoxia, shock or associated liver disease. In the present study the elevation of liver enzymes (SGOT, SGPT) were highly statistically significant in severe dengue patients. Elevated liver enzymes are also reported by Janak Kishore et al (49%), Sharma et al (90%) and in other studies[5,10].

Pleural Effusion was present in 28% of the patients in the present study whereas it was reported by Rachel Daniel et al (13.2%), Malavige et al (16%), NP Singh et al (2%)[3,5,12]. But pleural effusion is reported to be present in 76% patients by Sudhir Kumar Verma et al[14]. In the current study right sided effusion in 15%, left sided effusion in 8% and bilateral effusion in 6% was present. Sudhir Kumar Verma et al reported right sided effusion in 40%, left sided effusion in 0% and bilateral effusion in 36% of the patients[14].

Ascites was present in 18% of the patients in present study. This is in contrast to that reported by by Sudhir Kumar Verma et al (84%) and Adriana O et al (56%)[7,14]. In Malavige et al study 17% had ascites and in NP Singh et al study 2% had ascites[3,4].

OUTCOME

Out of the 144 patients, 0.02% patients developed renal failure while Seema Awashi et al reported renal failure in 1% of the patients[8]. They have reported encephalopathy in 0.3% of the patients and in this study encephalopathy is found in 2%[8].

In the present study, the mortality rate was 0.007% which is very less when compared to other indian studies like Janak Kishore et al (5%) and Bhaskar et al (14%) and is attributable to the close monitoring and early recognition of complications due to plasma leakage and treating them accordingly, mainly with IV Fluids[5,15].

CONCLUSION

In this study, the notable features were the high proportion of severe dengue cases associated with gastrointestinal symptoms and also with increased hematocrit and thrombocytopenia. When compared with previous studies, the clinical profile of dengue is everchanging. Dengue is a treatable disease provided close watching for warning signs and frequent monitoring of hematocrit and platelet count along with proper management with IV fluids.

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Original Article

STUDY OF THYROID FUNCTION IN PATIENTS WITH HIV INFECTION ON ANTIRETROVIRAL THERAPY

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M. Nageswar,*** Sudeep K.N***

ABSTRACT

Background: *There are only a few studies on thyroid dysfunction in HIV patients on ART in India. This study was undertaken to find the prevalence of hypothyroidism in HIV patients on ART and to find the pattern of thyroid dysfunction as well as correlation between ART and hypothyroidism.* ***Method:*** *The present study was conducted on 84 HIV patients taking ART for more than a year attending MKCG Medical College and Hospital on a non randomized prospective cross sectional study basis. Patients with known hypothyroid / sub clinical hypothyroid status, active opportunistic infections, AIDS related neoplasia, severely ill patients, neuro/pituitary/hypothalamic disease, pregnancy were excluded from the study.* ***Results:*** *Majority of patients in our study were found to have normal thyroid parameters. The prevalence of thyroid dysfunction in the study population was 10.7%.* ***Conclusion:*** *Subclinical hypothyroidism was the most common abnormality observed in the study population .The patients whom we evaluated comprised predominantly of males. There is no significant co-relation between hypothyroidism and age, sex, duration of illness, duration of anti retroviral therapy, on CD4 count.* ***Key words:*** *Hypothyroidism, HIV, AIDS, Antiretroviral therapy, HAART.*

INTRODUCTION

Human immunodeficiency virus (HIV) infection causes progressive destruction of part of the immune system. With time, a characteristic and relatively specific group of infections and malignancies develops; these make up the acquired immunodeficiency syndrome (AIDS).

HIV infection is a global pandemic, with cases reported from virtually every country. At the end of 2011 , an estimated 34.2 million individuals were living with HIV infection, from 28.9 million in 2001 according to UNAIDS (united nations programme on HIV/ AIDS)[1].

HIV infection is a chronic, systemic diseased possibly leading to multi- organ involvement and affecting the endocrine system as well. Among the individual infected with HIV, 1-2% experience overt thyroid disease and 35% may have abnormalities in thyroid function test finding [2,3]. In patients with advanced disease a variety of opportunistic infections that infect or infiltrate the thyroid gland and can cause increase or decrease in T4 secretion[4]. Cases of thyroiditis have been reported in association with pnemocystis jirovecii infection, Cryptococcus neoformans infection, CMV, visceral leishmaniasis and suppurative bacterial infections[5,6,7,8]. which recover after treatment of infection.

Antiretroviral therapy has changed the evolution of HIV infection. It has decreased the mortality and morbidity in HIV. It also has altered the clinical course of subclinical opportunistic infections and can induce autoimmune disease and endocrine dysfunction[7,9]. ART has increased the prevalence of thyroid function abnormalities like subclinical hypothyroidism[2,10,11,12,13]

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and clinically evident hyperthyroidism, in particular Graves disease [9]

Beltran et al found that subclinical hypothyroidism was associated with the use of stavudine and a lower CD4 count[2]. The cumulative daily dose of both stavudine and lamivudine was significantly related to the presence of hypothyroidism in Grappins series[11].

In view of the variability of thyroid function in patients with HIV on antiretroviral therapy in previous studies it was decided to undertake a prospective observational study on thyroid function in HIV patients on ART in stable clinical condition in our institute MKCG Medical College and Hospital, Berhampur, Odisha.

MATERIALS AND METHODS

This hospital-based observational study was done over a period of 22 months (November 2011 to August 2013) on 84 HIV positive patients on ART for more than 1 year attending the Medicine OPD or admitted in Medicine ward and ART centre.

The detection of HIV infection was done by ELISA (Enzyme Linked Immuno Sorbent Assay). The kit contains antigens for both HIV- I and HIV- II and use both natural and recombinant antigens.

Diagnosis of HIV infection in the included cases was done at ICTC (Integrated Counseling and Testing Centre) as per the NACO guidelines. Informed consent was taken in each case as per NACO ethical guidelines. Children below the age of 18years were excluded from this study.

Detailed history, clinical examination and investigations were done as necessary like, CBC, Urine routine and microscopy, ESR, HBsAg, LFT, RFT. CD4 cell count was done by FACS (flow assisted cell sorting) calibre technique by using BD FACS calibre machine.

The thyroid hormone assay (TSH and FT4) were done by Chemiluminescence Immuno Assay (CLIA) using ADVIA Centaur equipment.Anti-TPO antibody estimation was done by ELISA.

RESULTS

Among the 84 patients included in our study, 54 patients were male (64.2%) 30 patients (35.8%) female. Majority of the patients (60.7%) were in the age group between 30 and 39 years.

In this study population, no patients were having features of hyperthyroidism. In the study 9(10.7%) patients were having thyroid dysfunction and 75 (89.3%) patients of the study population were euthyroid.

In this study 9(10.7%)patients had having thyroid dysfunction and 75 (89.3%) patients were euthyroid.

Most common thyroid dysfunction was subclinical hypothyroidism which was prevalent in 5.9(5) of the study population, 2.4%(2) had overt hypothyroidism and 2.4%(2) had low T4 syndrome. No patient had features of hyperthyroidsm.(Table-1). Six patients had clinical features of hypothyroidism but only 2 patients had raised TSH level.

In this study population 2 patients have raised TSH level and have clinical features of hypothyroidism in favour of overt hypothyroidism.

The association between features of hypothyroidism and raised TSH is statistically significant as the p value is(0.02) significant. (Table-2)

According to age wise distribution, thyroid dysfunction is most prevalent in 40 – 49 yrs group followed by 30 – 39 yrs group and no case from the elderly age group above 60 years of age was reported.

In this study group, 6(11.2%) out of 54males are affected and 3(10) out of 30 females were affected. The distribution of thyroid dysfunction between the sex groups showed no statistical correlation as the p (0.87) value is not significant. Thyroid abnormality among the HIV positive patients was equally distributed in both the groups.

The TSH in this study is of range from 0.72 mU/L to 28.45 mU/L and free T4 levels ranging from 0.10ng/dl to 1.56 ng/dl. The mean free T4 value was 1.03±0.23ng/dl and the mean serum TSH values were 3.73±3.46μIU/ml. The mean values for free T4 was shifted towards lower side of normal range.

TABLE – 1
DISTRIBUTION OF THYROID PROFILE

THYROID STATUS	No. OF PATIENTS	PERCENT(%)
OVERT HYPOTHYROIDISM	2	2.4
SUBCLINICAL HYPOTHYROIDISM	5	5.9
LOW T4 SYNDROME	2	2.4
NO THYROID DYSFUNCTION	75	89.3

TABLE – 2
DISTRIBUTION OF HYPOTHYROIDISM IN OUR STUDY

TSH	FEATURES OF HYPOTHYROIDISM	NO FEATURES OF HYPOTHYROIDISM	P VALUE
INCREASED	2	5	0.02
NORMAL	4	73	

TABLE 3: ASSOCIATION BETWEEN DRUG [illegible] TION

DRUGS	TOTAL NO. OF PATIENTS	NO. OF PATIENTS AFFECTED	PERCENTAGE	P-Value
AZT	37	3	8.10	
D4T	47	6	12.7	0.27
3TC	84	9	10.7	
NVP	77	9	11.6	

The CD4 count in thyroid abnormal patients and in normal patients showed a difference with a mean of 373 and 434 respectively and the range of the CD4 count was 126 – 546in the thyroid dysfunction group and in thyroid normal patients 135 – 835. The CD4 count in thyroid abnormal patients is in lower side. But the correlation between CD4 count and thyroid dysfunction could not be established. (Table-3)

The predominant drug regimen was with stavudine, lamivudine and nevirapine, in both thyroid normal and abnormal group. Among the study population those patients who were treated with stavudine had increased prevalence of thyroid dysfunction 6 (12.7%) in comparison to patients treated with other drugs. But there was no statistical correlation between these different drug regimens and the thyroid status. (Table-4)

TABLE – 4: ASSOCIATION BETWEEN DRUG & THYROID DYSFUNCTION

(AZT – Zidovudine, 3TC – Lamivudine, NVP – Nevirapine, d4T – Stavudine.)

The duration of drug regimen in the thyroid abnormal population was of 28 ± 5 months and for the normal population was 24 ± 7 months. There was no correlation between duration of ACT and thyroid dysfunction. (Tabl-5)

TABLE –5: ASSOCIATION BETWEEN DURATION OF ILLNESS AND THYROID DYSFUNCTION

THYROID FUNCTION	DURATION OF DRUG IN MONTHS MEAN SD	P-VALUE
ABNORMAL	28±5	0.100
NORMAL	24±7	

The duration of illness in both the groups was nearly the same with abnormal group displaying a mean of 32 ± 7 and normal group displaying a mean of 30±7 months. The duration of illness and thyroid dysfunction was statistically in significant.

DISCUSSION

From this study population of 84 HIV positive patients who were on ART for more than 1 year.

The mean age of patients in this study was 38± 9, which was comparable to study group of Madeddu et al and Beltran et al.[2,12]

In our study the overall male population were more than their female counterpart, with a sex ratio of 1.8 in favour of males. The prevalence of thyroid dysfunction was found to be more in male than female. There was no statistical correlation between gender and thyroid dysfunction.

There are no studies available that has data available on thyroid dysfunction and gender influence in HIV patients on ART.

The thyroid dysfunction prevalence in our study was 10.7%. Madeddu et al reported a prevalence of 12.6% of thyroid dysfunction in their study group on ART and Grapin et al noted that 12.3% presented with at least one abnormal test of thyroid[11,12]. Beltran et al had reported 16% prevalence of thyroid dysfunction[2]. Abnormal thyroid function test was detected in 16% of patients in Thailand study[15].

In our study population 2.4% patients had overt hypothyroidism which is similar to the findings of beltran et al reporting 2.6% patients having overt hypothyroidism, 6.6% subclinical hypothyroidism, and 6.8% having isolated low T4. However, in a study reported by Nelson *et al*., a higher than expected incidence of overt hypothyroidism was found in patients receiving ART, and they recommend universal screening of subjects for any thyroid dysfunction, who are treated with ART. The highest prevalence of thyroid function parameter abnormalities during ART observed in this study points to hypothyroidism, in particular subclinical hypothyroidism. The population of subclinical hypothyroidism in our study was 5.9% .

A French study of 212 HIV-infected patients found that, 8.5% had subclinical hypothyroidism.[11] Calza et al. also reported a high prevalence (12.2%) of subclinical hypothyroidism among HIV-infected patients receiving ART[3].

An even higher prevalence of subclinical hypothyroidism (17.4%) was observed in a German study, but a small number of patients were included in that study[16]. In contrast, Collazos et al. reported a lower prevalence, of 3.5%, in a study on Spanish population of 202 patients[10].

Isolated low FT4 incidence in our study was 2.4%. Isolated low FT4 incidence showed marked variation in each of the population studied. While generally the mean FT4 was on the lower side of normal, isolated low FT4 incidence was reported in a widely distributed spectrum of values. Collazos et al. found 1.3% of the determinations of free thyroxine to be below the normal limits which is comparable with our population result[10].

Beltran et al observed an increased prevalence 6.6% of low FT4 in their study, whereas Madeddu et al observed an incidence of about 2.7% in their patients[2,12]. An even higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving ART, had this abnormality[20]

Drug regimens in our study comprised three drug regimen :

(1) AZT+3TC+NVP taken by 30 patients (2)d4T +3TC+NVP taken by 47 patients and (3) AZT+3TC taken by 7 patients.

The drug regimen consists of following drugs – zidovudine, stavudine, nevirapine, lamivudine. The 2nd drug regimen was consumed by larger population and those patients who were treated with stavudine had increased prevalence of thyroid dysfunction (12.7%) in comparison to patients treated with other drugs.

There was no statistical significance on the correlation between drug regimen and thyroid abnormality in our study population. Similar correlation by Afhami et al found no significance on the association of these drug regimens[20].

Madge et al in their cohort study showed neither ART regimen nor specifically stavudine use was significantly associated with either overt hypothyroidism or subclinical hypothyroidism which was in contrast to the findings of correlation between stavudine use and thyroid abnormality by Madeddu et al.[12,19]

The duration of drug regimen and correlation with thyroid dysfunction was of no statistical significance and this is in coordination with the findings of Quirino et al who found no significant relationship between the condition and drugs or CD4 cell count and reinforced by Afhami et al with no association between drug duration and thyroid abnormality[20].

Longer duration of disease in HIV-infected patients treated with ART might allow the development of autoimmune thyroiditis as observed by Beltran et al[2]. The observed values on the effect of duration of illness on the thyroid abnormality revealed no significant association in our study, statistically. Afhami et al observed that duration of HIV infection is not a significant risk factor of hypothyroidism in HIV-infected patients on ART[20].

CONCLUSION

· The prevalence of thyroid dysfunction in the study population was 10.7%. Subclinical hypothyroidism was the most common abnormality observed in the study population. Overt hypothyroidism and isolated T4 syndrome is observed in minority of cases. Statistical significance was not seen in association drug regimen and thyroid dysfunction, but patient treated with stavudine had more thyroid abnormality than treated with any other drug. Subsequent studies with larger sample may throw some light on this association. Screening of thyroid parameters is warranted in this population in view of increasing prevalence of the study population.

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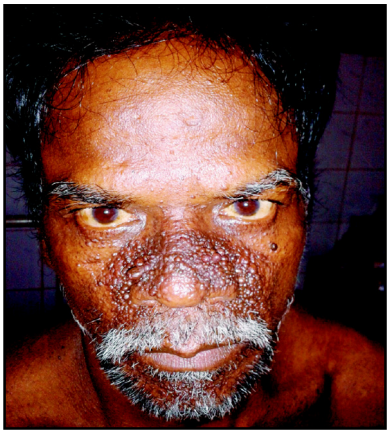
Pictorial CME

TUBEROUS SCLEROSIS

S.N. Das* , P.K. Rout, M. Pattnaik**, S. Sethy***, N.R. Parida#, D. Mahali#**



Photograph showing
Adenoma Sebaceum over face.

A 56 years aged patient was admitted with history of fever, headache, generalised bodyache for six days. There was no history of mental retardation, family history was not suggestive. On examination there was mild pallor, there was presence of adenoma sebaceum over face. Systemic examination revealed no other abnormalities.

Routine examinations including complete blood count, RFT, LFT were normal. Ultrasonography of abdomen & pelvis was normal . CT scan revealed no abnormality.

The classical clinical triad of TSC symptoms are mental retardation, seizures, and cutaneous angiofibroma (formerly called adenoma sebaceum]. Mental retardation and seizures are both neurologic manifestations of TSC. The overall incidence of mental retardation is 38 percent to 80 percent in TSC, while epilepsy is one of the most prevalent manifestations of TSC, occurring in more than 80 percent to 90 percent of patients with TSC .

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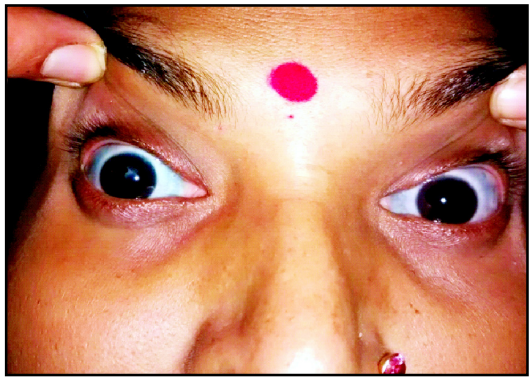
Facial angiofibromas ("adenoma sebaceum"): A rash of reddish spots or bumps, which appear on the nose and cheeks in a butterfly distribution. They consist of blood vessels and fibrous tissue. This socially embarrassing rash starts to appear during childhood and can be removed using dermabrasion or laser treatment. Other dermatological menifestations are hypomelanic macules ("ash leaf spots) , Shagreen patches: Areas of thick leathery skin that are dimpled like an orange peel,pigmented and usually found on the lower back or nape of the neck , *café au lait* spots or flat brown marks, and poliosis, a tuft or patch of white hair on the scalp or eyelids.

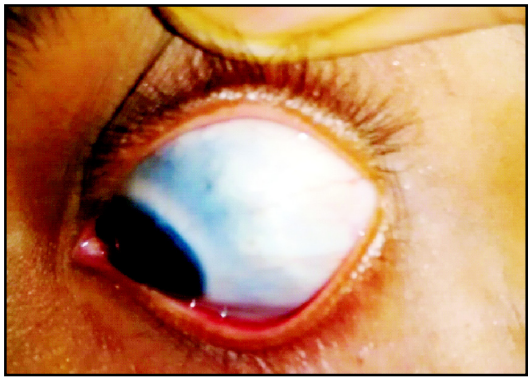
TSC is an autosomal dominant disease that is associated with gene mutations of TSC1 or TSC2, encoding hamartin and tuberin, respectively . However, two-thirds of cases are caused by sporadic mutations, and this may also contribute to the underdiagnosis of TSC cases without the classic triad. In our patient's case there was no family history of TSC, suggesting that this case was sporadic, though TSC gene mutations were not evaluated in our patient.Individuals with tuberous sclerosis may experience none or all of the clinical signs discussed above

Pictorial CME

SCLEROMALACIA

G. Bhattacharya*, A. Malla*, S. Sukriya*, R.R. Sahoo, B.K. Das*****





Scleromalacia of both the eyes, with visible pigmented uveal tissue. A systemic workup revealed rheumatoid arthritis as the cause of scleromalacia in this patient.

Scleromalacia occurs in the setting of necrotizing scleritis without inflammation. There is exposure of the underlying uveal tissue with thinning of the surrounding sclera. The area of scleral lack is surrounded with pathological vessels anastomosing with each other or crossing the abnormal area to join with perilimbal vessels. Scleromalacia may lead to perforation (scleromalacia perforans) which can result in loss of vision secondary to progression of astigmatism, anterior uveitis, cataract or glaucoma.

This condition is commonly associated with severe, progressive, long standing rheumatoid arthritis with extra-articular manifestation, more frequent in women. It was also described in other systemic vasculitic and collagen disorders (up to 66%) like systemic lupus erythematosus, polyarteritis nodosa, wegener's granulomatosis, behçet disease, limited cutaneous scleroderma, crohn's disease, graft-versus-host disease and rarely in porphyria and herpes-zoster infection.

Histopathologically, changes in the scleral nodules are similar to those of the subcutaneous nodules of the rheumatoid arthritis i.e. chronic granulomatous changes with epithelioid cells surrounding central, necrotic masses (collagen and noncollagen fibers, cell debris). Three determinants of scleral destruction are activation of scleral fibrocytes and resorption of pericellular matrix, infiltration of the scleral stroma by inflammatory cells, prolonged local vaso-occlusion.

We present the photograph of a 50 year old woman who had rheumatoid arthritis for more than 10 years with scleromalacia of both the eyes but no other extra articular manifestations.

There is no specific and efficacious therapy. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids are insufficient. Topical sodium versenate (an inhibitor of collagenolytic enzyme) and topically used cyclosporine A are used with some success. Irrespective of the final diagnosis, autoimmune reaction (type III hypersensitivity) is responsible for the vessels damage. So immunosuppressant drugs like cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil etc are used. Also biological agents like etanercept, infliximab, daclizumab, anakinra, rituximab, alemtuzumab have been tried.

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Case Report

RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS IN TYPE1 DIABETES MELLITUS WITH KETOACIDOSIS: A CASE REPORT

M.R. Kundu[*], M. Parida[*], R. Mohanty[**], N. Mohapatra[**], P.K. Thatoi[***], P. Jena[***], S. Khadenga[***], S. Rout[*]

ABSTRACT

Rhino-orbital-cerebral mucormycosis(ROCM) is a are opportunistic invasive fungal infection, with rapid progression and high mortality.It is usually associated with several immunocompromised states including Diabetis mellitus,haematological malignancies, haematopoetic stem cell or solid organ transplantation.It is characterised by an aggressive necrotizing infection spreading from the nose to the paranasal sinuses,orbit and the brain.Typical initial symptoms are facial pain and swelling,headache,fever,blood tinged rhinorrhoea which rapidly progress to facial or orbital cellulitis,proptosis,visual loss and facial nerve palsy.Definitive diagnosis of ROCM requires radiological and histopathological examination.Optimal therapy requires prompt institution of appropriate antifungal therapy,reversal of underlying conditions and surgical debridement of devitalised tissues.We report a case of 20 year old male patient with Type1 Diabetes mellitus who presented with Ketoacidosis and developed right sided proptosis, ophthalmoplegia, visual impairment and multiple cranial nerve palsies after 3 days of hospitalisation.Radiological and histopathological examination confirmed ROCM. He was treated with Amphotericin B and discharged after partial improvement with residual visual loss. ***Key words:*** *Diabetes mellitus, ketoacidosis, mucormycosis.*

INTRODUCTION:

Mucormycosis is an opportunistic and frequently fulminating fungal infection caused by members of family Mucoraceae,order Mucorales and class Zygomycetes.Among them are Rhizopus, Mucor, Absidia and Cunningmella species which are ubiquitous fungus.

The major predisposing factors for acquisition of mucormycosis are uncontrolled diabetes mellitus (DM) with ketoacidosis, haematological malignancies, haematopoitic stem cell transplantation, solid organ transplantation and immunusupression[1]. Mucormycosis manifest as rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated forms of disease. Rhino-orbito-cerebral mucormycosis is the most serious rapidly progressive fatal form of the disease with a mortality rate of 70-100% if not treaeted adequately[2].Rapid progression and high mortality necessitate prompt diagnosis and aggressive treatment to increase survival.

CASE REPORT:

A 20 year old male patient was admitted to the hospital with complaints of pain abdomen,vomiting, breathlessness and altered sensorium for 1day.He was a known Type1 diabetic and had discontinued injection Insulin for last few days. On examination he was drowsy, febrile(temp 101^0F), tachypnoeic with acidotic breathing. He was of thin body built, dehydrated, Heart Rate=110/min RR=40/min,BP-90/60mmHg.Systemic examination revealed no abnormality.Laboratory investigaton showed with TLC=16000/cmm, DC –

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Neutrophills 80%, lymphocyte 20%, Hb-10gm%, RBS-540mg/dl, HbA1c-9.86%, C-peptide value=.48ng/ml(.81-3.85), urine-pus cells 4-6/hpf, sugar +++ and urine ketone bodies positive. His liver function and renal function tests were normal. ABG Analysis showed pH=7.28,pCO_2= 12,HCO_3- 5.9 with base excess of -17.3, SpO_2 =94% Anion gap =28.5.So with a diagnosis of Type1 DM with ketoacidosis, treatment with IV fluids,Insulin and broad spectrum antibiotics was begun and the patient improved clinically and biochemically.On the third day he developed ptosis, pain in right eye and diplopia. On the next day he developed proptosis, complete ophthalmoplegia, chemosis and loss of vision of right eye.(Fig.1) Examination revealed Cranial nerve II, III, IV, V_1,V_2 VI and VII LMN palsies on the right side. On nasal examination, patient was found to have black necrotic mass on right nostril. Thus a provisional diagnosis of Rhino-orbital-cerebral mucormycosis was made.

MRI scan of brain, paranasl sinuses and orbit showed enhanced mucosal thickening involving the sinuses with saggy enhancement of right ethmoid right sphenoid, right maxillary, right intraconal contents suggestive of chronic inflammatory entity.

On ENT evaluation by endoscopy black necrotic debris was found in the right nostril extending posteriorly to nasopharynx. Endoscopic curettage and biopsy was done and sent for histopathologiccal and microbiological study. KOH mount revealed broad non septate branched hyaline hyphae which on culture revealed Rhizopus species.

Histopathological study of tissue collected by nasal endoscopy showed broad ribbon like branched nonseptate hyphae suggestive Mucormycosis and final diagnosis of Rhino orbital cerebral mucormycosis (ROCM) was made.(Fig.2) He was put on Inj. Amphotericine B (lyophilised) for 14 days. Patient and his relation did not consent for surgical intervention. At time of discharge patient's general condition had improved but the eye signs showed partial improvement. His left eye remained unaffected.

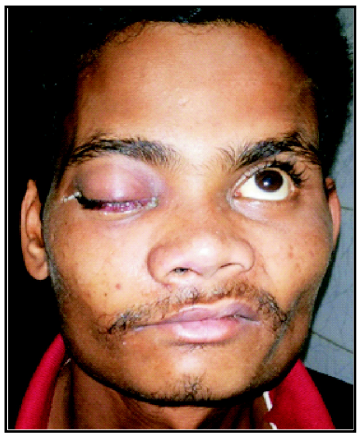

Fig 1:Patient's picture showing ptosis proptosis, facial palsy,cellulitis on right side

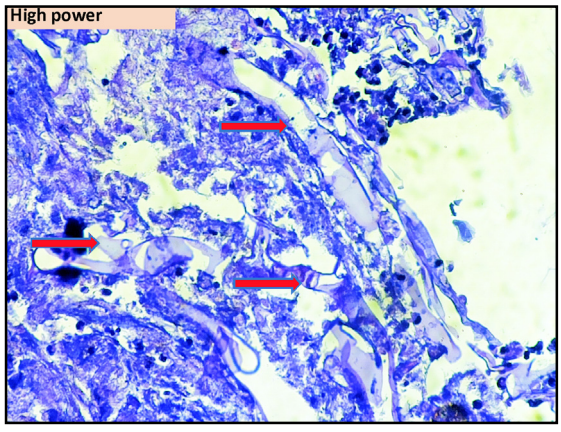

Fig 2:Histopathology slide showing broad ribbon-like branched nonseptate hyphae (Red arrow)

DISCUSSION:

Mucormycosis is an increasingly emerging lifethreatening infection. Out of all the clinical forms, Rhinocerebral variety is the most common and fatal form of the disease and presents in 35-50% of all the cases of mucormycosis[3]. Poorly controlled diabetes mellitus particularly if associated with ketoacidosis is an important predisposing factor for development of ROCM. It is estimated that diabetes is present in 36%-88% of cases of mucormycosis[4]. Mucormycosis is usually initiated by inhalation of spores. Diabetic ketoacidosis is associated with impairment in neutrophill function including chemotaxis,adherence and oxidative

burst. Acidosis decreases the neutrophil chemotaxis and phagocytosis,inhibits the iron binding of transferrin resulting in increased proportion of unbound iron which promotes the fungal growth as mucor is highly ferrophillic[5]. Mucormycosis primarily causes tissue and blood vessel invasion.Secondary effects are the development of thrombus,haemorrhage and tissue necrosis, causing local destruction of affected organs; further the resulting hypoxic environment promotes the fungal proliferation.[5] Rhizopus species alone responsible for 60% of total mucormycosis and 90% of rhinocerebral cases[6].

Typical clinical presentation includes nasal congestion, dark blood tinged rhinorrhoea or epistaxis, sinus tenderness, retroorbital pain, headache , fever, malaise, lethargy, cellulitis, presence of black eschar on palate or nasal mucosa. Proptosis, ptosis, chemosis, painful ophthalmoplegia and diminished visual acuity are the ominous clinical findings of orbital involvement. Loss of vision can occur with retinal artery thrombosis[1].

Our patient was a young patient of uncontrolled Type1 DM with ketoacidosis which was an important risk factors for development of mucormycosis. He developed ptosis, proptosis, ophthalmoplegia and visual loss along with multiple cranial nerve palsies on right side. There was black necrotic mass in his right nostril which prompted us to suspect ROCM.

A definite diagnosis of mucormycosis requires direct identification of characterstic hyphae and/or recovery of the organism in the culture from specimen obtained from the site of infection. Histopathology of a biopsy material from deep tissue if available is specific and reliably establishes the diagnosis of mucormycosis. In our patient the diagnosis of ROCM was established by culture and histopathology.

Optimal therapy requires prompt institution of appropriate antifungal therapy, reversal of underlying predisposing condition and where possible, surgical debridement of devitalised tissues.Medical management alone is not effective because of poor drug delivery to the site of infection due to extensive vascular thrombosis[7]. Our patient responded partially to antifungal treatment after recovery from ketoacidosis. Though visual loss persisted in right eye, his left eye remained unaffected. Jung at el and Sachdeva K in their case series reported 100% mortality in ROCM with diabetic ketoacidosis[8-9].

CONCLUSION:

ROCM is an acute opportunistic fungal infection which follows an invariably fulminant course in diabetic patients.Sinusitis with acute onset of blurred vision or diplopia or ophthalmoplegia in adiabetic patient should prompt careful clinical, radiological and histopathological evaluation for mucormycosis.Early diagnosis and prompt aggressive treatment can reduce the mortality of this lethal fungal infection.

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Case Report

DEEP VEIN THROMBOSIS ASSOCIATED WITH DENGUE FEVER: A CASE REPORT

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ABSTRACT:

Dengue virus infection may result in a wide spectrum of clinical illness ranging from mild flu-like syndrome to severe haemorrhagic manifestations and shock. Thrombotic events have not been frequently reported despite the increased procoagulant activity during the illness[1-4]. We present here a case of extensive Deep vein thrombosis in lower limb associated with dengue fever proved serologically. ***Key words:*** *Dengue fever, Deep vein thrombosis*

INTRODUCTION:

Dengue infection can be either asymptomatic or may result in a wide spectrum of clinical illness ranging from mild flu-like syndrome to the most severe forms of the disease characterised by coagulopathy,increased vascular fragility and permeability. Haemorrhagic events of different degrees have often been described in Dengue, but thrombotic events have not been extensively reported, despite wide range of increased procoagulant activity during the illness[1-4].

CASE REPORT:

A male patient aged 28 years was admitted to our hospital with the presenting complaints of fever with chills, myalgia, arthralgia, headache for 2days.On examination he was febrile, other vital parameters were stable with mild pallor and hepatomegaly.His blood picture showed normocytic normochromic anemia with haematocrit of 46%,TLC=5800/cmm, TPC=2.8lacs/cmm. Malaria parasite antigen test was negative and routine blood and urine examinations were normal.He was positive for Dengue NS_1 antigen on ELISA assay. His liver function test showed slight rise in transaminases and renal function tests were normal. Hepatitis A,B,C&E virus infection were ruled out serologically. He was treated symptomatically with oral fluids and antipyretics. After 3 days of hospitalisation he became afebrile but developed unilateral swelling of left lower limb and pain and was unable to move his leg or walk. On physical examination diffuse swelling and tenderness of his whole left leg was seen and Homan's sign was positive.We suspected deep vein thrombosis and investigated accordingly. There was no history of venous catheter placement in his lower limbs or any past or family history suggestive of venous thromboembolism.

Colour Doppler of both lower limbs showed evidence of deep vein thrombosis in the left Common femoral, superficial and deep femoral, popliteal, proximal part of posterior tibial vein and extending upwards upto left external illiac vein and thrombos seen projecting and extending to proximal great and short saphenous vein, with dilated great and short saphenous vein(distal part). USG abdomen and pelvis revealed no abnormality. 2D Echocardiography and Doppler ultrasonography of portal and mesenteric veins were normal. Screening of inherited thrombophillia did not reveal any abnormality.His Antithrombin III was 96.00% (80-120), Antiphospholipid antibodies IgM=1.80(<10),

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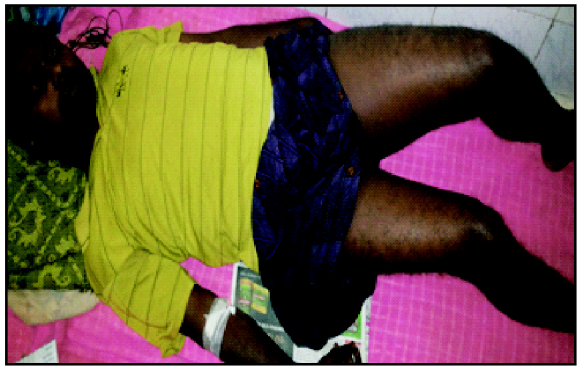

Fig 1: Swelling of the left lower limb

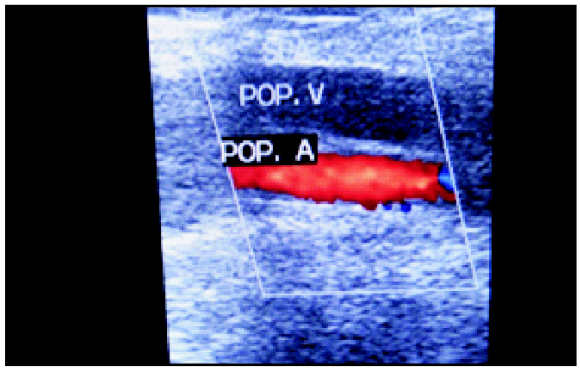

Fig 2:Colour Doppler of left poplitealvein

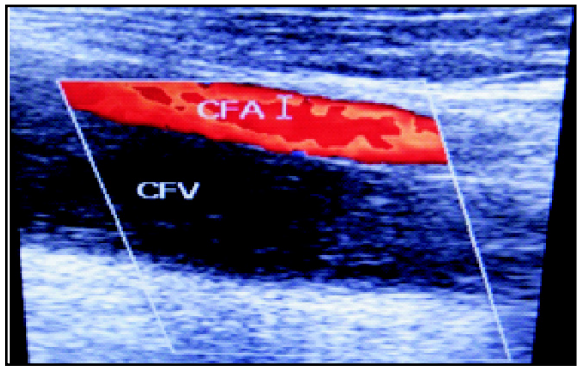

Fig 3: Colour Doppler of left femoral vein

IgG=2.77(<10)u/ml were normal. He was screened for protein C and protein S deficiency and prothrombin mutation analysis was done. Protein C(functional) was 54.00% (70-140), Protein S was 39.00%(60-140),both were found to be deficient. His D-Dimer was 300ng/ml(0-200ng/ml),prothrombin time PT=15.6, aPTT=36.1 , INR=1.15 . His lipid profile was Total cholesterol=176 mg/dl, TG=142mg/dl, HDL=14mg/dl, LDL=106mg/dl, VLDL=28 mg/dl.

Based on these reports with the risk of life threatening pulmonary embolism, the patient was started on subcutaneous Enoxaparin(low molecular wt. Heparin) 60mg twice daily for 2 weeks with twice weekly monitoring of aPTT, platelet count and INR. Warfarin was started on the tenth day of Enoxaparin and advised to continue the same and return for follow up every two weeks. At the time of discharge (after 2 weeks) he had improved partially and his INR was 2.

DISCUSSION:

Many factors may increase thrombotic complications in Dengue fever[1-5]. Dengue virus causes down regulation of the thrombomodulin-thrombin-protein C complex formation at the endothelial surface, with a reduction of activated protein C(APC). APC is the most important vasoprotective protein and downregulation of this anticoagulant pathway promotes thrombosis and amplifies the inflammatory and apoptotic processes and endothelial vascular cell dysfunction. Low concentration of plasma anticoagulants protein C, Protein S and Antithrombin III have been detected in severe Dengue [2,4]. Disseminated Intravascular Coagulation and consequent microthrombi formation may contribute to thrombus formation but have not been associated with large vessel thrombosis[1]. Host antibodies may be formed against Dengue non-structural protein that have cross reactivity with the host endothelial cell, which can lead to inflammatory response[5]. Increased PAI-I (plasminogen activator inhibitor) plasma levels have also been observed[3]. Antibody against phospholipids, cardiolipin and lupus anticoagulant have also been associated with thrombotic events in peripheral and cerebral vasculature[6].Venous cerebral thrombosis and ischemic stroke not associated with any risk factor have been rarely reported with dengue fever[7].

Our patient had protein C and protein S deficiency which was detected during the course of his illness. As his coagulation profile, TPC,Antithrombin III, Antiphospolipid antibodies were normal and he had

no history of thrombotic events earlier, deficiency of Protein C and Protein S could have contributed to his thrombotic event. Our patient had increased levels of D-dimer,but had no haemorrhagic complications and his vitals remained stable throughout his disease course. Few cases of DVT have been reported in direct association with Dengue fever.[1,6,8, 9] Recently deep vein thrombosis associated with dengue fever has been reported in a 11 year old boy in India with illiofemoral deep vein thrombosis associated with serologically confirmed infection with Dengue virus[8].Five cases of large vein thrombotic events associated with acute phase of dengue fever have been reported from Brazil, out of which two patients had illiofemoral DVT, two patients had pulmonary thromboembolism and one patient had mesenteric thrombosis. Increasd levels of IgM antibody against phospholipids was found in four patients and D-dimer level was increased in all the five patients. None of the patients had haemorrhagic manifestations[9].

CONCLUSION:

Thrombotic complications are possible in Dengue infection.Physicians should be aware of these thrombotic complications as the dilemmas in treating a blood clot in a Dengue patient who is at risk for excessive bleeding are very challenging.

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Case Report

SITUS INVERSUS WITH DEXTROCARDIA ASSOCIATED WITH VSD : A CASE REPORT

M Sanjay*, B.K. Behera, B. Pattnaik***, P.C. Biswal****, S.K. Rout*, M. Sooraj*, S.K. Mishra***

ABSTRACT

Incidence of congenital cardiac anomalies in dextrocardia with situs inversus is very low globally. We report a case having this rare anomaly situs inversus with dextrocardia associated with perimambranous VSD with MVP, PAH, TR. ***Key words :*** *Situs inversus, Dextrocardia, Congenital heart disease.*

INTRODUCTION :

Situs inversus(SI) is a rare congenital anomaly, in which there is general transposition of viscera due to reverse rotation including heart which rotates to right side and all abdominal organs are laterally transposed i.e. all visceras normally on right are on left and vice versa. The heart is structurally normal in 90% cases. Incidence of cardiac anomalies in dextrocardia with SI is low (3%), while in isolated dextrocardia it is high. Situs inversus occurs in 2 per 20,000 live births[1]. Recent research on mice suggests that situs inversus is caused by the absence of a single protein due to particular mutation on chromosome 12.

CASE REPORT

A girl aged 25 years from Badula, Ganjam, presented with a history of shortness of breath for last 2 months. On general examination pulse was 100 beats per minute, irregularly irregular, blood pressure was 108/86 mm Hg and respiratory rate was18 breaths per minute, JVP was not raised. Apex beat was on right 5th intercostal space in anterior axillary line parasternal heave on right parasternal region. Cardiac dullness detected on right side, liver dullness on left side and tympanic note over right hypochondrium on percussion. on auscultation there was loud pulmonary component of second heart sound in right second intercoastal space and pan systolic murmur of grade 4/6 in right fourth intercoastal space.

Investigations :

ECG: atrial fibrillation with tall Rs pattern and r/s pattern >1 in V1.RS pattern in V3 and V4. (Fig.1)

X- Ray chest (P-A view) - Evidence of Dextrocardia with apex pointing towards right cardiomegaly, fundic gas on right side. (Fig.2)

2-D Echocardiogram and Color Doppler:

Echocardiography demonstrated dextrocardia with ejection fraction of 68%, large VSD at peri-membranous position with left to right shunt, Mitral Valve Prolapse (MVP), Pulmonary Arterial Hypertention (PAH) and Tricuspid Regurgitation (TR). (Fig.3)

USG of Abdomen and Chest showed liver in left hypochondrium, dilated Inferior Vena Cava and hepatic veins, spleen in right hypochondrium, evidence of dextrocardia. (Fig.4)

Thus summarising findings on clinical examination like apex beat in right 5th inter coastal space in anterior axillray, ECG findings, USG of abdomen suggestive of liver in left hypochondrium and 2 D Echocardiogram with color Doppler showing dextrocardia with VSD,

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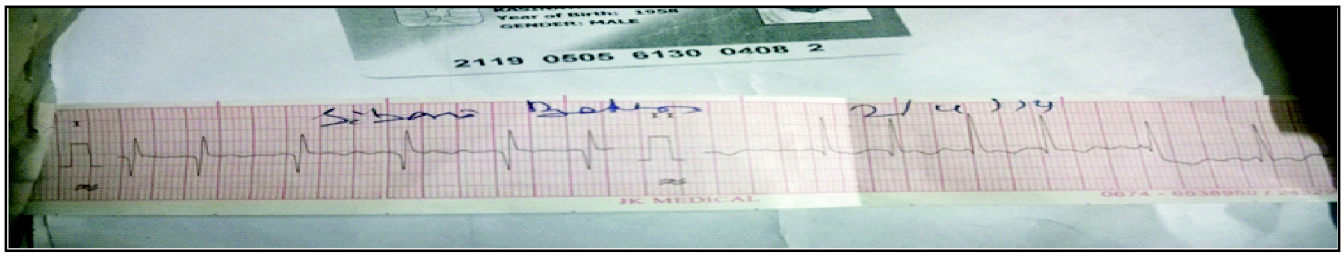

Fig 1 : ECG.

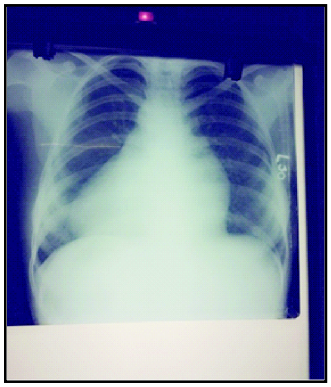

Fig 2 : Chest X-ray PA view showing cardiomegaly with dextrocardia

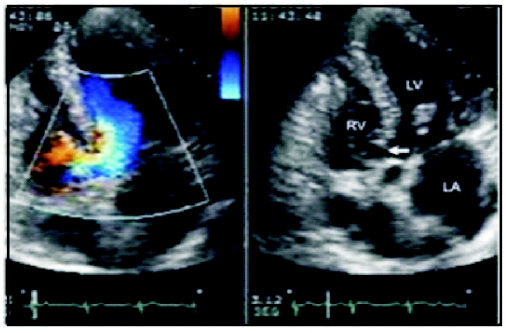

Fig 3 : 2D Echocardiogram showing large perimembranous VSD with MVP.

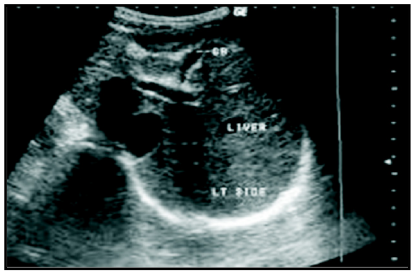

Fig 4 : USG of abdomen showing liver on left side and spleen on right side.

the final diagnosis made was: Situs inversus with dextrocardia associated with VSD.

Discussion

Situs inversus with dextrocardia also is termed as situs inversus totalis because the cardiac position as well as atrial chambers and abdominal viscera, is a mirror image of normal anatomy[2-5]. Situs inversus is present in 0.01% of the population of United States[4].Person having situs inversus with dextrocardia without other congenital anomaly experience normal longevity of life and have a similar risk of getting acquired disease as that of other person of same age and sex group. If angina pectoris or myocardial infarction occurs, the pain is located in the right anterior chest with radiation to the right shoulder and right arm. Symptoms related to acquired disorder may lead to discovery of suspected cardiac malposition. The recognition of situs inversus is important for preventing surgical mishaps that result from the failure to recognize reversed anatomy and atypical history[2,4]. Patients with situs inversus may have associated cardiac malformations such as VSD, ASD, Tetralogy of Fallot, tricuspid atresia, pulmonary stenosis, single ventricle, AV canal defect; but transposition of great arteries probably the most common. Presentation varies depending on associated malformation[2, 3, 6, 7, 8].

Peri-membranous VSD are much common in Caucasian and have a relatively low incidence of AR, whereas sub arterial VSD in the outlet septum are more common in Asian and have a relatively high incidence of AR. In

contrast to the equal sex distribution in uncomplicated VSD, the male to female ratio is as high as 2:1 when AR supervenes. Interestingly this patient had situs inversus totalis with cardiac lesions Perimembranous VSD, MVP, PAH and TR.

Medical Management

Digoxin, oral anticoagulants, Diuretics, Vasodilators, Oxygen, Rest, Salt restriction etc.

Advice

Surgical correction of VSD

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Case Report

STURGE WEBER SYNDROME : A CASE REPORT.

S.N. Das* , P.K. Rout, M. Pattnaik**, S. Sethy***, N.R. Parida#, D. Mahali#**

ABSTRACT

Sturge–Weber angiomatosis is a rare, nonhereditary developmental condition characterized by a hamartomatous vascular proliferation involving the tissues of brain and face. A report of a case with facial port wine stains, gingival overgrowth, and dilated ocular vessels is described. ***Keywords:*** *Angiomas, , port wine stain, Seizures, Sturge–Weber syndrome.*

INTRODUCTION

Sturge–Weber syndrome (SWS) belongs to a group of neurocutaneous disorders collectively known as the phakomatoses ("mother-spot" diseases)[1]. It consists of congenital hamartomatous malformations that may affect the eye, skin and central nervous system (CNS) at different times, characterized by the combination of venous angiomas of leptomeninges, face, jaws and oral soft tissues. SWS was first described by Schirmer in1860. More specific description was given by Sturge in 1879.

SWS is believed to be caused by the persistence of vascular plexus around the cephalic portion of the neural tube. This plexus develops during the sixth week of intrauterine development but normally undergoes regression during ninth week[2].

Angiomas of leptomeninges are usually unilateral, located in parietal and occipital region. The presence of angioma results in alteration of vascular dynamics causing precipitation of calcium deposits in cerebral cortex underlying the angioma. Seizures, mental retardation, hemiplegia, or hemiparesis may develop secondary to this and their severity depends on the extent of lesion[3].

The cutaneous angiomas are called port wine stains, which usually occur unilaterally along dermatomes supplied by the ophthalmic and maxillary division of trigeminal nerve[2,4]. It may be bilateral or totally absent or may extend to neck, limbs and other parts of the body. Involvement of the area supplied by ophthalmic division is pathognomic. Ocular involvement can result in glaucoma, choroidal hemangioma, buphthalmos, or hemianopis[4]. Intraorally angiomatosis may involve lips,

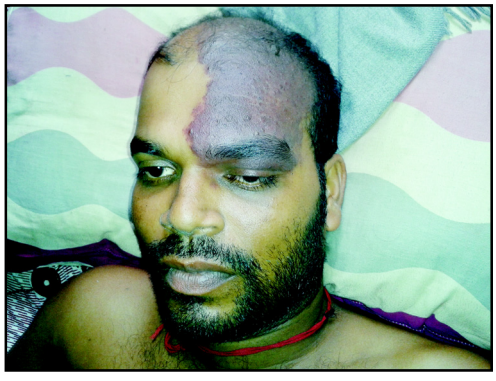

Fig.1 : Hemangioma over left upper part of face.

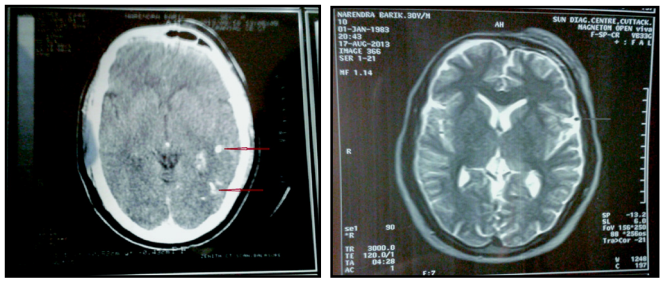

Fig.2 : MRI of brain revealed a vascular malformation over left parietal cortical vein along with calcifications over left parieto occipital lobe

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buccal mucosa, palate, gingiva, and floor of mouth. This syndrome is of rare occurrence and management becomes complicated due to risk of hemorrhage[5].

Case report:

A 30 year old male was admitted with recurrent seizures, fever for 2days. Past history & family history was not contributory. On examination patient was drowsy, febrile, a large hemangioma covering left upper half of the face and left eye was detected(Fig.1). Patient had left hemiparesis. All routine investigations including Hb%, DC, TLC, ESR, RFT, LFT were normal. FBS was 235mg/dl, 2 hour PGBS was 345mg/dl. So a diagnosis of Sturge Weber syndrome with Type 1 DM was made. MRI scan of brain revealed a vascular malformation over left parietal cortical vein along with calcifications over left parieto occipital lobe(Fig.2).

DISCUSSION

Port wine stains represent hamartomatous capillary malformations and are named so due to the deep red hue that they leave on the skin or mucosa. Such lesions characteristically bleed profusely when traumatized[6].

Not all patients with facial port wine stains have Sturge – Weber angiomatosis. Only patients with involvement along the distribution of the ophthalmic branch of trigeminal nerve are at risk for the development of full condition . SWS is referred to as complete when both CNS and facial angiomas are present and incomplete when only one area is affected without the other. The Roach scale is used for classification[3].

Type I- Both facial and leptomeningeal angiomas; may have glaucoma

Type II – Facial angiomas alone; may have glaucoma

Type III – Isolated leptomeningeal angiomas; usually no glaucoma

Differential diagnosis includes Rendu-Osler-Weber syndrome, angio-osteodystrophy syndrome, Maffuci's syndrome, Von Hippel Lindau disease, and Klippel Trenaumy-Weber syndrome[7].

Treatment and prognosis depends upon the nature and severity of clinical features. Presence of port wine stain can cause deep psychological trauma to patient and development of personality is affected in almost all patients. Portwine stains can be improved by dermabrasion, tattooing, and flash lamp pulsed dye lasers.

Intraoral involvement is common, resulting in hypervascular changes to the ipsilateral mucosa.[8-10] The gingiva in the present study showed hemangeomatous proliferation that felt soft on palpation and blanched under pressure. Such gingival overgrowth might be attributable to increased vascular component[9-11].

Conclusion.

Management of patient with Sturge–Weber syndrome may be challenging due to the risk of hemorrhage. Extra care must be taken when performing surgical procedures in the affected areas of mouth

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Case Report

AN UNUSUAL CASE OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH FOOT DROP

R.R. Sahoo[*], S. Behera[**], S. Sukriya[**], B.S. Behera[***], B.K. Das[#]

ABSTRACT

Peripheral neuropathies are relatively uncommon in systemic lupus erythematosus (SLE). Foot drop due to vasculitis is an unusual presentation in SLE. We describe a case of a 26 year old male with SLE who developed sudden onset right foot drop. Electrophysiological study showed no response in right common peroneal nerve. He was put on corticosteroids and hydroxychloroquine which resulted in significant improvement in several clinical parameters but failed to improve foot drop. ***Keywords:****Systemic lupus erythematosus(SLE),foot drop, vasculitis.*

INTRODUCTION

Systemic lupus erythematosus(SLE) is the prototypic immune complex disease characterised by excessive autoantibody production, immune complex formation and immunologically mediated tissue injury[(1)]. In SLE, tissue damage is multi-organ and is caused by autoantibodies and immune complexes, however, non-immunological processes like early atherosclerosis may also be involved[(1)]. The course of the disease is marked by flares alternating with remissions. Ninety percent of patients at diagnosis are women of child bearing years and prevalence is highest in black women and lowest in white men[(2)].

The neurological manifestations include the central nervous system, cranial and peripheral nerves and psychiatric manifestations include psychosis and severe depression. Neuropsychiatric lupus (NPSLE) is the commonly used terminology for a group of clinical features which includes intractable headaches (unresponsive to narcotic analgesics), seizures(focal or generalised), chorea, psychosis, psychoneurosis, neurocognitive dysfunction, organic brain syndrome, cerebrovascular accidents(paresis or subarachnoid hemorrhage), cranial neuropathies (visual defects, blindness, papilledema, nystagmus or ptosis,tinnitus, vertigo or facial palsy)[(3)]. Abnormalities of the optic nerve head manifested by papilledema or optic atrophy may also be seen. The pathogenesis is attributed to vasculitis or presence of anticardiolipin antibody syndrome[(3)]. Besides, non immunological mechanisms involve premature atherosclerosis, endocarditis leading to embolism[(3)]. A true vasculitis with inflammatory cell infiltrate, fibrinoid necrosis has rarely been demonstrated in brain pathology[(3)]. An increased incidence of antineurofilament antibody has been found in patients with SLE who have diffuse neuropsychiatric manifestations[(3)].

Incidence of peripheral neuropathy in SLE ranges from 20-27%[(4,5,6)]. It includes motor, sensory or mixed motor and sensory polyneuropathy or mononeuritis multiplex[(3)]. An acute ascending motor paralysis like GBS has also been reported. Transeverse myelitis has been observed in patients with SLE[(3)]. Pathophysiological mechanisms are multi factorial.Histopathological findings have varied from axonal degeneration with or without vasculitis, demyelination to immune mediated neuropathies[(7,8,9)].

The incidence of acute onset footdrop is extremely rare in lupus and there is no available data. It is presumed to be associated with vasculitis in vasa nervorum. It is difficult to estimate the incidence of vasculitis in lupus due to difficulties in accessing a blood vessel that can be subjected to an invasive procedure. Reports of vasculitis are mainly anecdotal

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and based on clinical manifestations. Vasculitis in SLE is due to a complex interplay between immune cells, endothelial cells, deposition of autoantibodies, and immune complex deposition.Reports of small- and medium-vessel vasculitis involving all the major organs including the skin, gastrointestinal (GI), pulmonary, cardiac, and genitourinary systems have been reported.We report a case of male SLE with foot drop as a presenting feature.

Case Report-A 26 year old male patient was admitted with chief complaints of irregular fever for 10 months, symmetric polyarthralgia of small and large joints for 8 months, erythematosus rash over face for 6 months, pain and swelling over left thigh for 1 month and dragging of his right foot for 20 days. His family members also reported delusional behaviour for several days prior to admission.He had no history of chronic cough,diarrhea, weight loss, oral ulcer, dry eye , dry mouth, Raynauds phenomenon, tightening of the skinor difficulty in standing from sitting position or combing hairs. He was a known alcoholic for last 5 years..On examination, the patient was emaciated with mild pallor, diffuse alopecia, increased pigmentation over chest and abdomen and had cellulitis of the left thigh. Examination of the nervous system revealed slow mentation, intact cranial nerves, atrophy of proximal and distal groupsof muscles of upper and lower limbs,

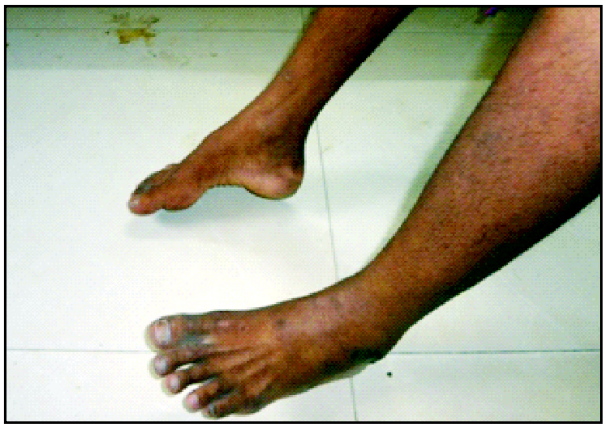

Figure 1-Foot drop(Right)

normal power(left lower limb could not be tested due to cellulitis), right foot drop(Figure 1), diminished deep tendon reflexes, normal plantar response and sensory loss over right L5 dermatome.There was no peripheral nerve thickening. Gait was high stepping on the right side. There was no abnormality in the other systems. He was then put on injection dexamethasone, 1mg /kg body weight, hydroxychloroquin, 6.5mg/kg body weight and antibiotics with a diagnosis of SLE flare, foot drop (right) with cellulitis of the left thigh. Clinical improvement was marked after 10 days but he continued to have intermittent attacks of delusional behaviour and footdrop persisted.A foot drop splint helped his mobility but bolus cyclophosphamide could not be initiated due to cellulitis. His neuropsychiatric manifestations and other clinical parameters improved with time but foot drop persisted and he was discharged on request after 3 weeks with oral prednisone, 1mg/kg and hydroxychloroquine, 6.5mg/kg and asked to follow up after 6 weeks.

Laboratory investigations-Hb – 11.4 g/dl, TLC – 14200 cells/cu.mm, DC-N84L12E3M1, TPC-2.4 lacs/cmm, ESR – 55mm/hr, Urine-Albumin-Nil Sugar-Nil RBC-Nil/HPF Pus Cell-4-6/HPF, Hbs Ag-Neg, HCV-Neg, HIV-Neg, FBS –100mg/dl, S.Urea – 18mg/dl, S.Creatinine – 0.9 mg/dl, S.Na – 139mEq/l, S.K – 3.9mEq/l, LFT- S.Total BR – 0.7mg/dl, Direct – 0.3mg/dl, SGOT – 72IU/L, SGPT – 74IU/L, ALP–459IU/L, S. TSH-1.99uu/ml, T4-7.15ug/dl, T3-0.75ng/ml, CRP – 65.9 mg/lt(Normal(N)-0-1mg/lt), RA – 7.6 Iu/ml(N-0-20Iu/ml),CPK-18 u/ lt (N-25-200 u/ lt),ANA – 3+ SPECKLED(Figure 2), ENA PROFILE- SS-A ++ RNP/Sm + dsDNA+, C3 – 96 mg/dl(N-75-180mg/dl), C4 – 33 mg/dl(10-40mg/dl), LDH – 1158U/L(N-140-280U/L), Chest X-ray – Normal, USG Abdomen and Pelvis – Hepatomegaly with fatty change, USG of left thigh- Myositis, EMG – Myopathic pattern, NCV– Decreased CMAP amplitude in right common peroneal nerve.

DISCUSSION

SLE is an uncommon autoimmune disorder that primarily affects women in the child bearing age group.

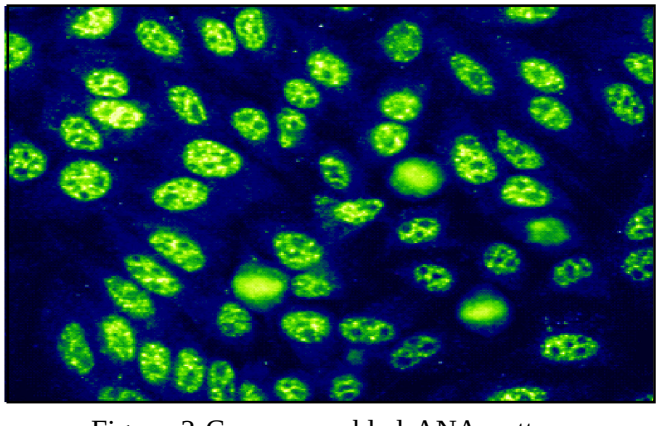

Figure 2-Coarse speckled ANA pattern

Male lupus are very rare and the clinical manifestations are invariably severe. Our case had SLE with cutaneous, neuropsychiatric manifestations besides foot drop which is an unusual presentation. There is one case report of SLE with sudden onset foot drop as the initial presentation[10]. Evaluation revealed antibodies against ganglioside GM1 and electrophysiological study showed axonal impairement. Biopsy of the sural nerve was consistent with vasculitis.

The postulated mechanism of foot drop in SLE is vasulitis of vasanervorum[11]. As the diagnosis of vasculitis in lupus is often based on the clinical presentation,a high index of suspicion is often required. Confirmation depends on sural nerve biopsy but it could not be done in our case since the patient was very sick and the procedure is not routinely done in our setting. We evaluated other causes of foot drop which are more common than lupus.The causes of foot drop are nerve injury due to trauma,leprosy, hip or knee replacement surgery,brain or spinal injuries (stroke, multiple sclerosis, cerebral palsy, Charcot-Marie-Tooth disease), muscle disorders(muscular dystrophy, polio, ALS)[12]. We excluded the common causes through physical examination and routine investigations.The foot drop in our case was probably due to SLE per se.

The peripheral neuropathy in lupus responds to immunosuppressants. In case of vasculitis high dose steroids, cyclophosphamide bolus (15mg/kg) monthly for six doses or azathioprine (2mg/kg) orally may be considered[13]. Patient could not be given cyclophosphamide in view of persistent cellulitis of the thigh and following recovery of infection patient wanted to be relieved.

CONCLUSION

We report a 26 year old male presenting with SLE flare and footdrop ,which is a rare clinical manifestation in lupus.Vasculitis is a common cause for acute onset foot drop. Electrophysiological studies and sural nerve biopsy are necessary for confirmation of diagnosis.

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Case Report

SINGLE CORONARY ARTERY - A CASE REPORT

T.K. Mishra*

ABSTRACT

Coronary artery anomalies (CAAs) are a diverse group of congenital disorders whose manifestations and pathophysiological mechanisms are highly variable. CAAs are usually encountered as coincidental findings during coronary angiography or at autopsy. Whereas some coronary anomalies are clearly anatomic variants without much clinical relevance, others can cause severe cardiac symptoms and death.[1] Anomalous origination of a coronary artery from an opposite sinus of Valsalva (ACAOS) [1] comprises a subset of coronary anomalies that may have severe prognostic implications.[2-4] A single coronary artery (SCA) is one of the most rarely seen coronary anomalies with an incidence of 0.05%.We report the case of a 68-year old male patient who presented with symptoms of chest pain associated with an acute myocardial infarction. Coronary angiography revealed an anomalous left anterior descending (LAD) and left circumflex (LCX) originating from the right coronary ostium as trifurcation and an occluded distal right coronary artery. In order to confirm the origin and course of the SCA, multi-slice computed tomography (MSCT) angiography of the heart was performed after coronary angiography (CAG). CT angiography showed that the anomalous LAD & LCX originated from the right coronary artery common trunk and then LAD passed anteriorly and LCX travelled in between aorta & pulmonary artery. The anomalous coronary arteries were thus classified as R-III C subtype according to Lipton's classification. ***Keywords :*** *Single coronary artery; Multislice computed tomography; Coronary angiography.*

INTRODUCTION

Coronary anomalies are inborn errors, and life-threatening symptoms, such as arrhythmias, syncope, myocardial infarction, or sudden death, can occur in up to 20% of patients. A single coronary artery (SCA), defined as an artery that arises from the aortic trunk from a single coronary ostium and supplies the entire heart, is rare. However, the majority of anomalies (80%) are benign and asymptomatic[5]. Whereas origin of the right coronary artery from the left sinus of Valsalva is a more common anomaly and its prognosis and treatment better known, left ACAOS is less frequent with its treatment less well understood. We report a case of SCA arising from right sinus of valsalva presenting as acute coronary syndrome.

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CASE REPORT:

A 68-year-old man presented with a history of progressive typical retrosternal chest pain of two days duration and patient was admitted suspecting acute coronary syndrome. Physical examination of the patient on admission revealed normal regular pulse of 66 per minute, blood pressure was 130/80 mmHg right arm supine and body temperature was 36.8°C. JVP was not raised. First & 2nd heart sound were normal whereas the 3rd & 4th sounds were not audible. No signs of heart failure were present.

Electrocardiogram revealed ST elevations in leads II, III, aVF with normal sinus rhythm. Transthoracic two-dimensional echocardiography (TTE) demonstrated regional wall motion abnormality with normal left ventricular function. A diagnosis of acute inferior wall myocardial infarction was made and the patient was subjected to coronary angiography.

TABLE 1: LIPTON'S CLASSIFICATION OF SINGLE CORONARY ARTERY

OSTIAL LOCATION	R	Right sinus of Valsalva
	L	Left sinus of Valsalva
ANATOMICAL DISTRIBUTION	I	Single coronary artery with normal right or left coursing (RC or LC)
	II	After leaving the right or left sinus the single coronary artery crosses at the base of the heart as a large transverse trunk in order to supply the contralateral coronary artery
	III	Single coronary artery arising from the right sinus, with the left anterior descending and circumflex arteries from separate coronary artery trunks instead of a single trunk immediately at the exit
COURSE OF THE TRANSFER BRANCH	A	Anterior to the large vessels (anterior to the right ventricle)
	B	Between the aorta and pulmonary artery
	P	Posterior to the large vessels
	S	Septal type (above the interventricular septum)
	C	Combined type

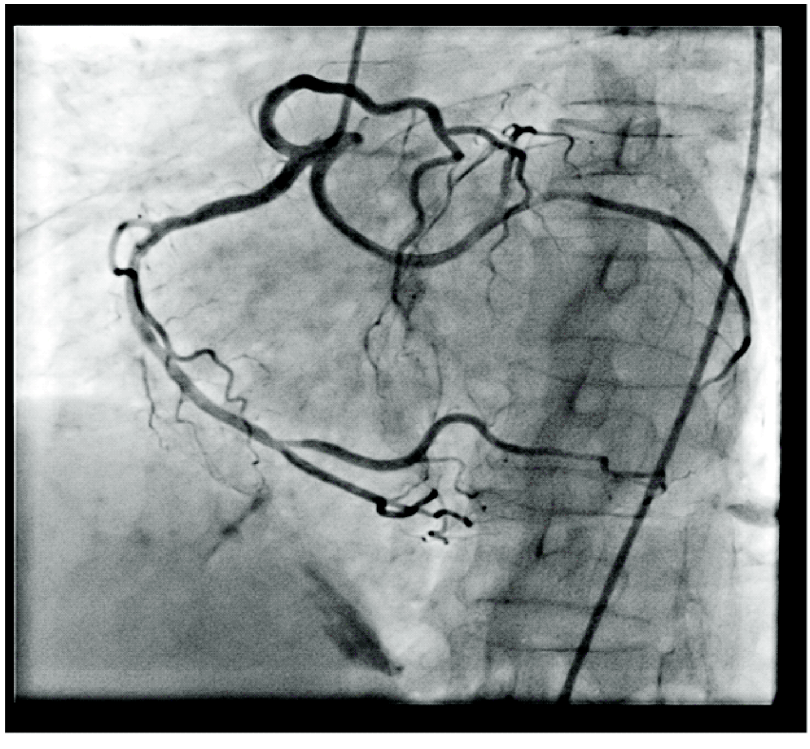

Fig: 1A: LAO Straight view. The angiogram demonstrated a SCA: the LAD & LCX originated from the same common trunk of the RCA as trifurcation.

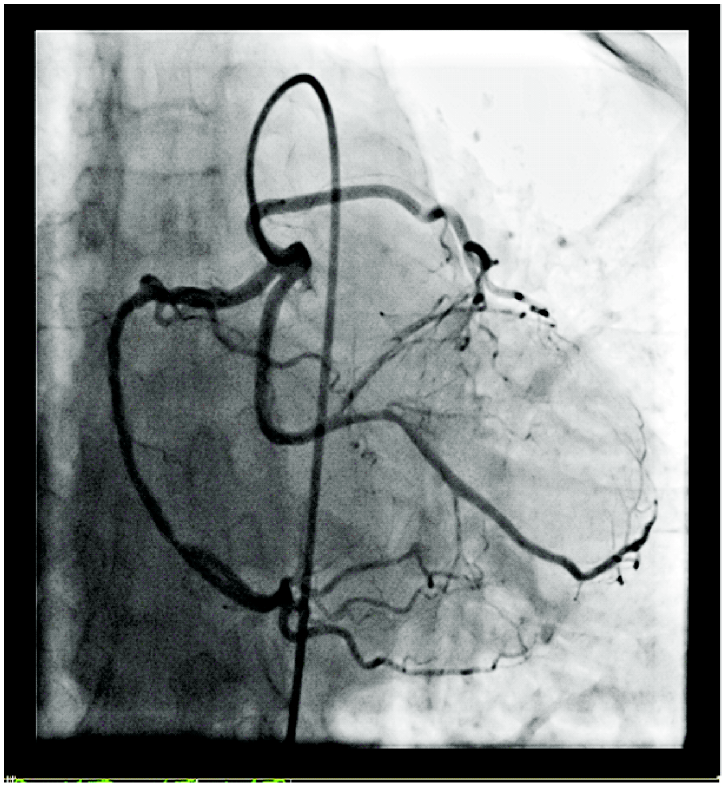

Fig: 1B: AP Caudal view. LAD & LCX originated from the same common trunk of the RCA as trifurcation.

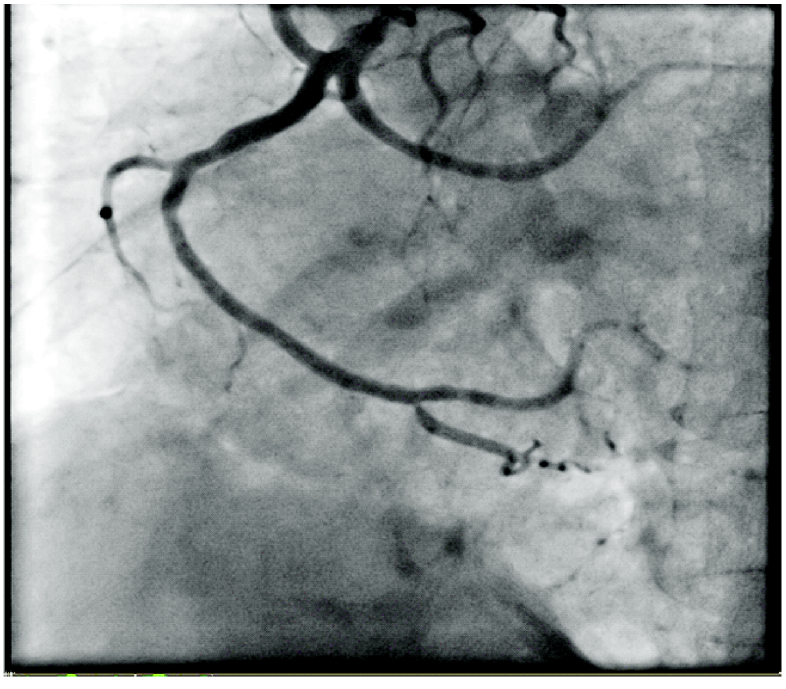

Fig 1C: PCI of the distal RCA with distally TIMI III flow.

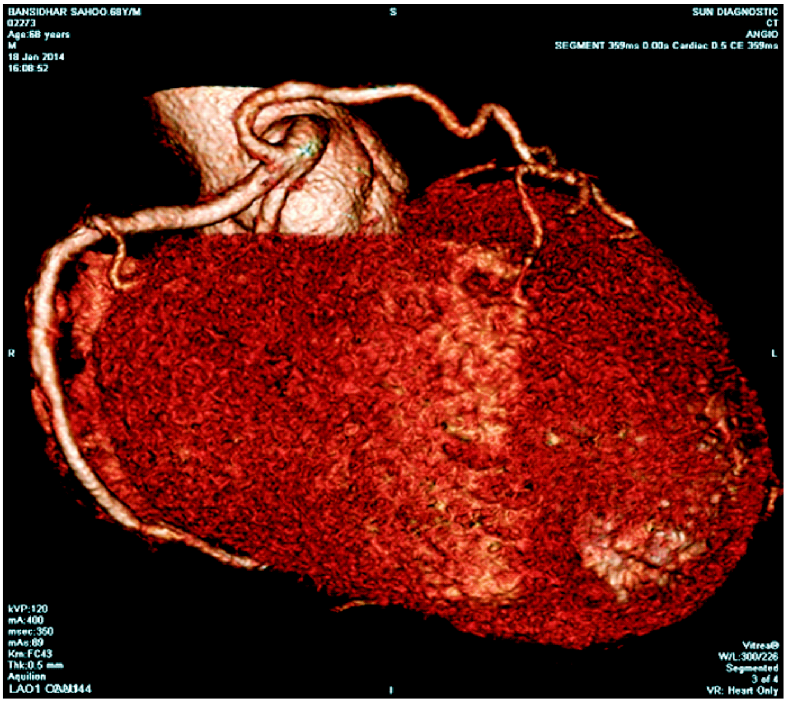

Fig:2: The origin and course of the anomalous LAD & LCX shown in multi-slice CT angiography. The results showed the anomalous LAD & LCX originating from the common trunk of the RCA.

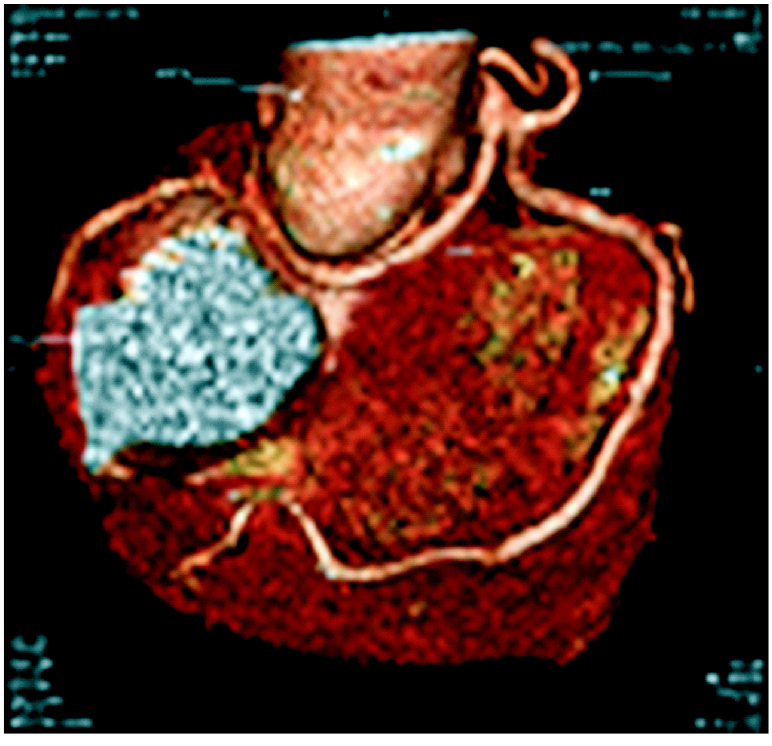

Fig:3: LAD passed anterior to the aorta and LCX travelled interarterially in between aorta and pulmonary trunk. According to Lipton classification this anomaly can be classified as Lipton R-III-C.

The angiogram demonstrated a SCA: the LAD & LCX originated from the ostium of the RCA (Figure 1A and B) as trifurcation. There was a lesion in the distal RCA and an occlusion of the posterolateral branch of the RCA (Figure 1A). Stenting of the occluded branch was performed successfully (Figure 1C). In order to confirm the origin and course of the anomalous LMCA, multi-slice CT angiography was performed (Figure 2). The results showed the anomalous LAD & LCX originating from the common trunk of the RCA, LAD passed anterior to the aorta and LCX travelled interarterially in between aorta and pulmonary trunk (Figure 3). The anomalous SCA was classified as R III C subtype (Table 1).

DISCUSSION:

Coronary anomalies are defined as those angiographic findings in which the number, origin, course, and termination of the arteries are rarely encountered in the general population. Coronary anomalies may occur in 1% to 5% of patients undergoing coronary arteriography, depending on the threshold for defining an anatomic variant The most commonly seen coronary artery anomaly include the LAD & LCX arteries arising from separate ostia in the left sinus of Valsalva. The LCX artery arising from the right sinus of Valsalva, the RCA arising from the left sinus of Valsalva, and coronary artery fistulae are also commonly seen. An isolated SCA anomaly is one of the most rarely seen coronary anomalies [6]. These coronary anomalies are classified by Lipton according to the site of origin of the left and right coronary arteries, the anatomical distribution on the ventricular surface, and according to the relationship with the ascending aorta and the pulmonary artery (Table 1)[6]. Our case provides an example of a SCA arising from the right sinus of Valsalva and which had separate origins of LAD & LCX arising as a trifurcation immediately after the origin of RCA. Then, LAD travelled anteriorly & LCX travelled in between pulmonary trunk and aorta. So the course of the transfer branch is combined. Thus, this SCA is classified as R-III-C. In patients with a SCA and an interarterial course, sudden death may take place since the coronary artery is compressed between the aorta and the pulmonary artery during vigorous exercise [7]. Though analysis of the course of artery can be done in cath lab by eye and dot method, proper anatomy of course of the artery must be analysed prior to the intervention with proper investigation like ct angiography to prevent catastrophe.

Intervention in single coronary artery is equivalent to intervention in unprotected left main coronary artery in which the guide catheter is decided according to the existing sinus rather than the type of artery involved and intervened & adequate bed preparation like left main intervention is mandatory i.e. temporary pacemaker back up & canulate the left femoral artery for need of intra aortic balloon pump in case of emergency.

In this patient, we diagnosed the SCA by coronary angiography and further delineated the course of the anomalous coronary artery in relation to the aorta and pulmonary artery by MSCT. The incidence of a LAD & LCX originating from the common trunk of the RCA is very low (0.05%). Our case of a 68-year old male patient with this coronary anomaly underwent MSCT to confirm the origin and course. The anomalous LAD passed anteriorly and LCX travelled as interarterial artery and therefore was classified as R-III-C subtype according to Lipton's classification.

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Case Report

CLINICAL SPECTRUM OF GRANULOMATOSIS WITH POLYANGITIS (WEGENER'S GRANULOMATOSIS): 3 CASE REPORTS

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ABSTRACT

Granulomatosis with polyangitis is a multisystemic disease of unknown etiology, characterized by granulomatous inflammation, tissue necrosis, and variable degrees of vasculitis in small- and medium-sized blood vessels. It is rare and usually missed. We present three cases of Wegener's Granulomatosis and the spectrum of their clinical profile. ***Key Words :*** *Granulomatous Inflammation, Necrotising Vasculitis.*

INTRODUCTION

Granulomatosis with polyangitis is a necrotizing vasculitis associated with granuloma formation characterized by a predilection to affect the upper and lower respiratory tracts and, in most cases, kidneys. The disease was first described in 1931 by Heinz Klinger, a German medical student[1,2,3]. In 1936 and 1939, Friedrich Wegener, a pathologist, provided detailed information about three patients with a similar illness[2]. It has been subsequently redesignated as granulomatosis with polyangiti[29]. It is classified under ANCA positive vasculitis and the disease is mostly localized to the small and medium- sized blood vessels.[4,6] Although distinctive patterns of organ involvement exists, any organ system can get affected[4,5] It has a predilection for causing destructive lesions in the upper respiratory tract, including nasal septal perforation, "saddle-nose" deformity, erosive sinusitis, middle ear damage, and subglottic stenosis.[8,9]Classic lung lesions are pulmonary nodules, cavitaties, alveolar haemorrhage and non specific infiltrates[11,14]. Renal involvement that leads to crescentic and segmental necrotizing lesions is often associated with rapidly progressive glomerulonephritis.[16,19] Migratory oligoarthralgias and oligoarthritis are common[4,8] Granulomatosis with polyangitis, those with severe, widespread disease, are often associated with antineutrophil cytoplasmic antibodies (ANCA)[6,14]. These antibodies look at two distinctive cytoplasmic antigens within the neutrophils called proteinase 3 (PR-3) and myeloperoxidase(MPO) The sensitivity of PR3-ANCA is about 90% in active Wegener's Granulomatosis (WG) and 40% when the disease is in remission. The specificity of PR3-ANCA in the diagnosis of WG exceeds 95%[4,16,20,21] For patients with limited WG, defined as the absence of an immediate threat to either the function of a vital organ or the patient's life, 30% or more lack ANCA.[12,13,15] Immunosuppressive therapy is effective in the induction of disease remissions in most cases. Untreated systemic WG have a dismal prognosis, with a mean survival of approximately 5 months.[16,17] Not much data is available on the epidemiology of WG in India. A study conducted at AIIMS, New Delhi reported 25 cases of WG between 1988- 2000. 16 of the patients were of classical wegener's and 7 were of the limited variety of wegwner's granulomatosis.). The mean age of patients was 35.5 years and the mean duration of symptoms was 5.5 months. Generalized wegener's was treated with oral prednisolone 1mg/kg body weight and oral cyclophosphamide 1mg/kg body weight for 1 year.limited wegener's was treated with oral prednisolone 1mg/kg body weight and oral methotrexate10-12.5 mg/week . Median time for remission was 6 months One patient

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was treated with i.v cyclophosphamide. [27] In another study conducted at KEM, Mumbai, 25 patients of WG were diagnosed over a period of 4 years. 23 cases were classical WG and two cases had limited WG.This study mainly concentrated on the ANCA serology .patient details with regard to clinical presentation and treatment protocol was not discussed in detail.[26]

We present our series of three case highlighting its myriad manifestations, and problems associated with long term management in our setup .

Case 1

A 43 year old female presented with four month history of fever, polyarthritis, purulent ear discharge, hemoptysis, parotitis , scleritis of left eye and decreased urination. Patient was treated for chronic sinusitis, and otitis media elsewhere but the condition did not improve. On the day of admission the patient was conscious afebrile, her pulse was regular 86/min, BP was 130/ 86mm of Hg. She had severe pallor, nodular scleritis of left eye, non foul smelling discharge from right ear, symmetrical polyarthritis and bilateral deafness. Examination of cardiovascular & respiratory system were normal. GI system and CNS were normal. On the fourth day of admission patient developed anuria and received haemodialysis. She developed hypertension during the course of her stay in the hospital which was controlled by calcium channel blockers and diuretics.

Laboratory investigations are shown in Table-1. X-ray of chest was normal. CT thorax (Fig.1) showed multiple nodules in left upper and right lower lobes, diffuse ground glass opacity, with septal thickening in bilateral perihilar region. Cavity was present in left upper lobe along with bilateral pleural effusion. All these findings were suggestive of WG as well as pulmonary tuberculosis. USG abdomen and pelvis revealed bilateral acute medical renal disease along with moderate ascites. Audiometry revealed bilateral sensorineural deafness.

A diagnosis of generalized granulomatosis with polyangitis (WG) was made based on the involvement of lungs, upper respiratory tracts , kidneys , positive ANCA and anti PR-3 antibody(>200Ru/ml)

Following confirmation of the diagnosis, patient was started on 1gm of methyl prednisolone bolus daily for three days followed by oral prednisolone 1mg/kg body weight . She was also started on oral cyclophosphamide 2mg/kg, with a starting dose of 50mg/day. It was increased to 75mg/day with dose modification based on her serum creatinine levels . She received four sessions of haemo dialysis and was given four units of blood transfusion. Patient was discharged with cycophosphamide 75mg/day. Prednisolone 50mg/ day, anti- hypertensives and calcium supplements. At the time of her discharge her Hb was 8gm%. Renal function had improved. Her serum creatinine was 2.6mg/dl and serum urea was 86mg/dl . She requested to be discharged and was asked to report after 1 month but failed to return.

Six months later, she was readmitted with complaints of generalized weakness and swelling of feet. Her Hb was 6.5gm%, serum creatinine was 4.6mg/dl, serum urea was 126mg/dl . Her TLC was 9800/cmm , DC-N-86% L 11% E 2% L 1%, RBS 100 mg/dl. Liver function was within normal limits. Urine contained traces of albumin, plenty of RBC, 20-30 pus cells/ HPF There was no scleritis, ear discharge,polyarthritis or fever. Her X-ray chest was normal. Anti-PR3 could not be repeated to assess disease activity. Based on her clinical and laboratory profile a diagnosis of WG with flare was made and she was given 3 bolus doses of methyprednisolone of 1gm each along with mycophenolate mofetil , 1gm/day which was to increased to 2gms/ day over 2 weeks period.She was unable to afford Rituximab for financial reasons, which would have been a good alternative in this situation. The other alternative was to continue cyclophosphamide at a higher dosage, but that option was set aside since she had already received oral cyclophosphamide and had poor compliance to follow ups. Therefore, mycophenolate was preferred to avoid damaging toxicity in the background of deteriorating renal function . The patient requested a discharge and was asked to follow up a month later. However, the patient never returned.

CASE-2 :

A 48 year old male presented with four years history of chronic frontal , maxillary sinusitis, and polyarthralgia. He gave history of epistaxis and nasal discharge for which he was treated by the ENT specialist. A nasal growth was observed for which he underwent a biopsy. Histopathological examination showed evidence of chronic inflammation. The problem persisted and subsequently he was admitted in the Unit of Clinical Immunology for problems of prolonged cough, fever and hoarseness of voice . On examination patient was afebrile, pulse rate 84/min BP 116/70 mmHg Examination of the lungs revealed basal crepitation and upper respiratory tract revealed evidence of maxillary sinusitis. He had a saddle shaped nose due to collapse of the nasal septum which had developed following attacks of epistaxis and biopsy for the nasal growth. (Fig.2) The vocal cords were congested and swollen on laryngoscopic examination. But there were no nodules or ulcers.

CVS examination was normal . GI and CNS examination revealed no abnormality. His laboratory results, showed persistent leukocytosis, neutrophilia, and high ESR. (Table-2) His HRCT thorax showed sub pleural nodules. He was diagnosed as a case of limited Wegner's granulomatosis based on involvement of upper respiratory tract, saddle nose deformity, lung involvement in the form of sub pleural nodules persistent leukocytosis and low positive anti MPO autoantibody.

He was put on 1mg/kg of oral predisolone which was tapered after 6weeks. He was lost to follow up for 3years and readmitted for fever , cough and hoarseness of voice. He was put on antibiotics and the dose of steroid was hiked to 0.5mg/kg and methotrexate 7.5mg/week was added and was advised to increase the dose by 2.5mg monthly. He reported after 3 months. Although the patient was asymptomatic, his renal functions showed border line derangements- serum creatinine was 1.5mg/dl. He could not repeat the ANCA test for financial reasons. He had evolved into classical Wegner's. Onset of renal dysfunction in a case of limited Wegner's is a hallmark of generalised disease and invariably carries a bad prognosis. He was started on oral cyclophosphamide 2mg/kg body weight for 6 months and also given tab cotrimoxazole DS once a day for pnemocystis carinii prophylaxis as per the recommendation. After six months, the patient was in complete remission. Cyclophosphamide was discontinued and maintenance with oral Methotrexate 7.5mg/week was started and increased by 2.5mg wkly up to 15mg/ week. Prednisolone was reduced to 5 mg /day. After a follow up of one and half years, patient is in complete remission..

CASE 3

Our third case was 54 year old women who presented wih six years history of chronic sinusitis, headache, hoarseness of voice and non productive cough.. There was no history of hypertension or type 2 DM On examination, the patient was febrile. Her pulse was 100/min, BP was 136/70.She had tender frontal and maxillary sinuses, eye lid oedema on the left , palpable purpurae on lower limbs. (Fig.3) ENT examination revealed laryngeal oedema and bilateral sensorineural deafness. Abdomen was soft and non tender. CVS and CNS examinations were normal. The laboratory evaluation (Table-3) showed leukocytosis , neutrophilia,, thrombocytosis and high ESR. X Ray PNS had evidence of pansinusitis which was confirmed by CT scan of PNS.X Ray chest was normal. HRCT thorax showed lower lobe infiltration. Her C-ANCA and anti PR-3 were negative.

She was diagnosed as case of limited form of Wegner's's based on involvement of upper and lower respiratory tracts, ,cutaneous vasculitis, leukocytosis, neutrophilia and high ESR. She was started on antibiotics for a possibility of secondary bacterial infection, and Prednisolone 1mg/kg body weight/day

A drainage of paranasal sinuses was planned but deferred due to reluctance of the patient for the invasive procedure Patient was readmitted a month later for PNS drainage, and routine investigation revealed RBS of 300mg/dl. Her recheck of HbA1C was 8.1, FBS was 286 and PPBS was 312 indicating development of diabetes following steroid therapy. Besides, she also had evidence of right lower lobe pneumonia. Patient was started on regular insulin and broad spectrum antibiotics which led to prompt recovery from infection.

Table-1 Laboratory Investigations of Case-1

TLC	23180/cmm
DC	N 90% L9%E1%
Hb	4.3gm/dl
TPC	5,20,000 cmm
ESR	155mm 1st hr
SERUM UREA	83mg/dl
S.CREATININE	5.9mg/dl
S.NA	125meq/l
S. K	5.9meq/l
S.BILIRUBIN(T)	1.2mg/dl
S.BILIRUBIN(D)	0.4mg/dl
SGPT	48IU
SGOT	48IU
ALP	185IU
URINE PUS CELLS	15 -20/HPF
URINE RBC	>100/HPF
URINE ALBUMIN	TRACE
URINE SUGAR	ABSENT
C-ANCA	POSITIVE
ANTI PR-3	>200 Ru/ml
	(0-20)Ru/ml

Table-2 Laboratory Investigations of Case-2

Hb	14.4gm%
TLC,/ESR DC	24,300 cmm/ 90 mm 1st hr. N85%, L 11%, E4%
RBS	105mg/dl
S.UREA, S.CREATININE	40mg/dl 1.3mg/dl
S.BILIRUBIN T S.BILIRUBIN D	1.2 md/dl 0.4mg/dl
SGOT SGPT	38IU 48IU
ALP	116IU
Anti MPO	28.9 RU/ml(N=9)
ANCA,	NEGATIVE

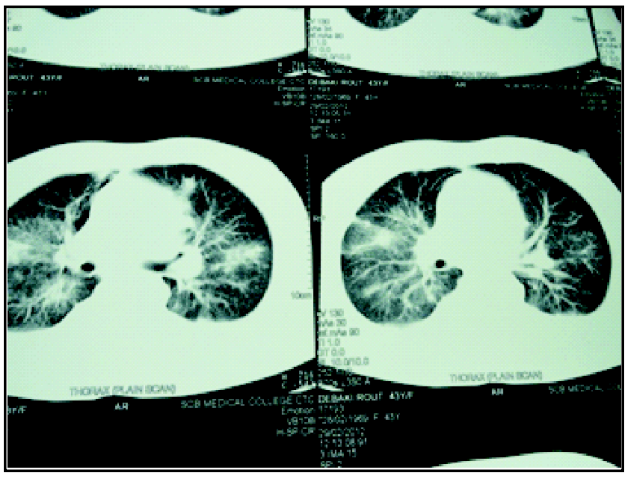

Fig-1 HRCT thorax showing multiple nodular opacities over bilateral lung fields. (Case-1)

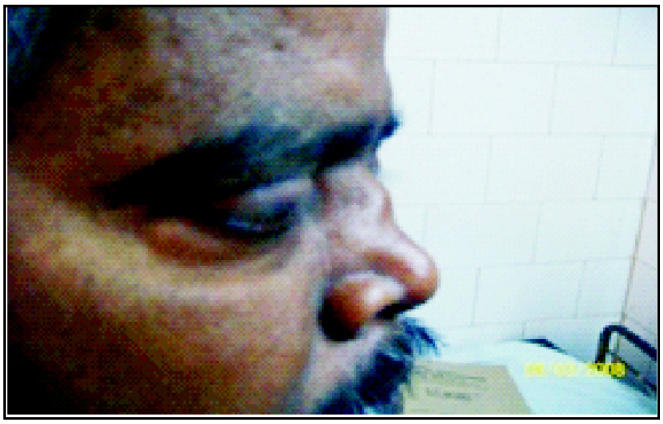

Figure 2 saddle shaped nose (Case-2)

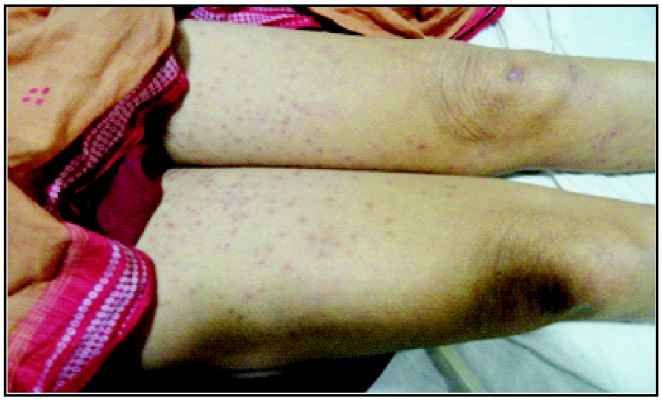

Fig. 3 showing cutaneous vasculitis of (case 3)

Table-3 Laboratory Investigations of Case-3

HB	12.6gm%
TLC, DC	18,600 N 89%, L10% E 1%
TPC ESR	20,6000 cmm 101mm 1st hr
S.urea	27mg/dl
S.creatinine	0.9mg/dl
Bilirubin(t)	1.0mg/dl
Bilirubin(d)	0.4mg/dl
SGOT SGPT	32IU 26IU
ALP	126IU
RBS	100mg/dl
CRP	30mg/dl

Subsequent drainage of maxillary sinuses showed evidence of chronic inflammation.

She was discharged after the infection subsided and blood sugar was stabilised. She was on maintenance dose of prednisone (7.5mg/day) methotrexate (10mg/day) and cotrimoxazole prophylaxis. After 2 years of followup the patient has remained relatively asymptomatic

DISCUSSION

Granulomatosis with polyangiitis (Wegener's) is an uncommon disease with an estimated prevalence of 3 per 100,000.[28]. There are no prevalence or incidence reports from India. It is extremely rare in blacks compared to whites; the male-to-female ratio is 1:1.[28] The disease can be seen at any age; 15% of patients are <19 years of age, but only rarely does the disease occur before adolescence; the mean age of onset is 40years.[28] Three of our patients were over 40yrs of age and there were two females and one male.

In the absence of larger number of cases it is difficult to predict gender susceptibility but the age does indicate that it uncommon in young people.

Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis (Wegener's).[10] Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with or without nasal mucosal ulceration [8,11,14]. Nasal septal perforation may follow, leading to saddle nose deformity. Serous otitis media occurs as a result of eustachian tube blockage[8]. Subglottic tracheal stenosis resulting from active disease or scarring occurs in 16% of patients and may result in severe airway obstruction.[8,10]

The clinical profile in our series does indicate a preponderance of upper respiratory tract involvement like sinusitis, hoarse of voice and nasal discharge, besides sensorineural deafness in 2/3 patients. The clue in the diagnosis of WG lies in persistence of the cluster of these signs and symptoms along with leukocytosis, neutrophilia and high ESR unresponsive to frequent use of antibiotics. In the absence of awareness of this disease patients are diagnosed late which allows the condition to progress.

Pulmonary involvement is clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort.[10,11,14] They may be manifest as asymptomatic infiltrates diagnosed by imaging. Pulmonary disease is present in 85–90% of patients. All three patients in our series had pulmonary signs and symptoms and the HRCT thorax findings of case number 1 was also consistent with pulmonary tuberculosis. Tuberculosis in India is far more common than Wegner's. A patient presenting with haemoptysis often has tuberculosis, and in fact most patients of Wegner's in India have been treated with antitubercular drugs before the correct diagnosis was made. Clues to suspect Wegner's in such a situation lies in appreciating the presence of ENT manifestations, persistent leukocytosis and nodular shadows in X-ray chest.

Renal disease occurs in 77% of patients of classical Wegner's, whic dominates the clinical picture and, if left untreated, accounts directly or indirectly for most of the mortality .[7,9,16] Two of our patients had renal involvement. The first had partial remission despite 6 months of oral cyclophosphamide therapy while the 3rd case had complete remission. This highlights the variability of response to recommended regimen Eye involvement in 52% of patients may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis,

granulomatous sclerouveitis,and ciliary vessel vasculitis. One patient in our series had nodular scleritis. Cutaneous manifestations have been reported in 40% to 50% of patients with WG and may be part of the initial presentation in 13% to 25% of cases.The cutaneous manifestations of WG include ulcers, palpable purpura, subcutaneous nodules, papules, and vesicles.[28] .Palpable purpura was the presenting feature of case number three.

The variability of clinical manifestations in WG is one of the reasons for poor patient care in India. A patient of WG may visit an ENT specialist, ophthalmologist, pulmonologist, dermatologist and nephrologist, depending on the presenting clinical profile, before a competent specialist makes a diagnosis. This is a major problem in our country and delayed diagnosis carries high morbidity and mortality.

Prior to the introduction of effective therapy, granulomatosis with polyangiitis (Wegener's) was universally fatal within a few months of diagnosis.[17,18] In 1990, the American College of Rheumatology (ACR) established the criteria for the classification of WG as nasal or oral inflammation, radiologically demonstrated pulmonary infiltrates, abnormal urinary sediment (red cell cast,haematuria), granulomatous inflammation on biopsy.[12] Patients are diagnosed with Wegener's granulomatosis if 2 of these 4 criteria are present.[12,19] The presence of autoantibodies to proteinase 3/ cANCA is not requried for diagnosis of WG, by either ACR or Chapel Hill consensus Conference (CHCC) definition.[12,19,22]

Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of disease.[24] The development of treatment with cyclophophamide dramatically changed patient outcome such that marked improvement was seen in >90% of patients, complete remission in 75% of patients, and 5-year patient survival was seen in over 80%. [17,18,26]After 3–6 months of induction treatment, cyclophosphamide is generally discontinued and switched to another agent for maintenance of remission .[26] The agents with which there has been the greatest published experience are methotrexate and azathioprine. In the absence of toxicity, maintenance therapy is usually continued for a minimum of 24 months before treatment is discontined[24,25]if the patient is stable.This regimen has been recommended for generalised WG. In limited disease, steroid for induction and maintenance with either methotrexate or azathioprine is preferred. In two of our cases cyclophosphamide was used for induction of remission. Two case with limited disease were maintained with methotrexate.

In two recent randomized trials that enrolled ANCA positive patients with severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, rituximab 375 mg/m^2 once a week for 4 weeks in combination with glucocorticoids was found to be as effective as cyclophosphamide with glucocorticoids for inducing disease remission.[24,25]. Wegner is a difficult disease to treat and to maintain remission. Nearly 50% patients develop relapse at some point of time and the whole regimen has to be repeated. The favourable trial with Rituximab provides hope for treating relapsed and refractory cases.

In our case report we have shown the wide spectrum of clinical presentation of the disease The first presented with features generalised disease,in the second case the spectrum gradually changed from limited disease to generalised polyangitis while the third case has remained in limited. The major constraint in our setup is delayed diagnosis for reasons discussed earlier . All the patient were treated for chronic sinusitis and were given NSAIDS/antibiotics for long durations before a diagnosis could be made. The perils of NSAID therapy are well known. They can precipitate renal failure and could pose diagnostic dilemma. Use of Moneleukast for upper respiratory tract infection/allergy has been associated with precipitation of ANCA associated vasculitis. Financial constraints prevent patients from adhering to long term treatment regimen.

CONCLUSION

Granulomatosis with polyangitis (Wegner's granulomatosis) has a wide spectrum of clinical manifestations. It should always be considered as a differential diagnosis in patients with intractable sinusitis, deafness and otitis media with presence of persistent

inflammatory parameters. Associated pulmonary and renal involvement demands aggressive investigation to avoid missing a case resulting in inappropriate treatment.

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Case Report

KERATODERMA BLENNORRHAGICA IN HIV - A RARE CUTANEOUS MANIFESTATION

A.K. Mahali,* S.Tripathy, B. Pradhan*****

ABSTRACT

Keratoderma blennorrhagica is a rare skin manifestation in HIV infected persons. This lesion is the component of Reiters syndrome. In this article we report a case of keratoderma blennorrhagica in a HIV patient who was admitted in our hospital with intermittent fever and vesicopustular lesions in both the soles. He was treated with antiretroviral therapy and glucocorticoid and systemic retinoids. ***Key words:*** *Keratoderma blennorrhagica, Reiters syndrome, HIV*

INTRODUCTION

Keratoderma blennorrhagica, first described by Vidal in 1893, is a syndrome of urethritis, arthritis often conjunctivitis, associated with a peculiar and characteristic skin lesion. Its gonorrheal origin was first established by Buschke and others. As occasional cases appeared presenting the characteristic syndrome without gonorrheal infection, it became increasingly evident even to Buschke that other agent might also be responsible for the development of this clinical picture.[1] Patient with HIV are at increased risk for developing Reiters syndrome (arthritis, urethritis, conjunctivitis) with an incidence of approximately 6%-10%. Reiter2s syndrome patients less commonly present with cutaneous manifestation, consisting of keratoderma blennorrhagica or circinate balanitis. [2,3]

CASE REPORT

A 55 yr old male presented with fever for last 2 yr which was low grade and intermittent type and not associated with chill and rigor or cough. He also had vesicopustular lesion over both the soles, which were progressive over last 2 months. The lesion began as multiple pinpoint fluid filled eruption, which later evolved to involve both the soles. There was no preceding history of dysuria, arthralgia or eye irritation, gastroenteritis or any other significant dermatological complaint. On Examination temperature was 99.2F, Pulse rate: 96/min and Blood pressure: 108/70 mm Hg. There was no lymphadenopathy. There were yellowish brown papules topped by vesicles and pustules, coalescing to form plaques with scaling and crusting over both the soles. (Pic.1) No other skin lesions were seen anywhere on the body. Investigations revealed Hb-8.8gm%,TLC-9800/cu.mm, DC: N-76% L-24%, ESR-90 mm in 1st hour, RBS-102mg%, Blood Urea-21mg, S. Creatinine-1mg, S. Na^+ 137 mmol/L , S.K^+4 mmol/L, CRP-12 mg/L, ASO titer: negative, RA factor : negative, S. typhi H = 1:160, S. typhi O= Negative, S. Paratyphi AH = 1:160, S.Paratyphi BH = Negative, HIV: Reactive, HBV : Negative, HCV : Negative, CD4 Count : 20 cells/µL, CT scan of Brain: Multiple hypodense areas over left basal ganglia, left frontal lobe, left paraventricular area. Sputum for AFB could not be done since the patient had no expectoration. The patient was put on antiretroviral therapy, Acitretin 0.5 mg/kg body weight and topical glucocorticoids i.e. Clobetasol propionate under occlusion.

DISCUSSION

Keratoderma blennorrhagica is a pustular or plaque like rash that most often occurs in a palmoplantar distribution. It typically begins as erythematous macules or vesicles. The vesicles are often pustular in nature, but they can also be hemorrhagic. Over time they can become thickened or popular, forming a horny

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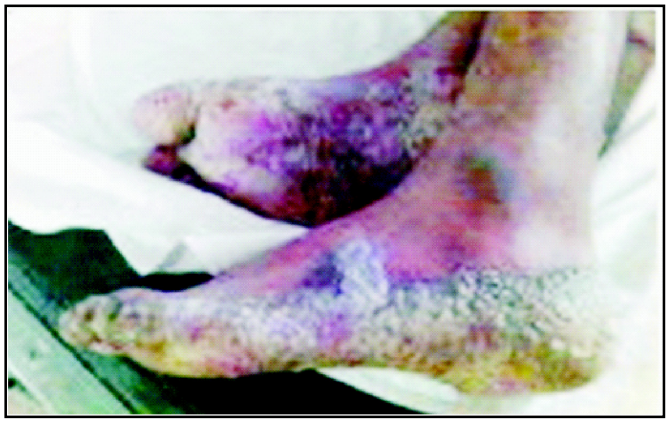

Picture-1 showing keratoderma blenorrhagica

excrescence. These chronic lesions become hyperpigmented and may coalesce. Rarely these lesions can occur in a more general distribution involving the entire body: this is seen to be more likely in the setting of HIV infection. Keratoderma blenorrhagica is clinically and histologically indistinct from pustular psoriasis. Histologic findings include hyperkeratosis and parakeratosis, elongation and hypertrophy of the rete ridges, general epidermal hyperplasia and extensive neutrophilic infiltration with formation of microabscess and spongiform pustules.[4]

In HIV patient when CD cell count falls < 500 cells/cu.mm and remain between 200 to 500 cells/ cu.mm non–life threatening mucocutaneous manifestation in chronic and intermittent forms develop and when CD cell count ranges between less than 50 and 200 cells/cu.mm and any type of opportunistic infection and cancer threatening to life; can lead to death. Advanced HIV disease CD cell count less than 50 cells/cu.mm is associated with profound immunosuppression and the occurrence of several co-existing infection and/or opportunistic neoplasm. [5,6,7]

In our patient, who was having low grade fever for last 2 yr and vesicopustular lesion in both the soles, which was progressive over last 2 month, without any preceeding arthralgia, dysuria, conjunctivitis, CD cell count was 20 cells/µL and ASO titer and RA factor were negative. Hence we diagnosed it as keratoderma blennorrhagica as a mucocutaneous manifestation in a HIV patient. The patient was treated with antiretroviral therapy and potent glucocorticoid cream i.e. clobetasol propionate under occlusion and systemic retinoids i.e. acitretin 0.5 mg/kg body weight. [8]

CONCLUSION

We are reporting this case because of the unusual isolated cutaneous manifestation of keratoderma blenorrhagica as a component of Reiters syndrome in HIV patient.

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Case Report

AUTOIMMUNE HAEMOLYTIC ANAEMIA IN VARICELLA INFECTION

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ABSTRACT

Autoimmune Haemolytic Anaemia (AIHA) is a rare complication of chickenpox. We report a young male who developed AIHA secondary to chickenpox. ***Key words :*** *Autoimmune Haemolytic Anaemia, Varicella infection.*

INTRODUCTION

Chickenpox is the most common exanthematous fever of childhood. Complications include syndrome of acute cerebellar ataxia and meningeal inflammation, aseptic meningitis, encephalitis, Gullian-Barre syndrome, transverse myelitis, myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses ,acute glomerulonephritis and hepatitis.[1] The term auto-immune haemolytic anaemia (AIHA) is used to describe a group of haemolytic anaemias that result from the development of antibodies directed against antigens on the surface of patient's own RBCs, that act as autoantibodies.[2] 50% cases are idiopathic. Infections (mycoplasma, infectious mononucleosis, cytomegalovirus, rubella), lymphomas, chronic lymphocytic leukemia, immunodeficiency states, autoimmune disorders, post transplantation and some uncommon causes like carcinoma, sarcoidosis, ovarian teratoma comprise the remaining 50%.[2] Chickenpox, a viral infection caused by varicella zoster virus is endemic in the population at large. The disease is often self limiting excepting in new born and immunocompromised. AIHA is a rare complication of chickenpox.[3]

CASE REPORT

A 24 year old male was admitted with complaints of fever for one day followed by pleomorphic skin lesions for 8 days. This was followed by relapse of fever along with jaundice and breathlessness for 2 days. There was no history of any blood transfusion, blood loss, repeated jaundice or drug intake.

On examination the patient was febrile, tachypnoeic. There was presence of pallor and icterus. He was conscious, heart rate-120/min, respiratory rate-30/min, BP-100/70mmHg. There were multiple scabbed skin lesions of chicken pox all over the body. There was no evidence of bleeding tendencies, bony tenderness or lymphadenopathy and the rest of the examination was unremarkable.

Investigations- Hb-3.1gm/dl, TLC-13,800/cmm DC:N83% L14% E2%,TPC-2.03 lakhs/cmm, ESR-115 in 1st hour, peripheral smear showed fragmented RBCs. Direct coomb's test was positive and serum LDH level was 3016U/L. urine microscopy showed WBCs-1-2,RBCs-nil; liver function test - total bilirubin 4.6 mg%,direct bilirubin 0.6 mg% SGOT:196IU/L, SGPT:109IU/L, ALP-60IU/L. HBsAg negative, IgM HAV negative, HCV negative; HIV negative.ICT for malaria parasite was negative.Hb electrophoresis was normal.USG abdomen and pelvis revealed hepatosplenomegaly.

A diagnosis of varicella AIHA was made and two units of packed RBCs were transfused. Patient did not improve symptomatically and on the third day of admission his Hb was 4.6 gm%. He was started on

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oral prednisone 1mg/kg body weight in view of continous haemolysis and another two units of blood was transfused. After two days of steroid he improved symptomatically, his vitals were stable and Hb was 7.8gm% after six days of treatment there was mild pallor no icterus and Hb was 8.4gm%. He was discharged on oral prednisolone 1mg/kg and followed up once a week for 6 wks. After 2 weeks he had no pallor, icterus and Hb was 11.8gm%. It was tapered over next 4 weeks. At the end of prednisolone therapy Hb reached 14.3gm%.The patient was followed up for the next 3 weeks without any problem.

DISCUSSION

In our case the onset of haemolytic anaemia was sudden with rapid development of anaemia and jaundice with constitutional symptoms as seen in cases of AIHA following minor bacterial and viral infections. Typical lesions of chickenpox led towards the diagnosis of AIHA secondary to varicella after ruling out other causes of haemolytic anaemia. Very few cases of AIHA including cold agglutinin disease and Evan's syndrome[4,5] have been reported till date.

Severe acute AIHA can be a medical emergency like in our case. The immediate treatment is blood transfusion. In our patient the process of haemolysis began 8 days after chickenpox. The 1st line of treatment is use of corticosteroids. In atleast half of the cases, prednisone will produce remission. Relapses are not uncommon and maintenance therapy may be needed. For the non-responders and for the patients who require more than 15 mg/day of prednisone to prevent relapse ,it is highly recommended to consider a second line treatment option,which might be either spleenectomy or rituximab. Azathioprine, cyclophosphamide, cyclosporine and IV immunoglobulin have become the third line of therapy since the introduction of rituximab. In sever refractory cases stem cell transpantation has been used [1].

Our patient had a good response to steroid. The patient was in full clinical recovery and treatment had been discontinued. As the clinical severity and course of AIHA is variable he was advised for regular follow up and to maintain his medical record.

CONCLUSION-

Severe acute AIHA can be a medical emergency. Early diagnosis and management can save the patient's life.

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Case Report

IDIOPATHIC HYPOPARATHYROIDISM WITH EXTENSIVE INTRACRANIAL CALCIFICATION

M.R. Behera[*], J.K. Panda[**], R.C. Sethy[*], B.L. Parija[***], S.K. Tripathy[#]

ABSTRACT

A female aged 25 years presented with multiple episodes of generalized tonic clonic seizure for last ten years not controlled with oral antiepileptic drugs. On examination, revealed clinical features of hypocalcemia like carpopedal spasm, Trousseau's sign, Chvostek's sign and bilateral cataract. Biochemical parameters revealed hypocalcemia, normal phosphate with low parathyroid hormone. CT scan of brain revealed bilateral extensive intra cranial calcifications. Patient was diagnosed as Idiopathic Hypoparathyroidism and treated with calcium and Vitamin-D_3 supplements and discharged with clinical improvement. ***Keywords :*** *Hypoparathyroidism, Hypocalcemic, Intracranial Calcifications.*

INTRODUCTION

Hypoparathyroidism is listed as "Rare Disease" by Office Of Rare Disease (ORD) of the National Institutes of Health (NIH). Extensive Intracranial calcification caused by hypoparathyroidism is still rare[1]. Idiopathic hypoparathyroidism is diagnosed when all possible causes of hypoparathyroidism is ruled out. We report a case of idiopathic hypoparathyroidism which presented with extensive intracranial calcification.

CASE REPORT:

A female aged 25 years presented with chief complaints of repeated attacks of generalized tonic clonic seizure for last ten years. The seizure used to occur once or twice in every 2-3 months interval. There was no history of fever, headache, vomiting. There was no history of birth trauma and milestones of development were normal. Her menstrual cycles were normal. She was being treated with oral phenytoin at a dose of 300 mg per day but the seizure was continued for which she was admitted.

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General examination revealed facial grimacing, carpopedal spasm, Trousseau's sign, Chvostek's sign. (Fig.1) There was bilateral cataract. Systemic examination revealed no abnormality.

Biochemical examination showed serum ionized calcium 2.12 mg/dl (N 4.48-5.28 mg/dl), phosphate 4.5mg/dl (N 2.5-4.8 mg/dl), serum Mg^{++} 1.6mg/dl (N 1.6-2.3 mg/dl), vitamin-D_3 30.94ng/ml (N 20-30ng/ml), alkaline phosphatase 176 IU/dl, serum PTH 0.71 pg/ml (N 15-65pg/ml) with normal serum T_3, T_4, TSH, FSH, LH, Cortisol level. Her renal function and plasma glucose levels were normal. Urinary pH was 7.0 and 24 hr urine calcium was 82.65 mg/day (N<300 mg/day). She was HIV, HCV, HB_SAg negative.

ECG showed prolonged Q-T interval and EEG was normal . CT scan of brain revealed extensive calcifications in bilateral basal ganglia, thalamus, bilateral cerebelli and cortical gyrus. (Fig.2 & Fig.3) Ultrasound of abdomen & pelvis revealed no abnormality.

A low serum calcium & a low PTH levels without any other metabolic abnormalities were consistent with the diagnosis of Idiopathic Hypoparathyroidism.

Figure-1: showing Tetany & Facial grimacing

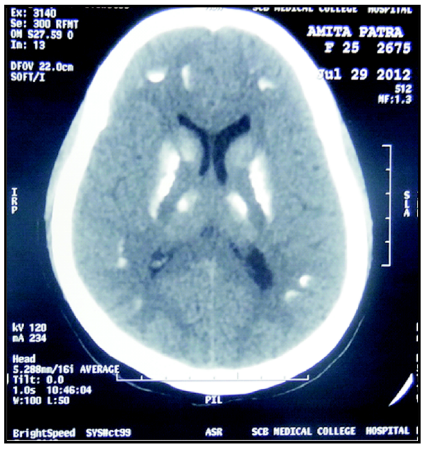

Figure-2: Extensive calcifications in bilateral basal gaglia, thalamus and cortical gyrus.

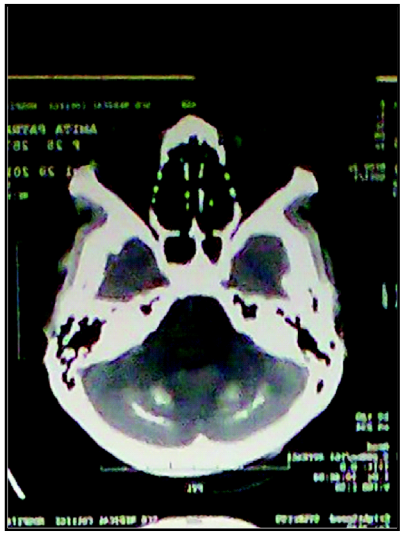

Figure-3: Extensive calcifications in bilateral cerebelli.

DISCUSSION:

Hypoparathyroidism, is an endocrine disorder occurs as a result of congenital disorders, iatrogenic causes (e.g. after thyroid and parathyroid surgery, radiation), infiltration of parathyroid gland (e.g. metastatic carcinoma, Wilson's disease, hemochromatosis), Infection (e.g. HIV/AIDS) or idiopathic.[2] A literature review showed that prevalence of hypoparathyroidism is equal in men and women in all age groups.[1] Idiopathic hypoparathyroidism presents most commonly in the age group of 5-10 years.[3]

Due to extensive intracranial calcification the clinical presentations are usually seizures, mental retardation, disorders of cerebellar or extra pyramidal function, movement disorders, chorea or Parkinsonism. In our patient the clinical presentation was only generalized tonic clonic seizure without any other neurologic manifestation.

The cause of generalised tonic clonic seizure (GTCS) in hypoparathyroidism may be due to intracranial calcification along with increased neuronal irritability due to hypocalcemia. Usually these patients have EEG abnormalities like bilateral synchronous sharp and slow wave discharges but our patient had normal awake EEG in interictal period. Radiologically hypoparathyroidism causes calcification of bilateral basal ganglia, globus palidus, cerebellum, sub-cortical white matter, corona radiate and thalamus.[2]

Our patient had calcification in bilateral basal ganglia, thalamus, bilateral cerebelli and cortical gyrus but there was no neurological manifastetions except GTCS.

Usually these patients present with bilateral cataract because of presence of hypocalcemia for prolonged period. Our patient has bilateral cataract. Usually hypoparathyroid patients don't show clinical findings of hypocalcemia like Trousseau's sign & Chvostek's sign because of chronic long standing hypocalcemia[3] but our patient had all such clinical finding of hypocalcemia like carpopedal spasm, Trousseau's sign and Chvostek's sign.

She was treated with intravenous calcium (calcium gluconate) followed by oral calcium carbonate and activated vit-D_3 supplement which usually must be taken for life.[4] Blood levels of calcium and phosphate are measured regularly and high calcium, low phosphorus diet is recommended.

CONCLUSION:

Clinical suspicion of the disease in extensive intracranial calcification will help the patient for early diagnosis of disease and adequate treatment may lead to marked clinical improvement. Due to the rarity of the disease all patients with intracranial calcification should undergo investigations like serum calcium, phosphate, PTH to rule out hypoparathyroidism.

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Case Report

DYKE-DAVIDOFF-MASSON SYNDROME WITH DISSEMINATED TUBERCULOSIS

Saroj K. Tripathy*, S. Behera, Sujit K. Tripathy*****

ABSTRACT

We report a rare case of Dyke-Davidoff-Masson-Syndrome (DDMS) presenting with disseminated tuberculosis in a 23 years male. ***Key Words:*** *Hemiatrophy, consanguinity, megalencephaly.*

INTRODUCTION

Dyke-Davidoff-Masson syndrome (DDMS) is characterized by seizures, facial asymmetry, contralateral hemiplegia and mental retardation. The characteristic radiologic features are cerebral hemiatrophy with homolateral hypertrophy of the skull and sinuses .[1]

It is typically caused by an in utero or early childhood cerebral insult such as infarct, trauma or infection. Left side hemiatrophy is more common (70%) than right and males are more frequently affected than female.[2] Age of presentation depends on time of neurologic insult and characteristic changes may be seen only in adolescence. The clinical findings may be of variable degree depending on the extent of the brain injury. Varying degrees of atrophy of one half of body, sensory loss, speech and language disorder, mental retardation or learning disability and psychiatric manifestations like schizophrenia may also be present.[3]

CASE REPORT

A 23 yrs male presented with swelling of abdomen, weight loss, decrease appetite for 1 month with recurrent seizures and weakness of right upper limb since 4yrs of age. There was no history of fever, jaundice, hematemesis, malena. No past history of tuberculosis . There was no history of seizure disorder or consanguity in marriage in the family.He is mentally retarded having no addiction.

His prenatal, antenatal, postnatal periods were uneventful and his developmental milestones were normal.

General examination revealed height 142cm(short stature), wt 48 kg, facial asymmetry (Fig.1) with sparse axillary and pubic hair. Pulse rate 82/min, regular, BP was 116/74 mm Hg.

Nervous system examination revealing mental retardation, cranial nerves intact, atrophy of right upper limb muscles, with power 3/5, exaggerated right bicep, tricep, supinator jerk without any other motor, sensory, autonomic involvement. (Fig.1) GI system examination revealing ascitis without hepatosplenomegaly. Respiratory system examination revealing right side pleural effusion. Cardiovascular System is normal.

Investigation like CBC, FBS, LFT & RFT were normal, Chest xray (PA) view showed right sided pleural effusion, USG of abdomen showed gross ascitis. Pleural and ascitic fluid analysis was exudative in nature with predominant lymphocytes.

Non contrast CT scan of brain revealed left cerebral hemiatrophy, ipsilateral dilated lateral ventricle, left calvarial and frontal sinus hypertrophy, with a few hypodensities noted in left temporal and frontal lobe suggesting gliotic changes. (Fig.2) Awake EEG recording was normal.

So the diagnosis Dyke-Davidoff-Masson Syndrome with disseminated tuberculosis was made and treated with category-1 anti-tubercular therapy and antiepileptic drugs.

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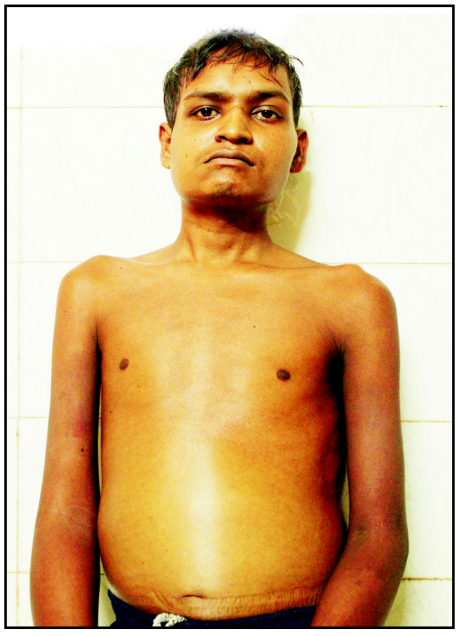
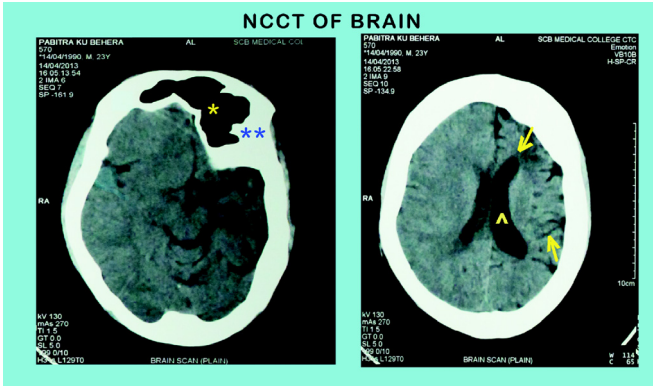


Fig.1 showing photograph of the patient : Facial asymmetry, atrophy of right upper limb muscles and ascites

Fig. 2



** Left Calvarial Hypertrophy.
* Left Frontal Sinus Hypertrophy.
∧ Dilated Ventricle.
→ Left Temporal & Frontal Lobe Gliosis.

DISCUSSION

The condition needs to be differentiated from[2]

a. Sturge-Weber syndrome: DDMS lacks the enhancing pial angioma, enlarged choroid plexus and typical dystrophic cortical calcification of Sturge-Weber syndrome.

b. Unilateral megalencephaly: The abnormal hemisphere is enlarged (not small as in DDMS) and has dysplastic appearing features caused by hamartomatous overgrowth.

d. Rasmussen encephalitis: It lacks the calvarial changes typical of DDMS and demonstrates more focal encephalomalacia, typically in the medial temporal lobe and around sylvian fissure.

Prognosis is better if hemiparesis occurs after the age of 2 yrs and in absence of prolonged or recurrent seizures. Children with intractable disabling seizures and hemiplegia are the potential candidates for hemispherectomy with a success rate of 85% in carefully selected cases.[3]

CONCLUSION :

This rare condition to DDMS should be suspected in any patient presenting with recurrent seizures, facial asymmetry, contralateral hemiplegia with mental retardation and characteristic radiological features of cerebral hemiatrophy, with dilated ventricles and homolateral hypertrophy skull and sinuses.

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Case Report

OSTEITIS CONDENSANSILII: A CASE REPORT AND REVIEW OF THE LITERATURE

R.R. Sahoo*, B.S. Behera, S. Sukriya***, S.K. Behera***, B.K. Das#**

ABSTRACT

Osteitis Condensans Ilii (OCI) is a rare, benign cause of chronic low back pain. It affects an average of 0.9-2.5% of the population, particularly obese multiparous females. It commonly presents with low back pain radiating to buttocks.X-ray pelvis (AP view) shows bilateral symmetric sclerosis of sacroiliac joints, particularly on the iliac sides.History, radiographic findings and laboratory work-up help in differentiating OCI from other causes of sacro-iliac joint involvement. Unawareness of this benign cause of low back pain may result in unnecessary investigations and overburden of medications. We herein, reported a thirty-five year old female presenting with chronic low back pain whose x-ray showed bilateral OCI. ***Keywords—****Osteitiscondensansilii, sacroilitis, low back pain.*

INTRODUCTION

Osteitiscondensans Ilii (OCI) is one of the rarer causes of axial back pain. Typically, the pain is exacerbated by activity and relieved by rest. The diagnosis is mainly radiological. Well defined triangular sclerotic area on the iliac part of the sacroiliac joint is seen on x-rays[(1)]. Sacral sclerosis may accompany[(2)]. It is not an inflammatory condition, but presence of sclerosis needs to be differentiated from other inflammatory causes of back pain. The disease is more commonly observed among females, during or following pregnancy. The etiology is unclear. The most common accepted hypothesis being the mechanical stress of pregnancy. However, this condition is also seen in males and nullipars[(3)].

We described a case of OCI with chronic low back pain whose x-ray showed bilateral sclerosis of both the sacro-iliac joints.

Case report— A female aged 35 years presented with low back pain for last 3 years. She had her last child birth 5 years back with no history of back pain during pregnancy. She described the pain was aggravated by walking or prolonged standing but was relieved by rest. There was no paresthesia or weakness of any leg. There was no history of trauma or any relevant family history. On examination, her gait was normal. There was no spinal tenderness or restriction of movement of the spine. Straight leg raise was 90 degrees on both sides. Modified Schober test was within normal limit. The neurological examination was normal. All the laboratory parameters were within normal limits.

The anteroposterior plain radiograph of the pelvis showed bilateral symmetrical radio-opaque condensation of both the ilium and sacrum without narrowing or irregularity of the sacroiliac joint. MRI of the sacroiliac joints further confirmed sclerosis without involvement of the joint space. A diagnosis of OCI was entertained and the patient was advised of conservative thearapy with NSAIDS and physiothearapy. Her pain relieved gradually

DISCUSSION—Low back pain is an extremely common complaint. There should be an increased emphasis to differentiate noninflammatory from

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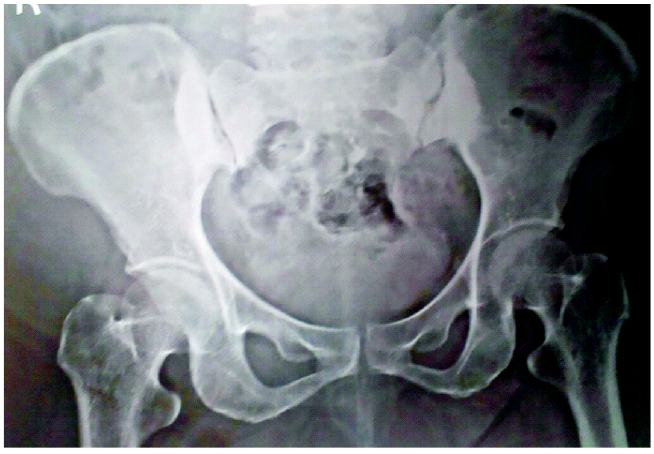

X-ray pelvis (AP view) showing bilateral sclerosis of both the sacroiliac joints without narrowing of the joint space

inflammatory causes of back pain. OCI is a rare cause of noninflammatory chronic back pain. It is mainly seen in women who have given birth. But our case presented with low back pain unrelated to pregnancy or postpartum period. The pathophysiology of OCI has not been established. The proposed mechanisms are the mechanical stress of pregnancy leading to sclerosis, compression of the abdominal aorta by the uterus causing ischemia and sclerosis[3]. However, OCI also affects females without pregnancy and males. Back pain is typically mechanical,i.e, exacerbated by activity and relieved by rest. The pain may radiate to thighs[4]. In a retrospective analysis of 13 OCI patients by K. Jenks et al, there was a significant association between OCI and sacroiliac joint tenderness[5]. It emphasizes the need to differentiate it from sacroiliitis, ankylosingspondylitis, metastatic diseases, primary hyperparathyroidism, renal osteodystrophy, lymphoma, Paget's disease[6]. Mechanical nature of pain, normal level of acute phase reactants, bilateral symmetrical triangular sclerosis on the iliac aspect of the sacroiliac joints with preserved joint space, absence of peripheral arthritis and enthesitis, absence of family history help in differentiating from inflammatory joint diseases. OCI is mainly a radiological diagnosis. The sclerosis is usually bilateral but it can also be unilateral[7].There is no erosion or narrowing of the sacroiliac joint space. The management of OCI is mainly conservative with analgesics, NSAIDS and physiothearapy. Patients with severe pain may undergo local injections to reduce pain. Recently, a mini-invasive surgical procedure with multiple percutaneous drillings has been reported of great benefit in refractory OCI cases[8]. Our case improved satisfactorily with NSAIDS and physiothearapy.

CONCLUSION

OCI is a benign pathology causing chronic low back pain, particularly in women during pregnancy or in postpartum period. Bilateral symmetrical sclerosis of the sacroiliac joints without narrowing of the joint space on x-rays clinch the diagnosis. Conservative thearapy with NSAIDS and physiothearapy are the mainstay of management.

Conflict of interest—None.

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Case Report

HYPOKALEMIC FLACCID PARALYSIS IS AN INDICATIVE OF GITELMAN'S SYNDROME

S.K. Lenka*, K.M. Tudu C.D. Majhi***, B.N. Mohapatra******

ABSTRACT

Hypokalemic flaccid paralysis is a common medical disorder which needs to be evaluated carefully to identify the heterogenous group of disorders included under this heading. We report here rare cases of Gitelman's syndrome in series of patients who presented as recurrent episodes of muscle weakness associated with tetany. There was no history of fever, diarrhoea, rash or abdominal pain without other urinary tract symptoms except having frequency of micturition. There were no history of medication usage including diuretics. Investigations revealed hypokalemia, hypomagnesaemia and hypocalciuria apart from metabolic alkalosis suggestive of Gitelman's syndrome. It is a rare inheritable disorder caused by NaCl transport at distal convoluted tubule and is linked to gene encoding thiazide sensitive Na-Cl cotransporter located on chromosome 16q. It is fully recovered with potassium , calcium and magnesium salts replacement. High doses of spironolactone or amiloride is used to treat hypokalemia , metabolic alkalosis and wasting of magnesium. Long term prognosis in terms of preserving renal function and life expectancy is good. ***Key words****: Hypokalemia, Gitelman's syndrome, Flaccid Paralysis, renal tubulopathy.*

INTRODUCTION

Gitelman's syndrome is a milder disorder usually diagnosed in adolescents and adults[1], an autosomal recessive trait caused by inactivating mutations in the SLC 12A3 gene encoding the thiazide sensitive Na-Cl^- cotransporter, or NCCT [2]. The carrier state of SLC12A3 mutations is 1% in the general population, suggesting a prevalence of Gitelman's syndrome of 25 per million population and making it the most frequent inherited renal tubule disorder[3]. Rare cases are caused by mutations in the CLCNKB gene, which encodes the renal chloride channel CLC-Kb, located in basolateral membrane of cells of the thick ascending loop (TAL) of Henle and the distal tubules[4]. This results in sodium and chloride wasting with secondary hypovolemia and metabolic alkalosis. Activation of the rennin – angiotensin-aldosterone system (RAAS)from volume depletion, plus increased sodium load to the cortical collecting duct lead to increased sodium reabsorption by the epithelial sodium channel , counter balanced by potassium and hydrogen excretion , resulting hypokalemia and metabolic alkalosis. Enhanced passive Ca^{2+} transport in the proximal tubule rather than active Ca^{2+} transport in the distal convoluted tubule explains hypocalciuria. Down regulation of the epithelial Mg^{2+} channel transient receptor potential channel subfamily M, member 6 (TRPM6) has been recently demonstrated and explains the hypomagnesemia [5].

CASE REPORTS

Four male cases in the age group between 24yrs to 40yrs, presented with sudden onset of weakness in both upper limb & lower limb making them unable to move on the bed with no history of difficulty in breathing or retention of urine with no history of any antecedent fever or any drug intake. The detail clinical presentations or data as follows:

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Table 1; Patients' characteristics in Patients on 24 hr presentation before therapy:

	Case-1	Case-2	Case-3	Case-4
Age (years)	30	24	27	40
Gender (M:F)	M	M	M	M
History				
Acute episodes	yes	yes	yes	yes
Episodic	yes	yes	yes	Yes
Recurrent Attacks	Yes	Yes	Yes	Yes
Family History	No	No	No	No
Provoking Factors				
Large carbohydrate meal	Often	Rare	Rare	Often
Physical findings				
Heart rate(beats/min)	Normal	Normal	Normal	Normal
Blood pressure (mmHg)	Normal	Normal	Normal	Normal
Carpopedal spasm	Often	Rare	Often	Often
Trousseu's sign	Often	Often	Rare	Often
Muscle strength(grade)				
Upper extremities	3/5	2/5	2/5	3/5
Lower extremities	4/5	3/5	3/5	4/5
Laboratory Findings				
Blood				
Na^+(mmol/l) (135-145)	145	134	141	133
K^+ (mmol/l)(3.5 – 5.0)	1.6	2.1	1.6	2.3
Cl^-(mmol/l)(100-108)	91	90	89	96
Urea(mg/dl)(10.0- 40.0)	92.2	20	22	28
Creatinine(mg/dl)(0.6 – 1.2)	4	0.8	0.6	1.01
Ca(mg/dl)(8.5 – 10.6)	8.4	8	8.3	8
Mg (mg/dl) (1.6 – 2.3)	1.5	1.41	1.4	1.51
Arterial Blood Gas Analysis	Metabolic Alkalosis	Metabolic Alkalosis	Metabolic Alkalosis	Metabolic Alkalosis
T3 (nmol/L) (1.1- 2.9)	2.3	1.8	2	1.6
T4(ng/dl)(4 - 12)	8.2	7	9.3	5.4
TSH(mIU/L)(0.35 – 5)	4	4.2	1.2	4.27
Urine				
Na^+(mmol/ltr) (30- 140)	78	144	127	68
K^+ (mmol/ltr)(15 -65)	24.7	22.6	48	46.3
Ca^{++}(mmol/d) (1.2 – 6.2)	1	0.9	0.2	0.8
Cl^-(mmol/ltr)(98 -106)	154	121	136	112
PH	7	7.5	6.4	6
Electrophysiological tests				
ECG	Uwaves	Uwaves	Uwaves	Uwaves
NCV	Normal	Normal	Normal	Normal
EMG	Normal	Normal	Normal	Normal

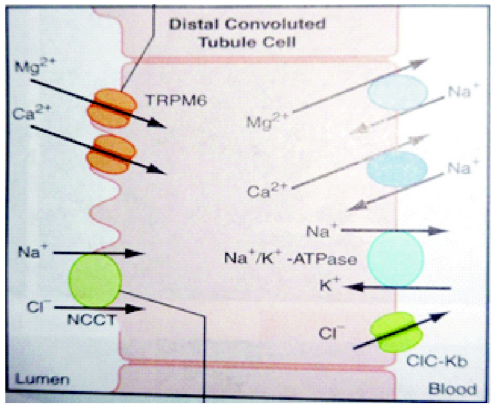

Fig – 1

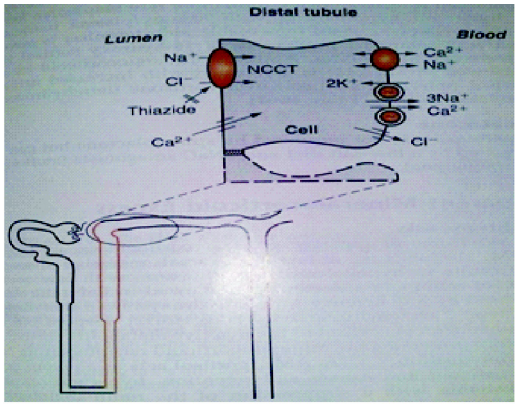

Fig – 2

Fig.1 & Fig.2 : **[**A model of transport mechanisms in the distal convoluted tubule. Sodium-chloride (NaCl) enters the cell via the apical thiazide – sensitive NCC and leaves the cell through the basolateral Cl- channel (ClC-Kb), and the Na+/K+-ATPase. Indicated also are the recently indentified magnesium channel TRPM6 in the apical membrane, and a putative Na/Mg exchanger in the basolateral membrane. These transport mechanisms play a role in familial hypokalemia-hypomagnesemia or Gitelman's Syndrome.**]**

With the findings of hypokalemia , hypomagnesemia and metabolic alkalosis in normotensive patients with high urinary potassium and low urinary calcium excretion, Gitelman's syndrome was diagnosed. The patients were treated with spironolactone , along with potassium and magnesium supplements and liberal salt intake leading to improvement of quadriparesis , maintaining normal serum potassium level (3.5-4.5mmol/lt). ECG showed decreased amplitude of T waves in chest leads with prominent U waves. Nerve conduction velocity was within normal limit

DISCUSSION

In Gitelman's Syndrome impaired sodium and chloride reabsorption in either the thick ascending loop or the distal convoluted tubule cause hypovolumia which activates the rennin-angiotensin- aldosterone system (RAAS). The consequent hyper – aldosteronism , together with increased distal flow and sodium delivery, stimulates increased sodium reabsorption in the collecting tubule via the epithelial sodium channel(ENaC). This promotes increased potassium and hydrogen ion secretion , causing hypokalemia and metabolic alkalosis. It remains unclear how this defect leads to severe magnesium wasting. It has been shown that passive Ca^{2+} reabsorption in the proximal tubule and reduce abundance of the epithelial Mg^{2+} channel TRPM6, located in the DCT explains thiazide-induced hypocalciuria and hypomagnesemia , respectively. Since thiazides are known to inhibit NCCT, and in view of the phenotypic resemblance between GS and chronic thiazide-treatment , it is very likely that similar mechanisms are involved in the pathogenesis of hypocalciuria and hypomagnesemia seen the Gitelman's Syndrome[6].

Patients have hypokalemic metabolic alkalosis , but in contrast with Bartter's Syndrome, they are hypocalciuric and hypomagnesemic, and do not have signs of overt volume depletion[7]. Polyuria and polydipsia are not features of Gitelman's Syndrome either. Patients suffer from arthritis caused by chondrocalcinosis in several joints, possibly secondary to hypomagnesemia. Urinary prostaglandin E2 levels are normal, compatible with the poor response observed to prostanoid synthetase inhibition[8,9]. The major differential diagnosis of Gitelman's Syndrome is diuretic abuse , laxative abuse and chronic vomiting. A careful history, as well as measurement of urinary chloride and detection of diuretics should help differentiate between these conditions.

Gitelman's Syndrome require lifelong therapy with potassium and magnesium supplements and liberal salt intake. High doses of spironolactone or amiloride used to treat the hypokalemia, metabolic alkalosis and magnesium wasting. However magnesium repletion is essential to correct the hypokalemia and to control muscle weakness, tetany and metabolic alkalosis[10]. Nonsteroidal anti-inflammatory drugs are usually not helpful because prostaglandin levels are normal.

In general , the long term prognosis of Gitelman's Syndrome is excellent. However , the severity of fatigue may seriously hamper some patient's daily activities. Cardiac workup is recommended to screen for risk factors of cardiac arrhythmias[11]. Progression to renal insufficiency is extremely rare[12].

CONCLUSION

Gitelman's Syndrome should be evaluated in each and every case of hypokalemic quadriparesis or paraparesis as it is the most frequent inherited renal tubulopathy.

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Review Article

NEWER ORAL ANTICOAGULANTS

B.K Kullu*, S.K. Mohapatra**

INTRODUCTION

A broad-spectrum of pharmaceutical agents is available which are very commonly used as an adjunctive therapy along with blood products in the treatment of patients with hemostatic disorders.[1,2] Antithrombotic agents are very commonly prescribed for prevention and treatment of venous thromboembolism. (VTE), arterial fibrillation (AF), and acute coronary syndromes (ACSs), and prevention of embolism from mechanical heart valves[3]. Both forms, oral and parenteral are very commonly available each with various indications and therapeutic targets. The oral anticoagulation therapy has been used synonymously with the oral vitamin K antagonists (VKAs) until recently when the advent of the novel agents has broadened the use of this term.

The first class of the oral anticoagulants available was the coumarin derivatives and around 11-21% of adults in the modern world have been taking VKA in the form of warfarin or acenocoumarol[4]. The novel oral anticoagulants (NOACs) were developed with more pharmacokinetic-pharmacodynamic relationships, faster onset of action, and fewer potential interactions.

CLASSIFICATION OF NOACs

Newer anticoagulants are broadly classified into two groups viz direct inhibitors of factors Xa and Direct thrombin inhibitors (DTI). It can be classified as follows.

1. Direct inhibitors of factor Xa

a. Rivaroxaban

b. Other orally active factor Xa inhibitor

i. Ly517717

ii. YM150

iii. Apixaban edoxaban of betrixaban

iv. PRT054021

v. DU-176b

2. Direct thrombin inhibitors (DTI)

The DTIs exert their effect by interacting directly with the enzymes thrombin without the need of a cofactor

a. Dabigatran & Dabigatran etexilate (Prodrug)

b. Ximelagatran

DIRECT INHIBITORS OF FACTOR Xa

Rivaroxaban

Rivaroxaban is a direct inhibitor of factor Xa in final common pathway of activation of coagulation cascade. Rivaroxaban has 80% bioavailability, a peak onset of action in 3 hours, and a plasma t1/2 of 7-11 hours. About one third of the drug is excreted unchanged in the urine, the remainder is metabolized by the liver and inactivate metabolites are excreted in the urine or feces. This drug is given in fixed doses and does not require coagulation monitoring. Like dabigatran etexilate rivaroxaban also is approved in the E.U. and Canada for thrombo prophylaxis after hip or knee replacement surgery. Rivaroxaban is not available in the U.S. Ongoing trails are going on comparing rivaroxaban with warfarin for treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation. Rivaroxaban was non inferior to warfarin in the prevention of subsequent stroke or rstimre embolisation[5,6].

Apixaban

Apixaban is a direct and competitive inhibitor of factor Xa. It has about 50% bioavailability and

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approximately 25% is excreted by the kidney. Apixaban at a dose of 2.5mg twice daily has been shown to be effective and safe for the prevention of venous thrombo embolism after elective orthopaedic surgery. Among patient with atrial fibrillation who are at high risk for stroke and for whom vit. K antagonist therapy is unsuitable Apixaban as compared with aspirin substantially reduce the risk of stroke with no significant increase in the risk of major bleeding or intra cranial bleeding. The net clinical benefit of Apixaban in these patients was therefore substantial[11]. In patients with atrial fibrillation for whom Vit. K antagonist therapy was unsuitable Apixban reduced the risk of stroke. Apixaban as a safety and efficacy at a dose of 5mg twice daily as compared with Aspirin at a dose of 81-324mg daily. For the treatment of patients with atrial fibrillation who are at high risk of stroke and whom Vit. K antagonist therapy was considered and suitable[15].

DIRECT THROMBIN INHIBITORS (DTI)

Ximelagatran

Ximelgatran is the first orally active thrombin inhibitor. It is prodrug of the active site directed thrombin inhibitor melagatran. Ximelagatran demonstrates 20% oral bioavailability that is minimally affected by food intake, with peak plasma ximelagatran concentration observed 1.8-22 hours after oral administration. It is eliminated via the kidneys. Ximelagtran has a plasma half life of 4 to 5 hours and is administered orally twice daily. Ximalegatran has been evaluated for the prevention of VTE in six phase III clinical trials in patients undergoing either elective hip surgery, major knee surgery or both. The comparator was enoxaparin in 3 studies and warfarin in 3 others. These studies showed significantly lower rates of DVT/VTE in the ximelagatran arm[8,9,10,11,12,13].

Dabigatran

Dabigtran is the most common tried drug in this group. It is a low molecular weight oral direct thrombin inhibitor currently in clinical development. Because of its poor oral bioavailability an orally active prodrug dabigatran etexilate has been developed to overcome this problem. It is specific competitive and reversible thrombin inhibitor. The bioavailabitlity of dabaigatran is 3.5 to 5%. The agent is renally excreted. The elimination half life is 14 to 17 hour[16]. Thus it can be given once daily. A pooled analysis having 8000 patients included in three phase III trails (REMODEL, RE-MOBILIZE RE-NOVATE) concluded that dabigatran was non-inferior to enoxaparin in the prevention of major VTE and VTE related mortality after both knee and hip replacement. Dabigatran etexilate is a prodrug that is rapidly converted to dabigatran, which reversibly blocks the active site of thrombin.

The drug has oral bioavalability of ~6% a peak onset of action in 2hrs and a plasma t1/2 of 12-14 hours. When given in fixed doses dabigatran etexilat produces such a predictable anticoagulant response that routine coagulator monitoring is unnecessary. Dabigatran etexilate is approved in the E.U. and Canada for prevention of venous thrombo embolism after elective hip or knee replacement surgery. It is not yet available in US. In phase III trial dabigtran etexilate was non inferior to warfarin for treatment of patient with venous thrombo embolism (Schulman et al -2009 and superior to warfarin for stroke prevention in patients with atrial fibrillation (Connolly et al -2009)[14]. Therefore this drug represents a promising alternative to warfarin for patients who require long-term anticoagulation.

The RELY trial shows the promise of these new agents for long term indication. These trial compared two different dose regimens of dabigatran etexilate (110mg or 150mg twice daily) with warfarin (dose adjusted to achieve an INR between 2 and 3) for stroke prevention in 18.113 patients with nonvalvular atrial fibrillation[14]. The annual rates of the primary efficacy outcome, stroke or systemic embolism were 1.7% with warfarin 1.5% with the lower dose dabigtran regimen and 1.1% with the higher regimen. Thus the lower dose dabigatran regimen was noniferior to warfarin while the higher dose regimen was superior. Annual rates of major bleeding were 3.4% with warfarin compared with 2.7% and 3.1% with lower and higher dose dabigatran regimens, respectively[14]. Thus the lower dose dabigatran regimen was associated with significantly less major bleeding than warfarin, while the rate of major bleeding with the higher dose regimen was not significantly different from that with warfarin.

Based on the result of the RE-LY trial is used for stroke prevention in patients with atrial fibrillation, the 150mg twice daily dose of dabigatran is recommended for most patients. In united state 75mg twice daily doses is recommended for patients with a creatinine clearance of 30 to 50ml/min, while in Canada the 110mg twice daily dose is recommended for those over the age of 80 years or for patients at high risk of bleeding. The drug is contraindicated in patients with a creatinine clearance less than 15ml/min.

Major highlights of the NOACs are as follows:

· The NOACs vary widely in their pharmacokinetic properties. The biovailability of rivaroxaban is high, while that of dabigatran is much less. The half-life of these agents is variable in normal individuals and patients. The elimination of dabigatran depends largely on renal excretion; patients with renal impairment are exposed to higher levels of dabigatran for a longer duration. Dose adjustment is suggested in such cases.

Although drug interactions with NOACs are not as frequent as with the older ones, drug interactions do occur and affect the pharmacockinetic parameters of these drugs.

TABLE I
PHARMACOKINETIC FEATURES OF NOVEL ORAL ANTICOAGULANTS[21,22]

Drug	Rivaroxaban	Apixaban	Dabigatran
Bioavailability	80-100%	50-85%	~6.5%
Time to peak drug Levels	2-4 hours	3 hours	0.5-2 hours
Half-life	5-9 hours in healthy subjects 7-11 hours in patients	9-14 hours	11 hours in healthy young subjects 14-17 hours in patients
Elimination	66% renal 33% fecal	27% renal 63% fecal	80% renal 20% fecal
Drug interactions	CYP 3A4 inhibitor P-GP inducers/inhibitors	CYP3A4 inhibitor P-GP inducers/inhibtors	PPls decrease absorption P-GP inducers/inhibitors
Antidote	None	None	None
Time to peak effect	2-4 hours	3-4 hours	2 hours
Dose regimen 20mg/do.d	20mg/d. od.	2x2.5-5mg/d b.d	110-150 mg/ d.bd
Approved clinical indication	• Pulmonary embolism and DVT treatment and reduction in risk fo recurrence • DVT prophylaxis after knee or hip replacement surgery • Strok prophylaxis in patients with non-valvular AF	• Stroke and systemic embolism resulting from non-valvular AF	• Reduce the risk of stroke and systemic embolism in patients with non-valvular AF • Postop-rative VTE prophylaxis for TKA and THR surgery

P-GP. P glycoprotein; PPls: proton pumb inhibotrs; DVT: deep vein thrombosis; AF: atrial fibrillation; VTE: venous thromboembolism; TKA: total knee arthorpalsty; THR: total hip replacement.

TABLE II
COMPARISON OF THE FEATURES OF NEW ORAL ANTICOAGULANT IN ADVANCED STAGE OF DEVELOPMENT

Feature	Rivaroxaban	Apixaban	Dabigatran etexilate
Target	Xa	Xa	IIa
Molecular wt	436	460	628
Prodrug	No	No	Yes
Bioavailability %	80	50	6
Time to peak (h)	3	3	2
Half life (h)	9	9-14	12-17
Renal excretion %	65	25	80
Antidote	None	None	None

Table III
SOME CLINICAL PROPERTIES OF THE DTI FOR PREVENTION OF VTE

Features	Ximelagatran	Dibagatran
Dose	24 mg twice daily	150ml /mg twice daily
Indication	Prevention and treatment of VTE prevention of stroke in AF	Prevention and treatemtn of VTE prevention of stroke in AF
Clearance	Renal	Renal
Half life	4-5 hrs	15-17 hrs
Binding to thrombin	Reversible	Reversible
Bmonitoring	Not required	Not required

TRIALS, ADVANTAGES AND DISADVANTAGES

The conventional oral anticoagulatns, despite having many drawbacks, remain the mainstay of oral anticoagulation therapy. Although newly introduced novel anticoagulants offer some benefits over the conventional ones, they have their own set of disadvantages. The advantages and disadvantages of the NOACs vs the conventional VKAs are listed in Table 4.

The twice-daily regimen of these NOACs may not be preferred by patients and may led to poor patient compliance[25]. in patients with poor adherence to therapy, the risk of stroke or systemic embolism is increased.[21]

Table-IV
Advantages and Disadvantages of Novel Oral Anticoagulatns over Older Oral Anticoagulants[24]

Advantages	Disadvantages
• Fixed-dose regimen • Good safety profile • Lesser drug interactions • No food interactions • No need of routine monitoring	• Patient compliance -twice-daily dosage regimen -short half-life • No assay method • No antidote • Cost • Dosage modification in renal impairment • Side effects: Gastric intolerance, dyspepsia, myocardial infarction, minor haemorrhages

the risk of stroke or systemic embolism will be increased in those patients who do not adhere to therapy.[25] No coagulation assay is easily available to precisely measure the anticoagulation effect[25] as the dose cannot be titrated, the cause of failure of therapy (poor adherence vs failure) cannot be assessed, the degree of coagulation inhibition cannot be easily assessed in emergency situations, such as need for urgent surgery or in patients with life threatening bleeding. No specific antidote is known till day to reverse the anticoagulant effect of these newer agents. This may be problematic in patients with overdose, or those requiring immediate surgical intervention.[25] the newer anticoagulants are much expensive than the conventional ones.[25] most of the newer anticoagulants depend largely on renal excretion for their elimination. Patients with renal impairment may be exposed to higher levels of such agents. Thus, dosage modifications are required. Some of these agents are contraindicated in patients with severe renal impairment.[18] the incidence of gastrointestinal side effects such as dyspepsia with dabigatran (reported incidence 12%) may lead to patient incompliance to the therapy. The incidence of myocardial infarction (MI) and hemorrhage is also a

concern with the use of dabigatran.[20] As the degree of anticoagulation cannot be assessed; bridging the anticoagulant therapy may be problematic.[23]

With the introduction of NOACs, many clinicians may be eager to switch their patients from VKAs to NOACs. Such a decision may be premature, and a careful judgment of risk-to-benefit ratio of these drugs should from the basis for such a decision[24]. The major advantage using novel anticoagulants is that they do not require frequent INR monitoring. Routine monitoring is beneficial in detecting occurrence of potentially harmful situations, such as over coagulation, and appropriate dosage adjustments can be done to prevent worsening of the situation. Such incidents also alert the clinicians and the recurrence of over coagulation can be prevented in future. The guidelines recommend 4-weekly INR monitoring in patients who are on VKAs, recently a study reported that time in therapeutic range of INR was more than 70% with 12-week INR monitoring. Further, fewer patients in 12-week INR monitoring group had any dose changes than in the 4-week monitoring group ($p<0.05$).[25] The Home INR Study (THINRS) reported that weekly home-based INR monitoring is as safe as clinical monitoring which may help reduce patient inconvenience by reducing the time spent in the anticoagulation monitoring clinics. The patients have to be trained properly and competence has to be ensured in using home-based INR testing.[26]

The pharmacokinetic studies have reported considerable variations in plasma levels of dabigatran. There may be variability in the therapeutic response of various patients and hence the fixed dose of NOAC does not apply well clinically. The patient compliance reduces by 10% due to the twice- daily dosage of NOAC and its shorter half-life. It is difficult to ensure the therapy in the patient as monitoring is not done and there is a higher probability of the patient skipping doses. Vitamin K antagonists have comparatively longer half-lives, so missing an occasional dose may not be problematic.[25] Unavailability of assay method to precisely measure the anticoagulant effect of novel anticoagulants further limits the clinical utilization of the novel anticoagulants, as measuring the anticoagulant effect may be required in acute conditions such as suspected under- or overdosing, comorbidity, potential interactions, renal impairments (rapid degradation due to dehydration or the use of antibiotics), and in patients undergoing surgery or cardioversion. In the absence of an appropriate assay method, altered renal function may led to unknown consequences as novel agents depend largely on renal excretion for their elimination. Renal function decreases with age and other comorbidities, making the dosage adjustments necessary.[23]

Full spectrum of drug/food interactions is not yet known, and an assay method to determine the effect of such interactions is also not available. This adds to the uncertainty with the use of novel agents.[21] there are few reports of dabigatran being contraindicated in patients receiving quinidine and varapamil. Dose reduction of dabigatran is recommended with concomitant use of amiodarone. Further concomitant use of dabigatran and aspirin is not recommended for the fear of an increased risk of bleeding. Rivaroxaban, being largely metabolized by CYP450 enzymes, is contraindicated in patients receiving ketoconazole, itraconazole, and ritonavir. Concomitant administration of rivaroxaban with strong CYP3A4 inducers (Such as phenobarbitone, phenytoin, carbamazepine) should be used with caution. an increased risk of bleeding suggests cautious use of non-steroidal anti-inflammatory drugs with rivaroxaban.[21]

Recent 2013 congress of the International Society on Thrombosis and Haemostasis meeting in Amsterdam highlighted the risk of MI with dabigatran. The meta-analysis included 10 studies and among the 23, 839 dabigatran-treated patients, there were 292 MIs. Compared with warfarin, the risk of MI was increased 38%, while the risk of MI was 70% higher among dabigatran-treated patients compared with placebo-treated patients.[1,2,27,28] in another meta-analysis combined data from 7 studies of dabigatran- The RELY and PETRO trials vs warfarin in AF patients; 3 studies

of short-term prophylaxis of deep venous thrombosis with enoxaparin as control; one study in acute VTE with warfarin as control; and one study in ACS vs placebo. Results showed that dabigtran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group.[27]

CONCLUSION

The rise in gastrointestinal bleeding with the novel agents is a cause of concern, particulary in elderly population. In the absence of a specific antidote to reverse their effect, management of life-threatening bleeding episodes is difficult. Also, the peri-operative reversal and bridging of anticoagulation with the novel agents are not yet determined.

New anticoagulants are being promoted for very few drug/food interactions. However, their use is not free of such concerns e.g. Poten P-glycoprotein inhibitors or inducers (such as quinidine, verapamil, and amiodarone) affect the serum concentration of the dabigatran. Dabigatran is thus contraindicated in patients receiving quinidine and verapamil.

Although VKAs are often criticized for the need of frequent monitoring, such a practice is very beneficial. Recommended 12-weekly monitoring, rather than 4-weekly, in patients with consistently stable INRs may help reduce patient inconvenience. In the absence of laboratory test and antidotes to reverse their effects, the use of NOACs is quite challenging.

Appropriate patient education and physician update is mandatory in order to achieve better patient compliance and target INR values as per the recommended OAC guidelines. The present scenario supports the usage of the VKAs as the efficacy of the newer oral anticoagulants needs to be studied in greater detail in the Indian population.

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Review Article

GLYCEMIC CONTROL IN DIABETES: CARDIOLOGIST'S PERSPECTIVE

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ABSTRACT

While type 1 Diabetes Mellitus (DM) is characterized by insulin deficiency due to pancreatic beta cell destruction, type 2 DM is characterized by a state of long standing insulin resistance (IR), compensatory hyperinsulinemia and varying degrees of elevated plasma glucose (PG), associated with clustering of cardiovascular (CV) risk and development of macrovascular disease prior to diagnosis of DM. Coronary artery disease (CAD) accounts for 70% of mortality and morbidity in patients with diabetes. Studies made in diabetes care have helped prevent or reduce microvascular complications in both type 1 and 2 diabetes. However the same cannot be said about macrovascular disease. Despite all data concerning the association of diabetes and cardiovascular disease (CVD), the exact mechanism by which diabetes is linked to atherosclerosis is incompletely understood, this is especially true in case of hyperglycemia. The positive effect of intensive glucose management in comparison to non intensive glucose control is far from proven. DCCT and UKPDS studies have shown that while a glycemic control is important for reaching long term macrovascular complications, early glucose control is far more rewarding (metabolic memory).Later trials like ACCORD, ADVANCE and VADT don't advocate tight glycemic control. In fact, ACCORD trial has shown increased mortality with tight glucose control. Tight glucose control may be beneficial in selected patients with short disease duration, long life expectancy and no CVD. In critically ill patients a blood glucose target of 140-180 mg % is fairly reasonable and achievable. The ESC/EASD guidelines of October 2013,Iike those of ADA, AHA and ACC continue to endorse a treatment target for glucose control in diabetes of HbAlc < 7%, based predominantly on microvascular disease with acknowledged uncertainty regarding the effect of the intensive glucose control on CVD risk. Management of hyperglycemia in diabetics should not be considered in isolation; diabetics require multifactorial intervention for hypertension, dyslipidemia and microalbuminuria besides hyperglycemia. In fact combined use of antihypertensives, aspirin and lipid lowering agent makes it difficult to discern salutary effects of anti hyperglycemic therapy.
KEY WORDS: *Diabetes, Glycemic control, Hyperglycemia.*

INTRODUCTION

Diabetes mellitus (DM) is a condition defined by an elevated level of blood glucose Type 1 diabetes is characterized by deficiency of insulin due to progressive destruction of pancreatic beta cells, progressing to absolute insulin deficiency .Type 2 diabetes is a combination of insulin resistance and beta cell failure in association with obesity and sedentary life style. However, not all overweight/ obese individuals have diabetes and vice- versa.

The increase prevalence of diabetes worldwide has led to a situation where approximately 360 millions people had diabetes in 2011, of which 95% would have type 2 DM.[1] This number is estimated to increase to 552 million by 2013 and it is presumed that half of these will be unaware of their diabetes status.

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The prevalence of diabetes is increasing world wide and more people with diabetes will die or be disabled as a consequence of vascular complications. Prospective studies have shown unambiguous association of blood glucose and glycated hemoglobin level with the risk of major cardiovascular events. In case of subjects with type 1 diabetes, in spite of the fact that CV rate is significantly lower compared with population with type 2 diabetes, their relative risk for coronary heart mortality is 7 fold higher than in matched counterpart without disease.

In spite of all these data concerning the association of diabetes and cardiovascular diseases (CVD), the exact mechanism by which diabetes is linked to atherosclerosis remains incompletely understood. This is especially true in case of hyperglycemia. The role of non-glycemic factors accompanying vast majority of patients with diabetes such as hypertension, dyslipidaemia and hemorrheological abnormality are better understood and appear to be independent of hyperglycemia. There also has been data regarding the future impacts of statins, aspirin, ACE inhibitors and aggressive control of blood pressure on progression of CV disease. In contrast, the positive effect of intensive glucose management on CV disease outcome is far from proven. Even some studies show a negative influence. The objective of the present article is to analyze trials related to glycemic control in diabetics and assess its impact on CV outcomes.

GLYCEMIC CONTINUUM AND CVD

Type 2 DM develops following a prolonged period of euglycemic insulin resistance(IR) which progresses with development of beta cell failure to frank diabetes with increase risk of vascular complications. While microvascular complications like retinopathy, nephropathy and neuropathy develop with overt hyperglycemia, macrovascular complications like coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD) appear earlier during the stage of IFG and IGT. Thus these complications are already established when type2 DM is diagnosed. Over 60% pts with type 2 DM develop CVD which is a more severe and costly complication than retinopathy.

MOLECULAR BASIS OF CVD

Insulin resistance has an important role in the pathophysiology of diabetes and CVD. Both genetic and environmental factors facilitate its development. The development of CVD in people with IR is characterized by early endothelial dysfunction and vascular inflammation leading to monocyte recruitment, foam cell formation and subsequent development of fatty streaks.[1] Over many years this leads to atherosclerotic plaque which in presence of enhanced inflammation becomes unstable and rupture to promote occlusive thrombus production. Atheroma from people of diabetes has more lipid, inflammatory change and thrombus than those free from DM. These changes occur over a 20-30 year period and are mirrored by the molecular abnormalities seen in untreated insulin resistance and DM.

Type 2 DM patients are obese and the release of free fatty acids (FFA) & cytokines from adipose tissue directly impairs insulin sensitivity in skeletal muscle and adipose tissue. FFA induces reactive oxygen species production, blunts activation of IRS 1 and P13K – AKT signaling leading to down regulation of insulin responsive GLUT 4. (Fig 1)

Hyperglycemia decreases nitric oxide bioavailability and affects vascular function involving over production of reactive oxygen species. [1] The mitochondrial electron transport chain is one of the first targets of high glucose with a direct increase in super oxide anion formation. A further increase in super oxide anion formation is driven by a vicious cycle involving ROS induced activation of PKC[1]. Mitochondrial ROS in tern activates cascades involved in the pathogenesis of the CV complications including polyol flux, AGE and RAGE. Hyperglycaemia induced ROS generation is involved in the persistence of vascular dysfunction despite normalization of blood glucose levels. This phenomenon is called metabolic memory which explains why vascular complication progresses despite

Table 1:

	ACCORD		ADVANCE		VADT	
N	10,251		11,140		1791	
Age (mean, years)	62		66		60	
BMI (mean, kg/m^2)	32		28		31	
Follow-up (mean, years)	3.5		5		5.6	
A1c target	<6.0% versus 7.0%-7.9%		=6.5% versus "standard"		<6% versus 8%-9%	
Baseline A1c (mean)	8.3%		7.5%		9.4%	
Endpoint A1c (mean)	Intensive 6.4%	Standard 7.5%	Intensive 6.43%	Standard 7.0%	Intensive 6.9%	Standard 8.4%
Severe hypoglycemic events	Intensive 10.5%	Standard 3.5%	Intensive 2.7%	Standard 1.5%	Intensive 8.5%	Standard 2.1%
Weight change	Intensive +3.5 kg	Standard +0.4 kg	Intensive - 0.1 kg	Standard - 1.0 kg	Intensive +8.1%	Standard +4.1%
Major macrovascular or microvascular event	Not reported		0.9 (0.82-0.98), *P* = 0.01		0.88 (0.74-1.05), *P* = 0.14	
Nonfatal MI/stroke, CV death	HR 0.9 (0.78-1.04), *P* = 0.16		0.94 (0.84-1.06), *P* = 0.32		Not reported	
All-cause mortality	HR 1.22 (1.01-1.46), *P* = 0.04		0.93 (0.83-1.06), *P* = 0.28		1.07 (0.81-1.42), *P* = 0.62	
Nonfatal MI	HR 0.76 (0.62-0.92), *P* = 0.004		0.98 (0.77-1.22), *P* = NS		0.82 (059-1.14), *P* = 0.24	

ACCORD = Action to Control Cardiovascular Risk in Diabetes trial ; ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation trial; A1c = glycosylated hemoglobin; BMI = body mass index; CV = cardiovascular; MI = myocardial infarction; VADT = Veterans Affairs Diabetes Trial.

Table 2:

CURRENT GLYCEMIC TARGETS (ESC/EASD guidelines) [1]

While an HbA1c target of less than 7% to reduce microvascular disease is a generally accepted level, the evidence for an HbA1c target in relation to macrovascular risk is less compelling
Consensus indicates that an HbA1c of less than 7% should be targeted but with acknowledgement of need to pay attentio
Fasting plasma glucose should be less th than 160-180mg % (9-10mmol/l) on an i
Ideally tight glycemic control should b younger people and without attendant co
Stringent targets like HbAlc 6-6.5% ma disease duration, long life expectancy hypoglycaemia or other adverse effect.
For critically ill indoor patients insulin than 180mg %(l0mmol/l) (ADA2008)
Once insulin therapy has been started in mg% is recommended.
With the preferred method of intravenous essential to minimize occurrence of hypoglycaemia and to achieve optimal glucose control.
Tight glucose control (80 – 110 mg %) has not been associated with mortality benefit in many trials. In past some trials show increase mortality.

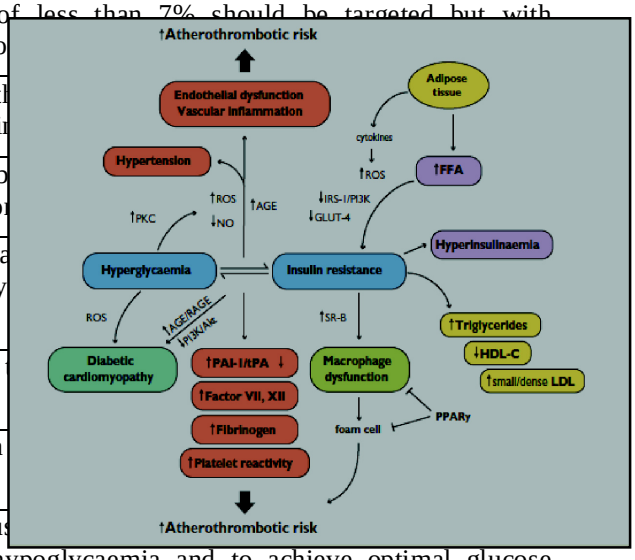

Fig 1. Pathophysiology of Atherosclerosis in Diabetes.[1] AGE = advanced glycated end products; FFA = free fatty acids; GLUT-4 = glucose transporter 4; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor 1; PKC = protein kinase C; PPARã = peroxisome proliferator- activated receptor-ã; PI3K = phosphatidylinositide 3- kinase; RAGE= AGE receptor; ROS= reactive oxygen species; SR-B = scavenger receptor B; tPA= tissue plasminogen activator.

intensive glycemic control. Elevated RoS generation despite euglycemic sensitivity undermines the clinical gold standard of indexing type 2 efficacy by blood glucose status.

Insulin resistant macrophage increases expression of oxidized LDL scavenger receptor-B, promoting foam cell formation and atherosclerosis. Macrophage dysfunction provide a crucial link between diabetes and CVD by both enhancing it and by contributing to the development of fatty streaks and vascular damage.

IMPACT OF GLUCOSE CONTROL ON CVD AND ITS COMPLICATION$

Randomised controlled trials provide compelling evidence that microvascular complications of DM are reduced by tight glycemic control. However the same cannot be said about macrovascular disease. Several prospective trials have been conducted which have so far failed to provide any conclusive evidence of the superiority of glycemic control in reducing macrovascular complications, or death rates in people with advance disease or those with long duration of diabetes.

LONG TERM EFFECT OF GLYCEMIC CONTROL

A. Diabetes Control and Complications Trial (DCCT) and Epidemiology of Dibetes Interventions and Complications (EDIC)[2]

In DCCT the rate of CV events was not significantly altered in the intensive treatment group of patients with type 1 DM.[2] After termination of study , 93% of the cohort were followed for additional 11 years under EDIC, during which the differences in HbA1C disappeared. During the combined l7 years follow up, the risk of any CV event was reduced significantly in the intensive group by 42% (9.63% p < 0.1).

B. United Kingdom Prospective Diabetes Study: (UKPDS) [3]

In the UKPDS trial, 3867 newly diagnosed subjects with type 2 DM were randomised to an intensive glucose control arm involving use of sulfonylurea or insulin and a conventional arm employing life style management. A subgroup of over weight subjects were included in the study that compared intensive glucose control with metformin (n=343) against conventional therapy (n=411). In the insulin and sulfonylurea group, a mean HbA1C level of 7% was achieved versus 7.9% in the control arm over 10 years. Intensive control decreased risk for a composite end point of all diabetes related complications (RRR=12%,p=0.029),and significantly improved microvascular disease risk (RRR=25%, p=0.01), where as a trend towards decreased risk of Ml was observed with intensive control (14.8 % vs 16.8%, p=0.052, statistically not significant). Stroke was numerically increased (5.6% vs 5.2%, p=0.05). In over weight subjects, metformin had better glucose control (Alc > 7.4% vs 8%) as well as significantly improved risk for MI (RRR=39%, p=0.01) and for all cause mortality (RRR=26% p=0.011). In extension phase UKPDS study, the patients were followed up for additional l0 years after completion of the trial, during which difference between HbA1c levels in both the groups disappeared. The follow up showed significantly reduced risk for MI in those originally randomised to intensive glycemic control both in insulin and sulfonylurea groups (RRR=15%, p-0.01) and in the metformin group (RRR=33%, p=0.05).

There was also significantly 13% reduction in all cause mortality in the intensively treated group. This persistent benefit generated from early strict glycemic control is known as legacy effect, which outlies the original reduction of HbA1c and subsequent loss of glycemic control. These observations are similar to those seen in DCCT follow up EDIC study where CV events, non fatal MI, stroke and CV death were reduced by 57% despite loss of glycemic separation. [2]

Combined UKPDS and DCCT / EDIC study show that

1. Glycemic control is important for reducing long term macrovascular complications.

2. Very long follow up period is necessary to demonstrate any benefit.

3. Early glucose control is important (metabolic memory).

MEDIUM TERM EFFECTS OF GLYCEMIC CONTROL:

1. **Action to Control Cardiovascular Risk in Diabetes (ACCORD)**[4]

The land mark study was designed to determine whether CV disease event rate could be reduced by intensively treating hyperglycemic hypertensive and dyslipidemia in a double 2x2 factorial design. The trial was based on the hypothesis that a 1.5% difference in HbAlc would result in 15% difference in a population of high risk diabetic individuals having a 3% annual CVD event rate.

The study included 10,251 patients with established type 2 DM and 1/3rd having a CV event. Patients were randomised to intensive glucose (targeting HbAlc < 6% and achieving a level of 6.4%) or standard therapy (targeting HbAlc of 7.0 - 7.9 % and achieving level of 7.5%). A variety of glucose lowering therapy was used. There was non significant trend towards reduction in primary outcome of trial (a composite of non fatal Ml, stroke or CV death) with intensive control. However, unexpectedly there was higher all cause mortality (CR-1.22, 95 % Cl-1.01-1.46, p=0.04). Higher rate of severe hypoglycaemia and weight gain were reported in intensive glycemic control group. Patients with high HbAlc level at base line were at higher rate of hypoglycaemia as were those who did not respond properly with a fall of HbAlc in intensive control group. The explanation for incremental mortality remains unresolved: possible explanations include hypoglycaemia precipitating CV death, pernicious effects of specific drug or combinations and a chance finding.

2. ADVANCE TRIAL [5]

The study was conducted to determine whether intensive lowering would reduce risk of microvascular and macrovascular events in individuals with type 2 DM and vascular risk factors compared to standard conventional case. The study involved 11,140 subjects. The mean duration of follow up was 5 years. The patients were randomised to intensive versus standard glucose control with gliclazide plus other drugs in the intensive arm compared with other drugs in the standard control group. Mean HbAlc achieved was 6.5% in the intensive group compared with 7% in the standard group. The incidence of combined major macrovascular and microvascular events was significantly reduced (HR-0.9, 95% CI 0.82-0.98, p=0.01) in the intensive control group. This was primarily driven by reduction in progression of albuminuria or emergence of new nephropathy. The CV component of the primary event was not significantly reduced by intensive glucose control. There was no evidence of increase in all cause mortality. Actually there is a non significant trend towards reduction in all cause mortality.

3. The VADT study [6]

The trial included American veterans, and 90% were males. A variety of glucose lowering agents was used including metformin, glimepiride, rosiglitazone and insulin. An HbAlc of 6.9% was achieved in the intensified control arm compared with HbA1c of 8.4% in the standard treatment arm. After a median follow up of 6.5 years, no significant lowering of composite CV outcomes was noted in the intensive control group. Severe hypoglycemia was more prevalent in the intensive control group. Benefits of intensive control were apparent only in individuals with shorter duration of diabetes, lower HbAlc and absence of CVD at base line. Table 1 shows the baseline characteristics of ACCORD, ADVANCE & VADT trials.

Insights from ACCORD, ADVANCE and VADT trial (Table 1)

1. Important finding of all 3 studies is the suggestion that a beneficial effect of glycemic control intervention is more likely in association with less disease duration.

In the ACCORD study participants with base line A1c < 8% rather than having adverse effects of intensive glycemic treatment on mortality, showed a significant reduction in primary out come favoring such

treatment. Similarly in ADVANCE trial, the combined macro and microvascular primary outcome benefit of glycemic control intervention was seen in participants without a baseline history of macrovascular disease. Similarly in the VADT trial, patients who had composite out come event had longer diabetes duration, higher HbAlc and coronary arterial calcification.

2. Effect of hypoglycaemia may be of importance. In the ACCORD study, although investigators stated that this was not a mediator of increased mortality associated with intensive therapy, intensive interventions was associated with significant severe hypoglycaemia. The ADVANCE and VADT study group similarly have reported high incidence of severe hypoglycaemia.

3. A meta analysis of these 3 trials suggest that HbA1c reduction of 1% is associated with 15% of relative risk reduction in non fatal Ml, but without benefit on stroke or all cause mortality.

4. Conclusion from these 3 trials is that intensive glycemic control should be appropriately applied in an individualized manner taking into account age, duration of diabetes and history of CVD.

5. Despite the fact that ACCORD, ADVANCE and VADT showed no benefit of intensive glucose control on primary CV endpoints in Type 2 DM, subgroup analyses suggest that any potential benefit on CV outcomes and mortality depends upon multiple interrelated factors such that medications capable of exerting direct CV therapeutic effects may be required to see a CV benefit.

6. One should also remember that HbA1c cutoff makes less sense for the cardiac events because cardiovascular risk depends upon various strong risk factors like hypertension and smoking [7].

GLUCOSE CONTROL IN ACS

Elevated plasma glucose during an ACS is associated with a serious prognosis in patients with DM than without diabetes. Hyperglycemia may relate to previously undetected glucose perturbations but also to stress induced catecholamine release increasing FFA concentration, decreased insulin production and increasing insulin resistance and glycogenolysis with a negative impact on myocardial metabolism and function.

Two strategies have been tasted in an attempt to improve prognosis in patients with ACS

1. Metabolic modulation

Metabolic modulation by means of glucose-insulin-potassium infusion regardless of presence of DM or elevated PG, is based on the assumption that increase in intracellular potassium stabilises the cardiac myocytes and facilitates glucose transport into the cell. Other potential benefits include decreased production of FFA, improved use of glucose for energy production and improved endothelial function and fibrinolysis. Despite these proposed mechanistic benefits of glucose, potassium and insulin therapy, the strategy has been proven futile in CREATE trial which enrolled more than 20000 patients with Ml who randomised to G&K therapy versus usual care. No benefit of G&K therapy was demonstrated. This lack of effect may be due to increased PG or negative effect of fluid load induced by G&K infusion.

The DIGAMI trial, which is often misinterpreted as a trial of intensive glucose control is actually a glucose insulin infusion therapy trial [8]. The first DIGAMI trial randomised 620 patients with DM and AMI to > 24 hrs insulin-glucose infusions followed by multi-dose insulin, or routine glucose lowering therapy. Mortality after 3-4 yrs was significantly reduced in the intervention group[8]. However DIGAMI-2 failed to replicate this prognostic benefit. The plausible reason for this discrepancy was that in DIGAMI-l admission HbAlc decreased more (1.5%) from a higher level (9.1%) compared with 0.5% from 8.3% in DIGAMI-2. Since DIGAMI-2 trial did not achieve a difference in glucose control between intensively treated and control groups, it is still an open question as to whether glucose lowering is beneficial.

2. Glucose control in ICU setting

In 2001 Van den Berghe published a randomised controlled trial of critically ill surgical pts showing that tight glucose control reduced hospital mortality[9]. Since

the greatest decrease in death occurred in subgroup of pts with multi system organ failure, it was speculated that benefits of tight glucose control might extend to medical ICU patients as well. However subsequent trials by the same group couldn't demonstrate any benefit with tight glycemic control. Further recent trial like VISEP and European glucontrol showed trend for increased rate with tight glucose control. The NICE SUGAR trial in fact demonstrated an actual 14% increase in mortality rate with intensive glucose regimen[10].

Few of these trials assessing glucose control in ICU settings included ACS patients. Therefore, general applicability of the observation remains uncertain. Because of paucity of data on tight glycemic control a glucose target of < l80 mg % is a reasonable approach in ACS patients.

WHY LOWER IS NOT NECESSARILY BETTER?

The UKPDS study was the first to provide evidence that in newly diagnosed type2 DM patients intensive glucose control may reduce the risk of microvascular complications, also with modest effect on CV outcomes. Thus the concept 'the lower, the better' (glucose level) was proposed by all diabetology guidelines as a paradigm for type2 DM patients. However, this concept has been challenged by 3 landmark trials: ACCORD, ADVANCE and VADT.

Numerous potential reasons have been put forth to explain the lack of benefits with intensive glucose control therapy. These include pernicious effects of specific drugs or drug combinations, increased incidence of hypoglycaemia precipitating CV death and a mere chance finding. The current glycemic target is < 7% of HbA1c with individualization of therapy. (Table 1)

HYPOGLYCEMIA AND ADVERSE CV EVENTS

In the ACCORD trial, which included diabetic patients with CV disease or high CV risk, symptomatic, severe hypoglycaemia was associated with higher mortality in patients in both study arms[4]. ADVANCE trial also showed that occurrence of severe hypoglycemic episodes has a detrimental effect on CV outcome.

The ORIGIN trial also showed evidence corroborating hypoglycaemia with adverse CV outcomes [11]. The trial randomised 12,537 people at high risk of CVD plus IGF, IGT or type2 DM to receive insulin glargine (with a target FBS level of < 95mg %) versus standard care. After a median follow up of 6.2 years, the rates of incident CV outcome were similar in both the groups. In this population of ORIGIN trial, severe hypoglycaemia occurred in 5.7% & 1.8% patients assigned for insulin glargine and standard therapy groups respectively. Severe hypoglycaemia was associated with a greater risk for primary outcome, mortality, CV deaths and arrhythmic deaths.

Compensatory mechanisms induced by hypoglycaemia, such as enhanced catecholamine release, may aggravate myocardial ischemia and provoke arrhythmia. Still then, it remains unclear weather hypoglycaemia is simply a marker of disease severity or contributes to adverse outcomes. Hypoglycemic episodes probably identify patients at risk for other reasons like malnutrition, HF, and renal dysfunction.

CARDIOVASCULAR EFFECTS OF DRUGS USED IN DIABETES

Few data are available regarding the net cardiovascular safety and efficacy of medications used to control glucose level in diabetes.

Metformin has best track record of safety, tolerability and low hypoglycemia risk. This drug remains the drug of first choice.

Concern always exists regarding ability of sulfonylurea, to impair ischaemic preconditioning. However, UKPDS has been able to allay such fear to some extent.

Of thiazolidinediones, rosiglitazone was withdrawn from market because of fear of increased myocardial infarction risk. Recently, it has been reintroduced. Pioglitazone reduces myocardial infarction risk but can cause fluid retention.

Dipeptidyl peptidase 4 inhibitors have so far

shown to have no adverse cardiovascular outcomes. Their safety track appears good.

Insulin increases the risk of hypoglycemia and retrospective studies show adverse outcome when insulin is used in diabetics with heart failure.

CONCLUSION

As the disease diabetes assumes alarming proportions and threatens to become the modern pandemic, every effort should be made to prevent diabetes related cardiovascular complications. Interventions to reduce fasting blood glucose levels have unfortunately been not translated to better cardiovascular outcomes in all individuals. Recent trials like ACCORD, ADVANCE, and VADT challenge this proposition. However, metaanalysis of these trials suggests that the subgroups of diabetics with shorter duration of illness are beneficial from tight glycemic control (HbA1c <7%). Hypoglycemia is always an issue, when the physician aims for tight glycemic control. As hypoglycemia adversely affects cardiovascular homeostasis, every effort should be made to avoid it at all costs while going for tight glycemic control.

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Current Concept

NON-ALCOHOLIC FATTY LIVER DISEASE : AN EMERGING CARDIOVASCULAR RISK FACTOR - EVIDENCE & CONTROVERSIES

D.R. Das

ABSTRACT

Non-alcoholic fatty liver disease(NAFLD) is a marker of pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state. This results in several deleterious pathophysiological processes including abnormal glucose, fatty acid and lipoprotein metabolism, increase oxidative stress, deranged adipokine profile, hypercoagulability, endothelial dysfunction, and accelerated progression of atherosclerosis. NAFLD affects up to a third of the population worldwide and may confer increased cardiometabolic risk with consequent adverse cardiovascular outcomes independent of traditional cardiovascular risk factors and the metabolic syndrome. It is characterized almost universally by insulin resistance and is strongly associated with type 2 diabetes and obesity. This ultimately leads to a dysfunctional cardiometabolic phenotype with cardiovascular mortality representing the main mode of premature death in NAFLD. This articleaims at discussing in-depth the evidence to date linking NAFLD with cardiovascular disease & reviewing the likely mechanisms underlying this association. ***Keywords :*** *Non-alcoholic fatty liver disease, non-alcoholic steato hepatitis, fatty liver, cardiovascular risk.*

INTRODUCTION

The role of non-alcoholic fatty liver disease (NAFLD) as a potential independent cardiovascular (CV) risk factor has now gained considerable prominence such that an awareness of this multi-faceted condition is essential for practising physicians, given that it affects 20-33% of the general population[1-4].As the pathogenesis of the condition is closely linked to insulin resistance(IR),its prevalence parallels that of increasing rates of obesity and type 2 diabetes worldwide, with up to 95% of obese persons and 75% of diabetics likely to have NAFLD, with most cases unrecognized.The potential future burden of NAFLD on public health-care utilization and costs is likely to be significant.As such,the cardio-metabolic risk conferred by NAFLD merits increased collaborative study between physicians,diabetologists, hepatologists, and especially cardiologists, given that CV disease appears to largely influence major clinical outcomes in NAFLD.[5-10] This article aims to present to the physicians summary of the evidence linking NAFLD with CV disease, the potential mechanisms underlying this association, as well as its relation to IR,obesity and the metabolic syndrome(MetS) in the context of increased CV risk.

DEFINITION OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD is the most common cause of chronic liver disease in the general population and is present when fatty infiltration affects > 5% of hepatocytes,in the presence of <20g (2.5 U) of alcohol consumption per day,without evidence of other causes of liver disease[11]. NAFLD is a slowly progressive condition and represents a spectrum of varying severity of liver

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disease,ranging from simple steatosis to co-existent inflammation with hepatocyte ballooning and necrosis,variable grades of fibrosis, and ultimately cirrhosis and an increased risk of hepatocellular carcinoma.[11.12] Nonalcoholicsteatohepatitis (NASH) represents the more advanced stages of this disease, i.e. the 'inflammatory' component in addition to steatosis, which carries ahigher risk of CV disease and mortality than simple steatosis.[13] Insulin resistance and obesity, both key features of the MetS, are strongly associated with NAFLD progression.[14] The prevalence of NAFLD in subjects with MetS is increased four-fold compared with those without the disease and 3% of NAFLD subjects have MetS.[2] Despite MetS itself conferring an approximate doubling of CV mortality risk,[15] there is still abundant evidence linking NAFLD to increased CV disease risk over and above that associated with the MetS criteria, suggesting that NAFLD per se contributes to accelerated atherogenesis.[16]

DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE

Current laboratory and radiological methods to diagnose NAFLD are either too insensitive or not specific enough to grade disease presence and severity. As the early stages of NAFLD are often asymptomatic, mildly abnormal liver enzymes are usually the only clue pointing to the disease. However up to 70% of NAFLD patients may have normal liver enzymes,[17] and although alanine aminotransferase (ALT) levels have shown to be the best single biochemical correlate of hepaticsteatosis, [18] they do not distinguish between varying stages of NASH and can be normal in histologically severe disease. [19] Furthermore, ultrasound imaging can only detect steatosis when >30% of the liver is affected, but is still recommended as the first-line investigation to 'confirm' the presence of fatty liver due to its widespread availability and low cost .[20] Although magnetic resonance spectroscopy (MRS) has excellent sensitivity in detecting and accurately quantifying hepatic steatosis, none of the non-invasive modalities can detect inflammation and/or fibrosis,i.e NASH.Consequently, liver biopsy is at present the 'gold-standard' (taking into account potential inaccuracies of sampling variability) for diagnosing NAFLD and staging the degree of NASH and fibrosis by histological assessment, as well as monitoring disease progression. [21] Because of the highly invasive and potentially risky nature of liver biopsy,various algorithms of combined clinical and specialized blood biomarkers,along with advanced imaging methods (e.g. MR/ultrasound elastography) are being developed to allow improved non-invasive detection of disease stage and activity.[20]

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN NON-ALCOHOLIC FATTY LIVER DISEASE

Numerous epidemiological studies have reported an increased incidence of adverse CV events in NAFLD subjects compared with the general populations [5-10,22-29] (Table 1). As NAFLD is the commonest cause of abnormal liver enzymes in developed countries, [20] many epidemiological studies have employed these as biochemical surrogates of NAFLD.Several studies have shown a significant association between increased gamma-glutamyltransferase (GGT) levels and CV mortality over an average median of 12-year followup,even after adjusting for typical CV risk factors and body mass index (BMI).[22-24] Additionally,a meta-analysis of 10 pooled studies confirmed the independent association between elevated GGT and adverse CV events.[25] However,GGT is also expressed in atherosclerotic plaques and has a role in oxidative stress, [30] as well as being associated with all components of the MetS.[31] ALT has been reported to be more closely related to liver fat content than GGT. [14] Similarly, several large population-based cohort studies have reported an independent association between elevated ALT and CV mortality after adjusting for CV risk factors.[26-28] Importantly, the correlation of raised ALT or GGT with CV disease in these studies may simply reflect their significant association with IR,[32] which is itself a strong risk factor for CV disease, rather than as a marker for the presence or severity of NAFLD.Employing ultrasound imaging as a more specific diagnostic determinant of NAFLD than liver enzymes, three large

community based prospective cohort studies also documented a significant independent association with CV events [5-7] (Table 1).Of note,Hamaguhi et al.[6] undertook a prospective analysis of 1637 healthy subjects recruited from a health check-up programme, and found 19% with ultrasound evidence of NAFLD. At 5-year follow-up, 5.2% of the NAFLD group suffered an adverse CV event, compared with 1.0% of the non-NAFLD group (P<0.001). By multivariate analysis, the association between NAFLD and future CV events was shown to be independent of the MetS, as well as conventional cardiac risk factors. Although these studies are strongly indicative of NAFLD as a predictor of CV disease independent of diabetic status, they are limited by the lack of sensitivity of ultrasound determination of NAFLD.

Even so, smaller long-term prospective studies in patients with biopsy-proven NAFLD show significantly higher total mortality rates compared with a matched reference population,with CV disease representing the main mode of death, outnumbering cancer- and liver-related mortality.[8-10] Of note, only subjects with NASH rather than simple steatosis had significantly reduced survival, although in one study even subjects with bland steatosis showed a trend to reduced survival (P=.006), primarily from CV-related causes over a median follow-up of 24 years .[8]

EVIDENCE OF ASSOCIATION OF NAFLD WITH CARDIOVASCULAR DISEASE

Cardiovascular risk assessment scores in non-alcoholic fatty liver disease

Given that traditional CV risk factors are commonly prevalent in NAFLD subjects, investigators have applied validated CV risk prediction scores to evaluate the risk profile of NAFLD patients,with most of these studies showing that NAFLD independently confers an increased CV risk score .[33-36] One study also documented that high-sensitivity C-reactive protein,a well-established marker of adverse CV outcome,was significantly elevated compared with the non-NAFLD group in both sexes. A strong association has been shown between histological severity and calculated estimates of CV risk [both QRISK2 and Framingham risk score(FRS)] independently of markers of glucose control and obesity.[37]

Although these global risk prediction studies may help to describe part of the association between NAFLD and increased CV risk,they are flawed by the inherent limitations of using risk scores based on traditional CV risk factor-derived multivariable statisticalmodels to identify at-risk patients.[38] Furthermore,we know that some of the important determinants of NAFLD, such as IR, obesity, and raised triglycerides(TG), all of which also increase the risk of CV disease in MetS,[39] which shares many features in common with NAFLD statusincluding its direct cardio-metabolic effects, before we can evaluate its added discriminant value when applied to current CV risk prediction models in cohort studies.

Studies evaluating coronary disease in non-alcoholic fatty liver disease

Coronary artery calcium (CAC) scoring with cardiac computed tomography (CT) is a very sensitive method of demonstrating the presence and extent of coronary atherosclerosis and significantly improving CV risk prediction in asymptomatic individuals beyond traditional risk factor scoring system.[40] Several studies demonstrate a significantly increased coronary atherosclerotic burden in the presence of NAFLD,[41-44] with one study also reporting a significant association between ‘vulnerable plaque’ and NAFLD in patients undergoing multislice CT for clinical suspicion of coronary artery disease (CAD).[42] This finding is consistent with data showing that NAFLD patients have significantly higher plasma markers of oxidative stress and inflammation, which are in part derived from the diseased liver causing a systemic inflammatory and prothrombotic state.[45-46] A strong association between NAFLD and prevalence of significant CAD determined by coronary angiography has also been consistently reported albeit with variable thresholds of ‘significant’ CAD between studies.[48-51] Althoughthese studies indicate an independent association between NAFLD

and CAD in terms of angiographic appearance even after adjusting for traditional CV risk factors and components of the MetS,none of them evaluated the functional significance of these coronary lesions. Given that the presence of ischaemia rather than coronary anatomy dicate clinical outcome,[52-53] the significance of these findings in association with NAFLD should not be overestimated.

Studies evaluating carotid disease in non-alcoholic fatty liver disease

Measurement of carotid intima-media thickness (CIMT) and plaque burden by ultrasound is a well-validated and widely accepted screening tool for the prediction of CV disease in asymptomatic subject.[54.55] Several studies link NAFLD independently with carotid disease ,although a few have described a weaker association after adjusting for MetS .[35,56-61] Importantly severity of histological features of NAFLD appears to correlate independently with increasing CIMT,[58] concordant with epidemiological data documenting NASH patients having a higher CV risk than simple steatosis. Additionally, a systematic review of seven published studies (total of 3497 subjects) reported a significant association between NAFLD and CIMT, showing an estimated increase of 13% in CIMT for NAFLD cases compared with controls. Prevalence of carotid plaque was also more frequent in NAFLD subjects.[62]

Studies evaluating cardiac function in non-alcoholic fatty liver disease

Studies in subjects with MetS have consistently shown increased left ventricular(LV) mass index and diastolic function impairment when compared with controls, which could be secondary to the effects of IR, obesity and hypertension on cardiac structure and function.[67,68] Only a few studies have focused specifically on NAFLD subjects, and the finding of abnormal LV geometry and diastolic dysfunction has similarly been reported .[69] One study also demonstrated a strong positive correlation between the degree of diastolic dysfunction and amount of liver fat, with diastolic dysfunction and IR the only independent parameters associated with NAFLD.[70] Another study reported that echocardiographic measures of coronary flow reserve (CFR) were significantly lower in NAFLD compared with healthy controls, after adjusting for obesity, traditional CV risk factors and the presence of MetS.[68] Although they correctly postulated that this result likely reflects impaired coronary endothelial function in the NAFLD group,they were unable to exclude the possibility of these patients having asymptomatic epicardial CAD. The consistent finding of subclinical cardiac dysfunction in an asymptomatic population with NAFLD is perhaps not surprising, given that LV dysfunction and LV mass are strongly correlated with IR,as well as subsequent prognosis.[2]

Studies evaluating endothelial dysfunction and myocardial metabolism in NAFLD.

Endothelial dysfunction is now recognized as the earliest detectable component in the development of atherosclerosis. In both diabetic and non-diabetic cohorts, studies have shown an independent association between impaired endothelium-dependent flow-mediated dilation (FMD) and NAFLD.[2]In addition, lower FMD was observed in NASH compared with simple steatosis, again confirming the graded association of CV risk with severity ofNALFD.[36] To gain further insight on the causes of sublinical cardiac dysfunction in NAFLD, the effects of hepatic steatosis on myocardial metabolism have also been examined.[2,69] One study found a novel positive association between hepatic fat content and myocardial IR. Patients with high liver fat content not only showed significantly lower whole-body insulin sensitivity as expected, but also reduced myocardial glucose uptake and extraction rate, reduced CFR, and increased plasma levels of inflammatory markers and vascular adhesion molecules. Only liver fat content remained significantly associated with impaired myocardial metabolism even after adjusting for IR, visceral fat mass, and other important variables.[64,69] Another study assessed myocardial energy metabolism in NAFLD, utilizing 31 P-MRS to determine the ratio of phosphocreatine to ATP in a young, healthy

cohort.[13] The authors reported significantly impaired LV energy metabolism as well as increased epicardial fat in NAFLD compared with controls. This was despite normal LV morphological features and systolic/diastolic function in both groups, and was independent of usual CV risk factors. This suggest that in patients with hepatic steatosis, abnormalities in myocardial metabolism may precede functional and structural cardiac remodelling,leading to increased LV mass and diastolic dysfunction.

The precipitating factor for this dysfunctional cardiac phenotype appears to be the development of systemic and hepatic IR, leading to hyperinsulinaemia and increased FFA availability with associated myocardial IR. This produces inefficient energy metabolism by cardiomyocytes, switching to fat rather than glucose oxidation in physiologically demanding states & yielding less ATP per oxygen molecule consumed. With progressive workload placing the heart under increasing strain, this potentiates myocardial dysfunction ultimately leading to myocardial adaptive remodelling and myocardial injury. The excess F F A supply also leads to cardiac lipotoxicity by causing intracellular lipid accumulation and overwhelming normal cardiomyocyte oxidative capacity, resulting in increased oxidative stress and consequent cardiac apoptosis and dysfuntion.[2,13]

PATHOGENESIS OF CARDIOVASCULAR DISEASE IN NON-ALCOHOLIC FATTY LIVER DISEASE

Insulin resistance

The majority of the above studies point to an independent link between NAFLD and increased CVrisk or adverse CV outcome. However, there is considerable heterogeneity in these studies in the method of NAFLD diagnosis & quantification of severity of NAFLD.This appears to be of paramount importance due to the disparate pathophysiological and metabolic consequences of the various stages of simple steatosis and NASH, both strongly linked to hepatic and peripheral IR. In fact, liver fat content appears to be the best independent predictor of IR in skeletal muscle, adipose tissue, and the liver.[12]Similarly, adverse CV outcome is likely to be associated with liver fat/inflammation, progressively increasing with more advanced stages of NAFLD.[58,70] This parallels epidemiologic evidence showing a progressive relationship between glucose levels and CV disease extending from well below the diabetic threshold. [57] Ultimately, the development and progression of IR appears to be key mediator in the initiation and propagation of NAFLD, primarily through adverse changes in glucose, fatty acid and lipoprotein metabolism, with both conditions subsequently driving each other in a synergistic fashion. Alterations in cellular FFA transport,possibly through hyperinsulinaemia, are involved in the pathogenesis of ectopic fat distribution by diverting the accumulation of TG away from adipose tissue and towards others key metabolic organs,such as skeletal muscle and liver. This results in impaired insulin signalling in these tissues, and further exacerbates IR & the consequent cardiometabolic dysfunctional cascade.[57,64] These processes are also exacerbated by associated subclinical inflammation,deranged adipokines, and increased ectopic fat accumulation in other organs including the heart, all ultimately contributing to increased CV risk .

Visceral fat

Visceral adipose tissue (VAT) appears to have astrong independent positive correlation with liver fat.[18]This is not surprising given that plasma FFAs appear to be the main source of hepatic TGs in NAFLD, arising in part by greater lipolysis from insulinresistant adipose tissue. This helps to explain somewhat the close association between the MetS and NAFLD, in that increased waist circumference is a mandatory criteria in the International Diabetes Federation guidelines for diagnosing MetS. Additionally, the independent link between centrally obese individuals and increased CV morbidity and mortality is well established. [67]Studies show that increased VAT mass is independently associated with impaired glucose tolerance, IR, and dyslipidaemia, conferring an increased risk of CV disease, irrespective of diabetic status. [48,49] Furthermore,

the 'portal hypothesis' suggest that increased VAT lipolysis secondary to IR leads to anelevated flux of FFAs into the portal vein for direct transport to the liver, resulting in increased hepatic fat, which would suggest that visceral fat is an important mediator of liver fat content. [47] In fact, in the Quebec Cardiovascular Study, elevated FFA levels yielded a two-fold increase in the risk of ischaemic heart disease, regardless of the presence of diabetes. [65] Additionally, high FFA concentrations in patients with angiographic CAD independently predicted CV morality. [13] Apart from being a fat-storage organ, visceral fat is also metabolically active, secreting several adipokines, cytokines, and hormones that serve to regulate inflammation, liver fat, IR, and modify CV disease outcome.[12] Importantly, obesity in certain situations represents a chronic low-grade systemic inflammatory state that contributes to vasculopathy and CV risk through the release of these proinflammatory and atherogenic bioactive molecules. [29]

Epicardial fat

Given that NAFLD and excessive visceral abdominal fat represent abnormal ectopic fat deposition in the body, with associated VAT-secreted adipocytokines contributing to subclinical inflammation and atherosclerosis, what about the role of epicardial adipose tissue (EAT), itself a visceral fat layer? Its anatomical location and proximity to the myocardium and adventitial layer of the coronary arteries, as well as sharing the same microcirculation, make it an ideal entity to exert a paracrine and vasocrine effect on the heart and its blood vessels. [36] Imaging studies have already shown that epicardialthickiness or pericardial (epicardial and paracardial) fat volume correlate with the amount of VAT in both obese and non-obese subjects. [2] Furthermore, EAT thickness is also positively associated with the presence and severity of angiographic CAD, and increased epicardial or pericardial fat volume measured by CT are each independently associated with the presence of

CAC[5]. Importantly, adiponectin expression was found to be significantly lower in epicardial fat isolated from patients with severe CAD compared with those without CAD, and pericardial fat volume also correlates with multiple markers of inflammation and oxidative stress, thus signifying potential similarities in proinflammatoryadipokine function between EAT and VAT. However, it is likely that increased epicardial and myocardial fat both represent abnormal ectopic fat storage and may indeed be a marker of the cumulative effects of NAFLD and IR in the setting of pathological adiposity, with consequent associated adverse CV outcome.[2]

Inflammation

The liver is a key metabolic organ and central to the regulation of systemic inflammation. It is a generator as well as a target of various inflammatory and humoralfactors,working in concert and against secreted molecules from adipose tissue, macrophages, and endothelial cells in the context of CV disease initiation and progression.[6] Increasing severity of NAFLD likely represents worsening inflammatory and insulin-resistant states, with poorer cardiometabolic outcomes. High-sensitivity C-reactive protein, which is primarily produced by the liver and a marker of inflammation, is an independent predictor of CV events inseveral large studies. [2]Similarly, fibrinogen and plasminogen activator inhibitor-1 (PAI-1) also originate from hepatic tissue and are activators of the coagulation system, enhancing atherothrombosis.Targher et al. showed that biopsy-proven NASH patients had significantly higher levels of high-sensitivity C-reactive protein, fibrinogen, and PAI-1 activity compared with controls. Furthermore, the severity of NASH by liver histology correlated significantly with these CV risk biomarkers after adjustment for potential confounders, including IR and visceral adiposity.[5] A similar correlation was found for serum IL-6 levels, as well as serum and hepatic TNF-á in NASH patients.[2] These studies suggest that increased liver-secreted factors in NAFLD play an important role in the pathogenesis of systemic inflammation and atherosclerosis.

Dyslipidaemia

Non-alcoholic fatty liver disease is characterized

Table - Main epidemiological studies relating NAFLD to increased cardiovascular risk

Authors	Study characteristics [N-O assessement of quality[a]]	Diagnosis of NAFLD	Main findings
Ruttmann et al.[22]	Austrian population-based cohort (n=163, 944), median F/U of 12 years [3,1,3]	Liver enzymes(GGT)	CV mortality increased in NAFLD, independent of traditional CV RF_S, alcohol and BMI
Wannamethee et al.[23]	British population-based cohort (n=7613 middle-aged men), median F/U of 11.5 years [3,1,3]	Liver enzymes(GGT)	Total and CHD morality increased in NAFLD independent of CV RF_S , alcohol and BMI
Lee et al.[24]	Finnish population-based cohort (n=28, 838), F/U of 11.9 years [3,1,3]	Liver enzymes(GGT)	CHD mortality and non-fatal MI increased in NAFLD independent of CV RF_S and alcohol
Fraser et al.[25]	Meta-analysis of 10 pooled population-based cohort studies[b]	Liver enzymes(GGT)	CV events (fatal and non-fatal) increased in NAFLD afteradjustment for CV RF_S and alcohol
Fraser et al.[25]	British Women's Heart and Health Study,population-based (n=2961 older women), median F/U of 4.6 years [3,1,3]	Liver enzymes(ALT and GGT)	No independent association between NAFLD and fatal and non-fatal CV events
Schindhelm et al. [26]	Hoorn Study, population-based (n=1439 middle-aged), F/U of 10 years [3,2,2]	Liver enzymes(ALT)	Fatal and non-fatal CHD increased in NAFLD, independent of CV and MetS RF_S
Dunn et al.[27]	NHANES-III, population-based cohort (n=7574), mean F/U of 8.7 years [3,1,3]	Liver enzymes(ALT)	Total and CV morality increased in NAFLD but only in 45-54 year age group. Independent of CV RF_S
Yun et al.[28]	Korean population-based cohort (n=37, 085), median F/U of 5 years [3,1,3]	Liver enzymes(ALT)	CV or diabetes-related mortality increased in NAFLD, independent of CV RF_S, alcohol, BMI, and socio-economics status
Targher et al[5]	Valpolicella Heart Diabetes study, community-based diabetic cohort, free of CV disease (n=2103), mean F/U of 6.5 years [4,2,2]	Liver ultrasound	Increased fatal and non-fatal CV events in NAFLD, independent of CV RF_S, diabetes control, and MetS
Hamaguchi et al. [6]	Japanese community-based healthy cohort (n=1637), mean F/U of 5.8 years [4,2,1]	Liver ultrasound	Increased adverse CV events in NAFLD, independent of CV RF_S and MetS
Haring et al. [7]	Study of Health in Pomerania population-based German cohort (n=4160 middle-aged),median F/U of 7.3 years [3,1,3]	GGT and liver ultrasound	Increased CV mortality in men with NAFLD and raised GGT (but not women) after adjustment for cardio-metabolic RF_S
Adams et al.[9]	Community-based North America cohort (n=420), mean F/U 7.6 years [3,0,3]	Majority had liver ultrasound (liver imaging or biopsy in all subjects)	Increased total mortality (mainly CV-related or cancer) in NAFLD compared with matched reference population
Ekstedt et al. [10]	Swedish hospital-based consecutive biopsy cases (n=129), mean F/U of 24 years [3,0,3]	Liver biopsy	Increased total mortality which was primarily CV-related (only in NASH patients but not in simple steatosis) compared with matched reference population
Soderberg et al.[8]	Swedish hospital-based consecutive biopsy cases (n=118), mean F/U of 24 years [3,0,3]	Liver biopsy	Increased total mortality in NAFLD was predominantly CV related, compared with matched reference population
Schwimmer et al[29]	Cross-sectional consecutive autopsy biopsy cases of child death (n=817) from accidental or unnatural causes [3,0,3]	Liver biopsy(autopsy)	Increased coronary and aortic atherosclerosis in NAFLD, independent of obesity

by an atherogenic lipid profile, consisting of high TG levels, low high-density lipoprotein (HDL) cholesterol, and increase in small, dense low-density lipoprotein (LDL) particles, increase very low-density lipoprotein (VLDL) cholesterol levels and elevated apolipoprotein B100 concentration. This type of atherogenicdys lipidemia is strongly linked to adverse CV outcome.[2] The increased hepatic production of TG-rich VLDL provides a limited compensatory mechanism for reducing liver fat content.However, this also results in abnormal HDL metabolism causing HDL reduction as well as compositional alterations. In fact, the amount of liver fat has a significant negative correlation with subfractions of HDL known to be athero-protective, which are reduced in NAFLD independently of peripheral insulin sensitivity.[37]

CONCLUSION AND FUTURE DIRECTIONS

Non-alcoholic fatty liver disease is a marker of a pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state affecting adipose tissue and characterized almost universally by IR. This results in several deleterious pathophysiological processes including abnormal glucose, fatty acid, and lipoprotein metabolism, increased oxidative stress, deranged adipokine profile, worsening subclinical inflammation, hypercoagulability, endothelial dysfunction, and progression of atherosclerosis, ultimately leading to a dysfunctional cardiometabolic phenotype with potentially unfavourable CV outcome. There is convincing evidence that worsening grades of NAFLD contribute to progressive cardiometabolic risk, such that NASH represents a marker as well as a mediator of increased CV risk more than simple steatosis. Although future studies should quantify liver fat using MR spectroscopy as a gold-standard, there remains an issue over how to obtain reproducible non-invasive measures of hepatic necro-inflammation and fibrosis to document NAFLD (or specifically, NASH) improvement , especially in randomized studies. Importantly, as steatohepatitis becomes more advanced there is often a reduction in liver fat due to replacement of fat-laden hepatocytes with necrosed and fibrotic tissue, rendering liver fat measurements as a marker of NAFLD severity inaccurate. It is therefore imperative that future therapeutic trials in NAFLD also aim to include measurements of a range of validated cardiac, metabolic, and inflammatory biomarkers linked to clinical outcome, to serve as alternative objective measures of the change in NAFLD status and its associated cardiometabolic phenotype. This may also allow better risk prediction when adjusting for the effect of conventional risk factors in determining the true CV risk of NAFLD. Importantly, current research evaluating easily accessible novel biomarkers or combined clinical and biochemical algorithms to accurately grade the severity of NAFLD tend to focus too narrowly on liver-based outcomes, ignoring the detrimental cardiometabolic effects which are often the main cause of adverse clinical events. Furthermore, the cardiometabolic consequences of NAFLD are remarkably heterogeneous in terms of its interplay with visceral adiposity, IR, and subclinical inflammation, and given that approximately a quarter of the general population are estimated to have this condition, ,a targeted strategy for pharmacological intervention would be challenging without outcome-based risk stratification. Therefore further research in this area is urgently needed to establish robust methods of predicting increased CV risk, as well as identifying novel treatments to improve the adverse CV outcome currently associated with NAFLD.

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Contemporary Issue

PSYCHOLOGICAL ISSUES OF AGEING

P. K. Rathor*, S. Moharana, D.N. Moharana*****

"Old age is a question of mind over matter, if you do not mind, it does not matter"- ***Mark Twain***

Psychology of ageing interrelates with the biological and social aspects of ageing. Important for the ageing persons are processing of information, cognition, feel good factor in life.

The Physician associated with geriatric care (Geriatrician) has to understand the psychology of ageing to assess person's ability to adapt to change, understand and cope with ageing ,illness and loss[1]. Successful psychological ageing is dependent on mental vitality. Mental vitality means how much the person is psychologically and intellectually engerised. This is individual's mental vigour to cope with changing bio-psychological changes. Ill health is related to problems with cognition,learning and motivation, thus incapacitating elder's ability to face the challenges of life and/or cope with it. It is to be noted that mood affects decision making abilities in elderly.

To keep mental vitality in an optimal state the silver citizen has to reduce stress,have adequate rest and relaxation,cultivate satisfying relationship and activities and avoiding know risk factors such as smoking, poor nutrition,weight problem and excessive alchol consumption[4]. Attitude and belief of the older adult about ageing is very important which reflects how successfully one is ageing . A mentally vigaorous older adult with a positive attitude will be able to cope better with life's challenges. It is the positive changes and adaptive abilities that may be more important in activities of daily living.

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Successful ageing consists of[1,2]

1. The importance of having a positive attitude and being adaptable.
2. Having security and stability with regard to living situation,finance and support resources.
3. Physical health and wellness
4. A Sense of engagement and finding meaning in life being involved in stimulating activities continuously

Age Related Psychological Change

Intelligence

Intelligence changes with age. Older people have increased verbal skills and they demonstrate slow performance skills. Life long experience and knowledge are reflected in verbal skills. Older adults tend to be more cautious in decision making activities. Pondering their option before responding, this deliberateness should not be misinterpreted as resistance[3].

Memory

Memory changes with age. Long term memory remains fairly constant. It is easier to do task of recognition over recall activities[3,4].

Sensory

Changes or decline in sense affect a person's participation in their environment and their quality of life. Losses or changes in vision, hearing, taste, smell and touch influence the individual's functioning activities, stimuli response and perceptions. Sensory losses can produce alteration in behavior, independence, confidence and self esteem. Sepctacles and hearing aids compensate for sensory losses and allows more independence[1,4].

Creativity

"Old age should wrinkle your body not your Mind"

Creativity is a part of mental vitality and quality of life. Creativity is usually not considered a component of psychological functioning. For silver citizens creativity is the integration of cognitive process, knowledge, thinking style, personality, motivation and environment over a life time[1]. Creativity is a way to address and resolve dissatisfaction and improve quality of life and can be a response to limits and uncertain future.

Conclusion

"You donot heal old age. You promote it, you protect it and you extend it."

An older person who ages successfully, has been able to use their accumulated knowledge and wisdom to accomplish most day to day living activities well. Rigidity and exaggerated maladapted behaviour may represent psychological and neurological problems and needs specialist care as these features are not components of normal ageing[1]. The individuals with suspected cognitive impairment have been recommended to be screened for delirium or depression.The evolution of depression that can complicate other medical illness can be particularly difficult to analyse as the somatic symptoms are comparatively much frequent presenting complaints in the elder population.

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API ODISHA STATE BRANCH

(Profit & Loss Account for the period of November 2013 to October 2014)

Date	Particulars	Amout (Debit)	Date	Particulars	Amout (Credit)
9-Nov-13	APICON 13 Burla Conf.	165,580.00	13-Nov	Opening Balance	23,094.00
2-Feb-14	Seed Money 2014	20,000.00	16-Jan-14	Fixed Diposit	246,699.00
2-Feb-14	1st GB Meeting	26,650.00	19-Mar-14	Refund of Loan & Seed Money 33rd APICON 13 Burla	349,000.00
9-Mar-14	APICON 12 Rourkela for local utilization	100,000.00	upto Oct 14	OPJ Advt.	65,000.00
12-May-14	APICON 13 Burla for local utilization	139,500.00	upto Oct 14	Bank Interest	11,051.00
15-Jun-14	1st CME Talcher	23,710.00			
14-Jul-14	News Bulletine	42,100.00			
21-Sep-14	2nd GB Meeting	20,250.00			
upto oct 14	Office Expenses	7,309.00			
6-Sep-14	Web Service	10,000.00			
upto oct 14	API Directory	39,000.00			
upto oct 14	Orissa Physician Journal-13	52,190.00			
upto oct 14	Bank Charges	120.00			
31-Oct-14	Cash at Bank	48,435.00			
					694,844.00
		694,844.00			

Fixed Diposit Details	
Account Number	Amount
30168562477	174,320.00
30168571061	156,274.00
30169638551	145,427.00
32181004318	200,000.00
total amt	676,021.00

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