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Prof. Sanjeeb Kakati

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ASSAM JOURNAL OF INTERNAL MEDICINE

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EDITOR : PROF. SANJEEB KAKATI

CONTENTS

Editorial

Tuberculosis Control – The Issue of Default

S.K.Baruah*

Self discontinuation of treatment is a major challenge in the management of Tuberculosis (TB). One the major cause of failure of any detected TB patient is default. The most important cause of TB programme failure is low rate of treatment completion. These defaulting patients continue to transmit the infection, sometimes with acquired drug resistance. Irregular or premature ceasation of treatment can result in serious consequences not only for the patient but the community as a whole. Since the interruption of treatment is a common human behavior, prevention and management of default are integral components of treatment and thus mainly responsibility of the doctor or person in charge. The Directly Observed Treatment-Short Course Chemotherapy (DOTS), strategy shifts the responsibility to patient cure from the patient to the Health care system.[1]

A revised strategy to control Tuberculosis (TB) was Piloted in 1993 in India with DOTS under the Revised National Tuberculosis Control Programme (RNTCP) in a population of 23.5 lakhs because of little impact on TB burden by the earlier National Tuberculosis Programme. This programme could not achieve the objective because of low priority, managerial weakness, dependence on X-Ray and inadequate funding. Inadequate treatment as the rule rather than exception due to low rate of treatment adherence and lack of supervision.[2] Observing the success of the Pilot project, RNTCP expanded gradually and nation wide coverage was achieved in March,2006.[3] More than 15 million people were put on DOTS till now.[4]

Between 1991 and 2000, the prevalence of TB as reduced significantly in areas of China by use of Short Course Chemotherapy(SCC) following WHO guidelines.[5] Patients treated without direct observation have a substantially higher risk of adverse outcomes than those treated under direct observation.[6] Following DOTS implementation, prevalence of culture positive TB decreased rapidly following a gradual decline for the previous 30 years. In the absence of a large HIV epidemic and with relatively low levels of Rifampicin resistance, DOTS was associated with rapid reduction of TB prevalence.[7]

The definition of default under RNTCP is that a patient, who has not taken anti – TB drugs for 2 months or more consecutively after starting treatment.[2] Initial defaulter is the patient who is diagnosed as Sputum Smear Positive as recorded in the RNTCP Laboratory Registrar, but has not been placed on either RNTCP DOTS Treatment Registrar or RNTCP Non-DOTS Treatment Registrar and has not been referred for treatment outside the district.[8]

The major contributory factors leading to default are symptomatic improvement after getting treatment, co-morbid conditions, adverse drug reaction, substance abuse, migratory population, lack of awareness about the duration of treatment, low literacy rate, lack of proper communication by the health care worker, etc. In 2011, the default rate in India in New Sputum Smear Positive (NSP) cases was 5.5% whereas in Assam it was 6.8%.[9] Morigaon District had the highest default rate of 20% in NSP cases in Assam in 2011.[10]

For adequate TB control in India, the default rate has to be minimized to interrupt the chain of transmission. As the responsibility of treating TB under RNTCP has shifted to Health system, the health care workers have to

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more vigilant about maintaining proper treatment adherence as well as defaulter retrieval .The need of the hour is to have a multicentric approach , including public private mix, for the future TB control effectively.

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Original Article

An Evaluation of Factors for Default in Smear Positive Pulmonary Tuberculosis Patients Treated with DOTS under RNTCP

R K Kotokey*, D N Bhattacharjee, P Dihingia***, A Ashok******

Abstract

Despite of the efforts of RNTCP and implementation of DOTS, there have been reports regarding treatment default cases of pulmonary tuberculosis. The present study was done to evaluate the factors for default in smear positive pulmonary tuberculosis patients treated under DOTS in RNTCP. This was a hospital based observational study done in departments of Medicine and TB and Chest, and microscopy centre of Assam Medical College and Hospital, Dibrugarh. All patients, aged >/= 13 years, presenting with default of pulmonary tuberculosis, who were registered under RNTCP and had taken CAT I or II DOTS for smear positive pulmonary tuberculosis were included in the study. Default is defined as per RNTCP guidelines. A total number of 625 smear positive cases were taken up during the one year study period. Out of the 625 smear positive cases 59 patients were included in the study as per the inclusion and exclusion criteria. From the present study, factors for default of DOTS observed are self discontinuation of treatment after getting symptomatic improvement of the disease, worsening of co-existing illness or appearance of a new illness during treatment period, substance abuse during the treatment period, adverse effects of the drugs, migration, lack of awareness about the duration of treatment to get complete cure, lack of communication by the DOTS provider at the time of default, male gender, patient being the economically productive member of family and low literacy level. Steps should be taken for strict monitoring of the functioning of the DOTS providers to improve the efficacy of DOTS programme.

Keywords:- *DOTS, Smear positive pulmonary tuberculosis, default.*

INTRODUCTION :

Tuberculosis (TB) is still one of the leading causes of death world-wide. The disease is caused by Mycobacterium Tuberculosis, TB has affected mankind for over 5000 years, and is still continues to be a leading cause of morbidity and mortality. The core element of **RNTCP** in Phase I (1997-2006) was to ensure high quality DOTS expansion in the country, addressing the five primary components of the DOTS strategy[1,2] .

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Directly observed treatment (DOT) is one of the key elements of the DOTS strategy. In DOTS, an observer (health worker or trained community volunteer who is not a family member) watches and supports the patient in taking drugs. The DOT provider ensures that the patient takes the right drugs, in the right doses, at the right intervals, for the right duration. DOT thus facilitates relapse free cure for TB and also helps to reduce development of drug resistance, because direct observation ensures adherence. Direct observation of treatment by a DOTS provider should be accessible and acceptable to the patient[1,2]. A patient who was declared cured, but who reports back to the health service and is now found to be sputum smear positive is considered as a relapse case. A default is define when a patient after treatment initiation has interrupted treatment consecutively for e" 2 months. In various prospective community cohort and case control studies conducted in various parts of India and abroad on the risk factors involved in default, several conditions like male

sex, alcoholism, smoking, poor awareness about the disease and the treatment, inadequate communication with the DOTS provider etc are found to be independently associated with the above mentioned outcome. Besides these, co-existing illness like diabetes mellitus, chronic liver disease, renal disease etc are also risk factors for treatment default. Side-effects of the anti-tubercular drugs while on treatment may influence the patient to discontinue the medication[2]. HIV-infection is among the strongest known risk factors for progression of latent TB infection to active disease. Early detection of such factors and prompt introduction of remedial measures are necessary to ensure success of DOTS programme. Multi-drug resistant and extensively drug resistant tuberculosis are emerging challenges for RNTCP. It should be stressed that MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB[1,6].

Dibrugarh district is one of the most important districts of Assam having two Tuberculosis Units (TU), out of which one unit is attached to Assam Medical College. In this centre the patients are undergoing treatment of DOTS in RNTCP since 2004. It is observed that there are default cases of smear positive pulmonary tuberculosis taking DOTS in the TU of Assam Medical College & Hospital, Dibrugarh. But so far our knowledge goes no study has yet been conducted to examine the factors for the afore mentioned problems in the TU. Therefore the present study is conducted to study the clinical profile and to evaluate the factors for default, with the following aims and objectives.

AIMS AND OBLECTIVES :

1. To study the clinical profile of patients presenting with default, who had taken DOTS in RNTCP for smear positive pulmonary tuberculosis.
2. To study the factors for the default of treatment.

MATERIALS AND METHODS: The study was conducted in Assam medical college and Hospital, Dibrugarh from 1st September 2010 to 31st August 2011, for a period of one year. This is a hospital-based observational study. Patients attending out-patient departments or admitted in the departments of Medicine and TB and Chest Diseases, Assam Medical College and Hospital, and those attending the Microscopy Centre of Assam Medical College and Hospital, Dibrugarh were brought under the study.

The inclusion criteria were as follows:

(1) Patients with age >/= 13, (2) All patients presenting with default of pulmonary tuberculosis, who were registered under RNTCP and had taken Cat I or II DOTS for smear positive pulmonary tuberculosis.

Exclusion criteria:

(1) All patients with age less than 13 years, (2) Those who had not taken ATT (DOTS) under RNTCP, (3) Those patients with history of smear negative pulmonary tuberculosis who were on cat I or DOTS, (4)Those with extra pulmonary tuberculosis .

A total number of 625 smear positive cases were undertaken during the one year study period. Out of the 625 smear positive cases 59 patients were included for the study as per the inclusion and exclusion criteria.

Default : A patient after treatment initiation has interrupted treatment consecutively for e" 2 months.

HISTORY AND CLINICAL EXAMINATION:

A detailed clinical history with special emphasis on the details of the previous anti-tuberculous treatment was taken from the patient and/or the attendant. History of any side-effects of ATT, history of associated medical, surgical or psychiatric illness, patient's socio-economic status, educational and occupational history were also given equal importance. Any history of any stigma regarding tuberculosis in the family or locality was also noted. The data regarding the duration of treatment (DOTS) taken was obtained from the patient's previous TB card and from the history. The body weight of the patient before starting the DOTS as well as the sputum AFB status at the end of initiation phase were obtained from the patient's previous TB card. The education status was considered as per the modified Kuppuswamy scale of 2007.

A detailed general and systemic examination were done in all patients. The history and physical findings were recorded in pre-designed Proforma. Drug irregularity was calculated from the patient's treatment card and/or from the history[8]. Patients who habitually drank alcohol were considered alcoholics, and patients who habitually smoked and were currently smoking were considered smokers for the purpose of the analysis[8]. Body Mass Index was calculated from patient's body weight (in kg) and height(m)[5].

BACTERIOLOGICAL EXAMINATION: Sputum smear examination was done before including the patients

in the study as only patients declared as default formed the study group. Smear microscopy was done with the Ziehl-Neelsen Technique as per RNTCP guidelines[3]. The other laboratory investigations done include the following: Routine Haematological Investigations,Routine urine Examination, Blood sugar (Fasting and Post-Prandial blood sugar were done in relevant cases),Serum creatinine and blood urea levels, Liver function tests,X-Ray Chest (PA view).

All patients were given advice for voluntary testing (serological testing for HIV) and counseling and the same carried out in the ICTC centre, Dept. of Microbiology, Assam Medical College & Hospital, Dibrugarh, Investigations to look for underlying co-morbid illness as suspected from history and clinical examination were also carried out. This included Fasting and post-prandial blood sugar (ADA 2010 guidelines),12 lead ECG, serology for HBsAg etc. in relevant cases. These findings were also tabulated in the Performa and subjected for analysis. Diabetes mellitus was diagnosed based on the criteria given by the American Diabetes Association, 2010. (1) symptoms of diabetes plus a random blood sugar >200mg/dl, or (2) fasting blood sugar >/= 126 mg/dl, or (3) 2-hour PPBS >/= 180mg/dl, or (4)HbA1c (glycosylated hemoglobin) >/=6.5. The diagnosis of COPD was based on the typical history with or without documents of past history, risk factors, physical examination, X-ray of the chest and spirometry. Nephrotic syndrome was diagnosed from the history including documents of past history, physical examination, 24- hour urine protein estimation, estimation of serum protein and fractions.

RESULTS AND OBSERVATIONS :

Out of the 625 smear positive cases during the one year period of study, 59 patients were taken up for the study as per inclusion and exclusion criteria.

The median age of the defaulters was found to be 35 years, maximum -75 years, minimum- 15 years. Most of the patients belonged to the age group of 21-40 years, (20 patients in 21-30 years and 17 patients in the 31-40 years group). Most of the defaulters were males-44 (74.5%), while there were 15 female patients (25.5%). 25 patients who defaulted DOTS were illiterate (42.4%). 18.6% of patients each had primary and middle school level of education respectively. Among the defaulters 39 patients (66.1%) were from rural areas whereas 20 (33.9%) patients came from urban areas. 25 patients (42.4%) took DOTS for 4 months, after which they discontinued. While 18 patients (30.5%) took for 3 months and 16 patients (27.1%) took for 2 months before defaulting the treatment (mode -4 months).

The factors for default obtained from patient's history

Table-1
Age and sex distribution

Age Group (years)	Male		Female	
	Number	Percentage (%)	Number	Percentage (%)
13-20	0	0	4	6.8
21-30	15	25.4	5	8.5
31-40	16	27.1	1	1.7
41-50	10	16.9	4	6.8
51-60	2	3.4	1	1.7
>60	1	1.7	0	0
Total	44	74.5	15	25.5
	Grand Total : Male + Female = 59, 74.5 + 25.5 =100%			

Table-2
Literacy Status

Education	Number	Percentage (%)
Illiterate	25	42.4
Primary School	7	18.6
Middle School	6	18.6
High School	15	11.9
Intermediate	0	0
Graduate/ Post-graduate	6	8.5
Profession or honours	0	0
Total	**59**	**100**

Table-3
Locality

Locality	Number	Percentage(%)
Urban	20	33.9
Rural	39	66.1
Total	**59**	**100**

were depicted in table 4. 19 patients (32.2%) discontinued DOTS after getting symptomatic improvement of the disease. Of the 59 defaulters, only 23 patients (39%) were aware of the duration of treatment required to get complete cure while the rest 36 patients were unaware. Only 36 patients (61%) had interaction or communication with the DOTS provider at the time of default, while the rest 23 patients did not have any communication. There was no stigma regarding the disease in the family or the locality of residence. 3 patients (8.5%) gave history of adverse effects of the anti-tubercular drugs during treatment following which they were not willing to continue the treatment. Of these, 1 (one) patient gave history of drug induced hepatitis and the rest 2 patients gave history of recurrent abdominal pain and vomiting after taking drugs due to which they were reluctant to continue the treatment.

5 patients (8.9%) had co-existing chronic obstructive pulmonary disease (COPD), of which 2 patients had cor-pulmonale during the treatment period. 4 patients (6.8%) had co-existing diabetes mellitus. Peptic-ulcer disease and chronic liver disease were other co-existing diseases observed in 3 and I patients respectively. 8 patients had history of pneumonia which had worsened underlying COPD and diabetes, following which they discontinued the anti-tubercular drugs. Peptic ulcer disease was worsened by pain abdomen and vomiting, Upper gastro-intestinal bleed worsened the underlying chronic liver disease in 1 patient (1.7%). One patient had history of viral hepatitis (1.7%). 19 patients (32.2%) had history of substance abuse during the treatment period. Out of which; 13 patients gave history of alcoholism alone, during treatment, 5 patients had history of alcoholism and cigarette smoking during the treatment, 1 patient gave history of alcoholism and cannabis addiction during treatment. 5 patients (8.9%) had history of migration to their current locality of residence, after which they did not go for follow up or check up in the nearest health facility.

The relevant findings on physical examination were as follows. Pallor was present in all patients. 49 patients (83.1%) had tachypnoea, while 39 patients had (66%) tachycardia. Other findings include:- edema (17 patients, 28.8%), clubbing (7 patients, 11.9%), hepatomegaly (6 patients,10.2%), hypotension (5 patients, 8.5%). 1 (one) patient with COPD had cyanosis. Ascites was seen in patients with cor-pulmonale and chronic liver disease (3 patients, 5.1%). Peripheral neuropathy was in 2 patients (3.3%), one with diabetes mellitus and the other with history of alcoholism. Average current body weight of patients was 37kg, with a standard deviation of 6.67, (maximum-50kg, minimum-25kg). The average current BMI was 15.2. Positive findings in investigations were as follows:- (1) average hemoglobin level -7.9% (standard deviation -1.17), 2) leucocytosis was seen in 18 patients (30.5%), (3) abnormal FBS/2hrPPBS were seen in 2 patients, both of whom have diabetes mellitus, (4) Proteinuria was seen in 4 patients (6.9%), all were patients with diabetes, (5) Hypoalbuminemia was seen in 22 patients

Table-4
Factors for default obtained from history

Factors	No.of Patients	Percentage(%)
Discontinued self after symptomatic improvement	19	32.2
Adverse effects of drugs	3	8.5
Worsening of co-existing illness or a new illness	14	23.7
Migration to the place of residence	5	8.9
Substance abuse during treatment	19	32.2
Lack of awareness about the duration of treatment for complete cure	36	61
Lack of interaction or communication with the DOTS provider at the time of default	23	39
Stigma regarding the disease in the family or locality	0	0

Table-5
Clinical features

Signs	Number of Patients	Percentage (%)
Pallor	59	100
Cyanosis	1	1.7
Edema	17	28.8
Clubbing	7	11.9
Hypotension	5	8.5
Tachycardia	39	66
Tachypnea	49	83.1
Hepatomegaly	6	10.2
Ascites	3	5.1
Peripheral Neuropathy	2	3.3

(37.2%), otherwise liver function test was normal in all patients, (6) 27 patients (45.8%) were smear positive in all the three sputum samples, (7) serology for HIV 1&2 was non-reactive in all patients, (8) serology for HBsAg was negative in all relevant cases (patients with history of substance abuse and patient with chronic liver disease).

DISCUSSION :

The implementation of DOTS was aimed in providing accurate diagnosis, improving the cure rate, reducing the incidence and prevalence of tuberculosis.[1] it also aimed completion of treatment, prevention of treatment failure and relapse, and emergence of MDR-TB. Despite of the efforts of RNTCP and implementation of DOTS, there had been reports regarding treatment default of pulmonary tuberculosis.

In the present study, out of the 625 smear positive cases, default cases comprised of 9.4% (59 patients). In the RNTCP status report TB INDIA 2010[1], by the central TB Division of Directorate of health and family welfare, 6.6% were defaulters of cat I DOTS in Assam in the year 2008. In the district of Dibrugarh there were 5.7% defaulters of cat I DOTS. The default cases obtained were cat I DOTS defaulters, no cat II defaulters were found during the study. The present study was a hospital based observational study done in a tertiary care hospital. The departments of Medicine and TB and Chest received patients from Dibrugarh as well as from the neighbouring districts like Sivsagar, Tinsukia, Golaghat etc, and neighboring states like Arunachal Pradesh. This explained the higher percentage of default cases found in the present study. Comparative results were obtained in studies by Sweta Gupta et al(2011)[7], Thomas A et al(2005)[8], Santha T et al(2002)[9] , Tripathy RM et al(2009)[10], Chhaya Mittal et al(2011)[11] ,Kaur G et al(2008)[12] , and Chang et al(2004)[13].

Among the patients presenting with default in the present study, 33.9% of defaulters belonged to the age group of 21-30 years, and 28.8% belonged to 31-40 years of age group, together comprising 62.7%. Therefore majority of the defaulters belonged to the middle-age and adolescent age. The median age found was 35 years with a maximum age of 75 years and a minimum age of 15 years. Sophia Vijay et al(2003)[14] shows median age of defaulters of cat I DOTS as 30 years. Majority of the defaulters were those above the median age of 30 years in that study. Kumar et al(2002)[15] observed maximum default in the 35-44 year of age group. More default cases in the 21-40 years age group was mainly due to the subjects being the economically productive members of the family, which lead them to leave the treatment rather than to leave their earning of the day. Sweta Gupta et al(2011)[7] , Chhaya Mittal et al(2011)[11] also showed that male patients defaulted twice as common than females. More default among males was supposed to being the earning members of the family and so they could not afford to leave on job that frequently[11]. 42.4% of the patients were illiterate, 37.2% had received only primary and middle level of school education. The study conducted by Sahu SK et al(2008)[16] showed that there was an increase in cure rate and a decrease in default rate with an increase in the prevalence of literacy. Abdul Salam et al(2009)[17] also showed that 55% of defaulters were illiterate, 35% primary school pass and 7% secondary school pass. Illiteracy played a vital role for default behavior of patients. In the present study, 66.1% of defaulters were from the rural areas and the rest were from the urban areas. According to G.V.J Baily(1983)[18] the vast majority of pulmonary tuberculosis cases were found in rural and semi-urban areas, where more than 80% of the country's population lived. The probability of higher number of defaulters from rural areas could hence be explained in this background. Residing in remote interiors of villages also limited the access to health centers as well as patient provider communication.

In the present study, 32.2% discontinued treatment self after getting symptomatic improvement of the disease. Improvement in symptoms was found an important reason for non-compliance and self discontinuation was reported by Chhaya Mittal et al(2011) which was (14.4%)[11]. A study from Bihar and West Bengal reported that improvement in symptoms (40% and 56%) caused defaults in some patients. Abdul Salam et al(2009)[17] stated that the patients in their study abandoned treatment due to premature self-judgment to be cured on disappearance of symptoms.

Only 39% of the defaulters were aware of the duration of treatment required to get complete cure of tuberculosis, the rest 61% were not aware of this fact. Sweta Gupta et al(2011)[7] shows that 9.02% of defaulters

were unaware of the treatment duration. Lack of awareness was sited as a reason for default by Chhaya Mittal et al(2011)[11] which was also (9.9%). These two studies mentioned here, were conducted in urban and sub-urban areas of Agra and Delhi respectively, while most of the patients in the present study were from the rural areas, thus explaining the higher unawareness among patients. In the present study there was no stigma regarding the disease in the family or in the locality.

In the present study, 39% of defaulters did not have regular communication or interaction with the DOTS provider at the time of default. When a patient defaulted or did not return for the next dose or did not return for the empty kit, the DOTS provider was supposed to enquire at the patient's residence[14]. The person should have direct communication with the patient and should motivate him to continue with the treatment. Sophia Vijay et al(2003)[14] also found that inadequate patient provider interaction was a potential factor for default of DOTS. Poor patient provider interaction was also found as a risk factor for default in studies reported by Jaiswal A et al(2003)[19] and Gopi PG et al(2007)[20]. Effective patient provider interaction was a means of providing treatment related information particularly the importance of DOT and clearing the doubts regarding disease and treatment. This played a decisive role in enhancing treatment compliance. Inadequate and improper patient provider interaction often stemed from the lack of time and knowledge of the provider themselves[21].

8.9% patients had co-existing COPD while 6.8% had associated Diabetes mellitus. 13.5% had history of pneumonia during the treatment period which worsened the underlying co-existing disease, and following which patient defaulted DOTS**.** 3 (5.1%) patients had history of associated peptic ulcer disease and patient had chronic liver disease. There was history of worsening of peptic ulcer disease and the patients gave history of pain abdomen and vomiting following which they didn't resume DOTS. There was history of upper GI bleed in patient with chronic liver disease while one patient defaulted following viral hepatitis.

In the present study 32.5% defaulters gave history of substance abuse during the treatment period, out of which 13 patients had history of intake of alcoholism alone, 5 patients gave history of alcoholism and cigarette smoking, one patient had history of alcoholism with cannabis addiction. In the study conducted by Tripathy RM et al(2009)[10], addiction to alcohol was noted among 22.4% of the study population and it was found as a major factor for defaulting and death in the study. Sweta Gupta et al(2011)[7] found alcoholism as a cause of treatment interruption in 4.4% of patients. Jokubowiak et al(2007)[21] found alcohol use to be the second commonest reason for treatment default. 3 patients (8.5%) gave history of adverse effects of the anti-tubercular drugs during treatment following which they were not willing to continue the treatment. Of these, 1 patient gave history of drug induced hepatitis and the rest 2 patients gave history of recurrent abdominal pain and vomiting after taking drugs due to which they were reluctant to continue the treatment. Tripathy RM et al(2009)[10] showed that side effects due to ATT (50%) was the most common cause of default. ATT-induced side effects were found to be the cause of default in 12.8% of patients by Sweta Gupta et al(2011)[7] , while 43.2% defaulted due to side effect of the drugs in the study by Chhaya Mittal et al(2011)[13]. The DOTS providers needed adequate orientation regarding possible side effects and prompt referral of patients to the medical officer for remedial measures. Frequently reported minor side effects could be successfully dealt with proper instructions on drug consumption, reassurance to patients and prompt symptomatic treatment before it leaded to default[14]. 8.5% patients defaulted the treatment as they migrated to their current place of residence from a distant locality. Similar result was seen in the study by Sweta Gupta et al(2011)[7] . Serology for HIV 1&2 were non-reactive in all patients with default. Amoran OE et al(2011)[22] also found that HIV status was not a factor for default.

CONCLUSION :

From the present study, factors for default of DOTS observed were self discontinuation of treatment after getting symptomatic improvement of the disease, worsening of co-existing illness or appearance of a new illness during treatment period, substance abuse during the treatment period, adverse effects of the drugs, migration, lack of awareness about the duration of treatment to get complete cure, lack of communication by the DOTS provider at the time of default, male gender, patient being the economically productive member of family and low literacy

level. Enhanced motivation for treatment completion , proper counseling to reduce substance abuse, effective regular patient-provider communication, focused on improving patient's nutrition were needed to prevent default and success of DOTS. Treatment of co-existing disease conditions, monitoring for side-effects of drugs and early management were equally important. Moreover avoiding frequent instances of missed doses by strict supervision as well as completing the missed doses is essential to prevent emergence of MDR-TB and death in TB patients. RNTCP depends on a great deal on the DOTS-providers for the successful completion of treatment and to prevent emergence of MDR-TB. Therefore steps should be taken for strict monitoring of the functioning of the DOTS providers to improve the efficacy of DOTS programme. The present study was a hospital-based observational study carried out in a stipulated period of one year and with a considerable number of patients. Still then further studies covering wider population in a longer period of time are required to estimate the prevailing picture of default cases in this part of the country and to assess the factors for the same as well. So far our knowledge goes this type of methodical study on default on DOTS in RNTCP in this area is not yet conducted. Therefore, this study will definitely reflect some aspects of the programme as this is the first of this kind.

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Original Article

Pseudothrombocytopenia — Incidence, cause & methods of detection

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Abstract

Background: Pseudothrombocytopenia or spurious thrombocytopenia may be defined as ex vivo thrombocytopenia, counted by an fully automated haematology cell counter .It has been recognized as an important laboratory problem stemmed from a technical advance . Pseudothrombocytopenia is an often unrecognized phenomenon that results in errors in the interpretation of platelet counts with consequent inappropriate clinical decisions or useless, and sometimes dangerous, therapeutic interventions.Incidences of pseudothrombocytopenia reported in different studies range from 0.09-0.21 %,which could account for 15-30% of all cases of thrombocytopenia. Clinically, it may cause concern and confusion because there could be worries about the patient's health. Failure to identify pseudothrombocytopenia can lead to a lot of clinical problems like unnecessary platelet transfusion,glucocorticoid therapy etc.Thus, it is important to evaluate patients carefully to avoid potentially costly and invasive testing like bone marrow biopsy, platelet function tests etc.

Objective :The study was conducted in order to evaluate the incidence & etiology of pseudothrombocytopenia, the significance of lab artifact and to arouse awareness & concern amongst all levels of medical & paramedical personnel regarding issuing of haematological reports in general and specially platelet counts.

Materials & Methods : A prospective study that included 6500 routine clinical blood samples of which 560 cases of thrombocytopenia(less than 1,50,000/cmm platelets)reported by 5 part fully automated cell counter(sysmex 800i)between January 2011 to December 2011 in the haematology laboratory of AMCH,Dibrugarh. In cases with thrombocytopenia(by cell counter-XS800i) platelet counting was done by three other manual methods ie. By Neubauer's chamber,by peripheral smear & platelets per 1000 RBC's.

Results : The study detected 560 cases of thrombocytopenia by cell counter , of which only 56 cases (10%) were found to have true thrombocytopenia whose platelet count ranged between 10,000/cmm to 1,10,000/cmm & 504 cases(90%) of pseudothrombocytopenia whose platelet count ranged from 70,000/cmm to 1,45,000/cmm.The major causes of pseudothrombocytopenia were presence of large platelets (45 %),excess EDTA in sample (35%),and few others like pregnancy, autoimmune diseases, malignant diseases.No apparent cause could be found in 17% of cases.

Conclusion : Direct microscopic examination of well stained blood smear from EDTA venous blood(as early as possible) & direct counting under Neubauer chamber is almost mandatory before releasing a report of platelet count .Also factors related to ratio & storage of EDTA blood , regular calibration of automated instruments, monitoring the quality of reports by trained pathologists/haematologists along with clinical correlation is of utmost importance in the present clinical scenario.

Pseudothrombocytopenia or spurious thrombocytopenia is the appearance of low platelets in a blood test that is caused by an in-vitro problem with the blood collection, rather than a disorder in the patient. It can also be defined as ex vivo thrombocytopenia , counted by an fully automated haematology cell counter,not recognized by microscopic examination of a well prepared blood smear .It has been recognized as an important laboratory problem stemmed from a technical advance.

Thrombocytopenia can be defined as platelet count less than 150 x 10^9/l (1.5 lakhs/cmm) though spontaneous bleeding usually occurs at counts below 20,000/cmm.[1] Automated cell counters define platelets as particles

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(volumes) between 2 femtolitre and 20 femtolitre(fl). Thus,Giant platelets may be counted as red blood cells whereas fragmented RBCs as platelets & platelet clumps more than 20fl will be counted as leucocytes[1].

Pseudothrombocytopenia is an often unrecognized phenomenon that results in errors in the interpretation of platelet counts with consequent inappropriate clinical decisions or useless, and sometimes dangerous, therapeutic interventions.Clinically, it may cause concern and confusion because there could be worries about the patient's health. Failure to identify pseudothrombocytopenia can lead to a lot of clinical problems like unnecessary platelet transfusion,glucocorticoid therapy ,postponed surgery,withdrawal of medications and even splenectomy apart from mental,physical &financial trauma to the patient [2].Different studies have shown incidences of pseudothrombocytopenia ranging from 0.09-0.21% which could account for 15-30% of all cases of thrombocytopenia.[3,4]

Thus, it is important to evaluate patients carefully to avoid potentially costly and invasive testing like bone marrow biopsy ,platelet function tests etc.

Studies have shown in- vitro platelet clumping in blood samples collected into ethilenediaminetetraacetic acid (EDTA) anticoagulant ranging from 0.01% to 0.27%[5]and in hospitalized patients the incidence is about 1.9%[6]. The clumping activity is greater at temperatures less than 37 degrees C, and the EDTA concentrations required for clumping are 20 times below anticoagulant concentrations [3].EDTA chelates calcium & exposes cryptic antigenic sites on the surface of platelets causing agglutination of platelets by antibody binding to conformer of platelet glycoprotein IIb/IIIa complex which causes the low blood platelet count.[7]

Some other causes of pseudothrombocytopenia are platelet satellitism[8],hyperlipidaemia or aggregation secondary to platelet activation resulting from improper blood sampling techniques or delayed mixing with anticoagulant in the test tubes (i.e., pre analytical errors)[1]

MATERIALS AND METHOD:

This prospective observational study was carried out on 560 cases of thrombocytopenia(platelet count less than 1.5 lakhs/cmm of blood) detected by 5 part Sysmex XS 800i Analyser(based on the principles of electrical impedence & light scatter) out of 6500 routine clinical blood samples analysed during the period of January 2011 to December 2011 in the Hematology laboratory of Assam Medical College & Hospital, Dibrugarh.Patients of all age group & both sexes were included in the study. All the samples were collected in EDTA vials and first hand assessment was done by fully automated 5 part haematology analyser(Sysmex XS800i)Blood smears of the patients were prepared from EDTA blood immediately after blood collection and stained by leishman's stain .The thrombocytopenic cases as detected by cell counter are re-evaluated for platelet counts by three different standard manual platelet counting methods adopted .These are:

1) By Neubauer's Chamber counting :

EDTA-blood thoroughly mixed with 1% ammonium oxalate (1 : 20 dilution)for 20 minutes and then the Neubauer's Chamber is charged,which was then covered moist petri dish & kept undisturbed for 20 minutes.Manual count was done with 40 X objective & low down condenser.A minimum of 200 platelets were counted in 25 small squares in the RBC square & the following calculation adopted[9]

$$\text{Platelet count per cumm}(\mu l) = \frac{\text{No. of cells counted}}{\text{Volume counted}} \times \text{dilution}$$

$$= \frac{N \times 20}{25/250}$$

$$= N \times 200/\mu l$$

PERIPHERAL SMEAR EXAMINATION :

Number of platelets in 20 oil immersion fields (x100)in different areas of the blood film was counted & calculations and calculation was done as given below-

Calculation:

Suppose,Number of platelets in 20 oil immersion fields=N

Then,Number of platelets per oil immersion field

= N/20

Total Platelet count= N/20× 10,000/cumm.

(1 platelet per field=10,000 platelets/cumm)

COUNTING BY PLATELETS PER 1000 RBC's :

Peripheral blood smears were examined under oil immersion (x100) and platelets were counted per 1000 RBCs. RBC count was taken from cell counter(sysmex 800i). Calculations were made as follows[10]

Calculation:

If,Number of platelets/1000 RBCs = N

Number of RBCs counted = Y

Then, total platelet count will be N×Y/1000 per cumm of

blood.

An average of the results of the three different counts (by the above mentioned methods)was taken as the mean value (manual platelet count under conventional microscope)

Observations : The study detected 560 cases of thrombocytopenia by fully automated 5 part haematology analyser(Sysmex XS800i) , of which only 56 cases (10%) were found to have true thrombocytopenia whose platelet count ranged between 10,000/cmm to 1,10,000/cmm & 504 cases(90%) of pseudothrombocytopenia whose platelet count ranged from 70,000/cmm to 1,45,000/ cmm.The major causes of pseudothrombocytopenia were presence of large platelets ,excess EDTA in sample ,and few others like pregnancy, autoimmune diseases, malignant diseases.No apparent cause could be found in 16.8% of cases.

Table-1
Distribution Of Cases According To Causes Of Pseudothrombocytopenia(N=504)

Causes of Pseudothrombocytopenia	No. of Cases(%)
Presence of large platelets	226 (44.8%)
Excess EDTA in sample	176 (39.9%)
Malignant disease (non-haematological)	5 (0.99%)
Hyperlipidaemia	5 (0.99%)
Autoimmune diseases	4 (0.79%)
Pregnancy	3 (0.59%)
No apparent cause detected	85 (16.8%)

DISCUSSION :

Thrombocytopenia is a serious situation that causes anxiety in doctors and patients due to its relationship with serious hemorrhagic manifestations. Pseudothrombocytopenia, however, is a situation without clinical interest because it is an in vitro decrease in platelet count but it has emerged as a relatively common problem faced by pathologist and clinicians all over the world[4][11] Many causes have been postulated by different workers like ethylene diamine tetra acetic acid (EDTA) dependent platelet agglutination[2][3] and platelet satellitism,[8] or aggregation secondary to platelet activation resulting from improper blood sampling techniques or delayed mixing with anticoagulant in the test tubes (i.e., pre analytical errors),hyperlipidaemia etc, Studies have shown that clumping is observed in EDTA blood stored at less than 32ÚC for more than 2 hrs due to fibrinogen induced stickiness[1].The clumping activity is greater at temperatures less than 37 degrees C, and the EDTA concentrations required for clumping are 20 times below anticoagulant concentrations. Pseudothrombocytopenia can complicate an accurate determination of a platelet count in a patient with an underlying thrombocytopenic disorder. Platelet clumping may be a result of poor mixing - too little and/or too late, and/or a small, whole blood clot or very small fibrin clots in the EDTA-anticoagulated specimen.

Pseudothrombocytopenia can occur in both healthy individuals and patients.Some workers have [12][13]found it to be associated frequently with diseases like autoimmune diseases, chronic liver disease,septicaemia, lymphoproliferative disorder with cardiolipin antibodies[14] while others [15]have failed to find such association.In our study,presence of large platelets was found to be the commonest cause(44.8%)followed by excess of EDTA(39.9%) The findings of EDTA excess are in consistence with the findings of Payne and Pierre[4],Vicari *et a*l [3] and Savage[8]This high incidence of EDTA associated pseudothrombocytopenia is mainly attributed to the pre-analytical errors in sample collection & storage(time dependent fall of platelet count) which needs to be emphasized.Giant platelets was also found to be the major cause of pseudothrombocytopenia in our study population which needs further workup for evaluating its etiology.However ,clinicians should be aware of the five basic criteria that should be fulfilled to raise the clinical suspicion of EDTA-dependent pseudothrombocytopenia, i.e., (i) abnormal platelet count, typically <100×10(9)/L; (ii) occurrence of thrombocytopenia in EDTA-anticoagulated samples at room temperature, but to a much lesser extent in samples collected with other anticoagulants and/or kept warmed at ~37°C; (iii) time-dependent fall of platelet count in the EDTA specimen; (iv) evidence of platelet aggregates and clumps in EDTA-anticoagulated samples with either automated cell counting or microscopic analysis; (v) lack of signs or symptoms of platelet disorders.

This study has also detected pseudothrombocytopenia in 5(0.99%) cases of Malignant disease(non-haematological), 5 cases (0.99%) of Hyperlipidaemia, in 4(0.79%) cases of Autoimmune diseases (systemic lupus

erythematosus, rheumatoid arthritis), in 3(0.59%) cases of Pregnancy,which also have been reported in some studies[12][13][16].However no apparent acuse could be detected in 85 cases (16.8%). Bizzaro[15] have also failed to appreciate any particular association with any single disease after a 10 year follow-up.

Faulty or improper blood collection technique(using excess EDTA), lack of strict quality control management are important factors for report generation and this can be taken care of. However issues like inherent biochemical properties of EDTA and particle counting principle of cell counters have to be tackled judiciously EDTA blood should be processed as early as possible (within 2hrs)of collection and be preferably kept at 37ÚC. Although multichannel electronic cell counters are now in widespread use in haematology laboratories , care should be taken that these cell counters are regularly calibrated . Platelet count should therefore be always supplemented by microscopic examination of a well stained blood smear,although it is to be remembered that smears prepared by capillary blood (finger prick)tend to have lesser count due to platelet adherence at puncture site.Thus though time consuming,direct manual counting of platelets using 1% ammonium oxalate diluting fluid should be considered which is quite reliable & quick also .

With the advent of newer technologies ,modern analysers which have the combination/convergence of flowcytometry principles(eg, laser light and hydrodynamic focusing) with impedence technology which can offer a range of platelet counting methods including impedence counting ,optical counting (light scatter or fluorescence) and immunological platelets counting using antibodies to CD61[17].However,these instruments are very expensive and can't be used routinely .

Hence, factors related to ratio & storage of EDTA blood, regular calibration of automated instruments, monitoring the quality of reports by trained pathologists/ haematologists along with clinical correlation is of utmost importance in the present clinical scenario.

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Original Article

Rheumatological Manifestations in Diabetes Mellitus

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Abstract

Rheumatological manifestation in diabetes mellitus is not rare and is a major cause of morbidity. It affects the glycaemic control through decreased physical activity. The study was undertaken to see the rheumatological manifestations in diabetes mellitus. Along with the clinical presentation of rheumatological syndromes.

Out of 75 cases, 70 (93.33%) were type 2 DM and 5 (6.67%) were of type 1. Male patients were 42(56%) and female 33 (44%), 54 had rheumatological disorders, 49 cases of T2DM and 5 of T1DM. Diabetic hand syndrome (DHS-LJM) (10) was the most common finding followed by adhesive capsulitis (8), hyperostosis (7), calcium pyrophosphate dehydrogenase disease (6), shoulder hand syndrome (4), flexor tenosynovitis (4), Dupuytren's contracture (3), carpal tunnel syndrome (3), gout and hyperuricemia (3), skin manifestation (2), and I case each of osteolysis, osteopenia, osteoarthritis, neuroarthropathy. Among the 54 patients 24 (44.44%) had high HbAlc (8.5-10) levels. Duration of the illness was greater than 5 years in 29(53.7%) patients and greater than 10 years in 7 (12.97%) patients. Rheumatological manifestations were maximum in the late age group (51-60 yrs.) Out of 54 patients affected, 28 were male and 26 female. LJM and gout with hyperuricemia was related to T1DM.

It can be concluded that rheumatological manifestation are common association and complication of diabetes mellitus and directly associated with duration of the disease.

Keywords:- *Diabetes mellitus, Rheumatological manifestation, Diabetic hand syndrome Periarthritis of shoulder*

INTRODUCTION :

The association of diabetes mellitus with specific skeletal and rheumatological complications had received recognition only during the last two decades. Probably because these disorders are not life threatening, they have not received the same degree of attention as cardiovascular, neurological, renal or ocular complications. Nevertheless, the skeletal and rheumatological disorders do add to the morbidity of diabetes and can alter life styles to a degree that affects the glycaemic control through decreased physical activity. The changes in the connective tissue of patients with diabetes are probably due to disturbance in the structural macromolecules of extra cellular matrix. The pre-existing neuropathy and micro vascular damage also contribute to the pathogenesis.

The important aspect of association between diabetes and rheumatological manifestations has not yet been investigated methodically in this part of the country. Therefore a humble approach has been made to investigate and observe the rheumatological presentation in diabetes mellitus. Considering all the facts, the present study is conducted with the following objectives.

AIMS AND OBJECTIVES :

To study the rheumatological manifestation in diabetes mellitus.

To study the clinical presentation of rheumatological syndromes and disease.

MATERIALS AND METHODS :

75 cases of Diabetes Mellitus admitted in Assam Medical College and Hospital, Dibrugarh, in the different Units of Department of Medicine, during the period April 2003 to March 2004 were taken up for the present study.

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Selection of cases

Criteria of Inclusion :

Diabetes mellitus as diagnosed on the basis of known history of diabetes, taking insulin or hypoglycemic agent and/ or WHO Criteria for diagnosis of diabetes.

Criteria for the Diagnosis of Diabetes Mellitus :

Symptoms of diabetes plus random blood glucose concentration e" 11.1 mmol/L (200mg/dl) or,

Fasting plasma glucose > 7.0 mmol/L (126mg/dl) or,

Two hour plasma glucosee"11.1 mmol/L (200mg/dl) during an oral glucose tolerance test.

In the absence of unequivocal hyperglycaemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Random is defined as without regard to time since the last meal.

Fasting is defined as no caloric intake for atleast 8 hour.

The test should be performed using a glucose load containing the equivalent of 75gm anhydrous glucose dissolved in water; not recommended for routine clinical use.

Source : Adapted from—American Diabetes Association, 2000.

The cases were selected in following ways :

More than 12 years of age and both sexes were taken.

Duration of disease, Family history, habit of smoking, Alcohol consumption were determined from history and available documents.

BMI was determined using by Quatelet Index (Weight in Kg./Height in meter^2).

Blood pressure was categorized according to JNC-7 (VII) classification.

Complication of diabetes mellitus were detected by clinically or by relevant investigation e.g. Fundoscopy, Urine examination, Resting ECG, etc.

The conditions which give rise to some abnormal consequences was excluded from the study e.g. Sepsis, Acute Hepatitis, Pregnancy, Other preexistence of autommune diseases and rheumatological disorders.

Blood sugar was determined by Glucose Oxidase and Peroxidase Method. The other investigations done were— RE BLOOD, RE URINE, HBAlc, LIPID PROFILE, ECG, USG ABDOMEN, CHEST X-RAY, URIC ACID AND RENAL FUNCTION TESTS.

THE VARIOUS RHEUMATOLOGICAL MANIFESTATIONS WERE ASSESSED BY METICULOUS CLINICAL EXAMINATION.

RESULT :

Out of 75 cases 70 (93.33%) patients were of Type-2 Diabetes Mellitus and 6.67% Type-1 Diabetes Mellitus. 42(56%) patients were male and 33 (44%) female. In 45(60%) of cases, duration of diabetes mellitus was between 6-9 years, 23 (30.66%) cases more than 10 years and 7 (9.33%) cases were in between 0-5 years. Nutritional status was measured according to Quatelet Body Mass Index and 47 (62.67%) cases were having BMI <26. It was observed that in 28(37.33%) cases BMI was between 26-29. 30(40%) cases were having hypertension of Stage-I & II under JNC VII-Classification. Prehypertension/ normal level blood pressure of JNC-VII Classification were found in 45(60%) cases.

The incidence of Rheumatological Manifestation in Diabetes Mellitus

Rheumatological Manifestations	Type-2		Type-1		Total	
	No.	(%)	No.	(%)	No.	(%)
ADC	8	14.81	--	--	8	14.81
SHS	4	7.42	--	--	4	7.42
DHS (LIM)	7	12.96	3	5.56	10	18.52
FT (Trigger)	4	7.42	--	--	4	7.42
Dupuytren's contracture	2	3.70	1	1.85	3	5.55
Hyperoarthropathy	7	12.96	--	--	7	12.96
Carpel Tunnel	1	1.85	--	--	1	1.85
Osteoarthritis	3	5.56	--	--	3	5.56
Gout & Hyperuricemia	1	1.85	--	--	1	1.85
CPDD	2	3.70	1	1.85	3	5.55
Osteopenia	6	11.11	--	--	6	11.11
Osteopenia	1	1.85	--	--	1	1.85
Osteolysis	1	1.85	--	--	1	1.85
Skin Manifestations	2	3.70	--	--	2	3.70
Total	**49**	**90.74**	**5**	**9.26**	**54**	**100.00**

What is revealed from the above Table is that 90.74% of rheumatological manifestations are from Type-2 Diabetes Mellitus and 6.66% presented in Type-1 Diabetes Mellitus. Total 54 numbers of patients were

suffering from rheumatological disorders in diabetes mellitus (75 cases taken). Out of 54 patients 28(51.85%) were male suffering from rheumatological manifestations in comparison to 26(48.15%) female patients. 18(33.32%)patients presented with the symptoms of disease in between 51—60 years, 13(24.08%) presented at the ages>60, another 13(24.08%) presented in between 41—50 years of age. So most of the patients were in later age group in the study.

Association of Rheumatological manifestations with other complication of Diabetes Mellitus

Rheumatological Manifestations with others	Numbers of Cases	Percentage (%)
With Neuropathy	14	25.93
With Nephropathy	1	1.85
With Retinopathy	--	--
WithNephropathy & Retinopathy	1	1.85
With Neuropathy & Retinopathy	3	5.56
With Neuropathy & Nephropathy	3	5.56
With Neuropathy, Nephropathy & Retinopathy	15	27.77
Total	**37**	**68.52**

37 (68.52%) cases had association with other complication of diabetes mellitus. Among the complications 27.77% of the rheumatic problems were associated with neuropathy, retinopathy and nephropathy (together) followed by 25.93% with neuropathy.

Out of 54 patients 24 (44.44%) presented with high glycosylated hemoglobin level.

Glycosylated Haemoglobi (HbA1C) Level in Rheumatological Manifested patients of Diabetes mellitus

HbA1C Level	Number of Cases	Percentage (%)
<7.0	2	3.70
7.0 - 8.5	20	37.04
8.5 - 10.0	24	44.44
>10	8	14.82
Total	54	100

DISCUSSION :

In the present study out of 75 diabetic cases 93.33% belongs to Type-2 diabetes mellitus, where as only 6.67% patients belongs to Type-1. Shah Shekar et al in the year 1994—95 found that the prevalence of Type-2 diabetes mellitus was 83.3%, where as Type-1 diabetes mellitus comprises only 16.7%. In an another study conducted A. Ramachandran et al in 1995 found the prevalence of Type-2 diabetes mellitus of about 90% among the diabetes population in India.

The overall male: female ratio in the present series is 3:2. Patel & Dhirwani(1958) reported a male to female ratio of 3:1, while Vaishnava et al (1979), ICMR, observed male:female ratio to be 1:0:8.

The age of diabetic cases varied from 25 years to 70 years with mean age distribution is 51.62 +- 12.32 years. The maximum group was of 51—60 years with the incidence of33.33% followed by 26.67% present in the age group of 41—50 years. McDonald(1968) reported the largest number of cases at ages 45—64 years (42%). A recently published study of National Urban Diabetes by Ramachandran A. et al(2001) observed the maximum number of individuals was diagnosed to have diabetes between the ages of 40 and 59.

In the present study, most of cases (60%) have presented with longer duration of disease (>5 years). The mean duration of illness from initial diagnosis is 8.16 $\pm$ 2.64. This result is similar with the study conducted by Sivasankari S. et al (2000) where the mean duration of diabetes was 7.6$\pm$5.6 years. Ahuja M. M.S. et al in 1979 observed that BMI>25 was nearly seven times in diabetes than in non-diabetics (23.28 vs 3.24%). In the present study 65% of cases were having BMI <26 keeping the pace of present trend of diabetes, which is quiet common in under nutritional persons.

The prevalence of hypertension is six times more common in diabetes mellitus than normal population (Ra P.V.,1994). About 20-25% of type2 patients are hypertensive at the time of diagnosis. In the present study also, 40% of diabetic patients were hypertensives.

In our study out of 75 diabetic cases rheumaological involvement was found in 54 cases (72%). (Out of these 54 cases Type-2 Diabetes Mellitus comprises 49 (65.33%) cases, where as Type-1 Diabetes Mellitus was seen only in 6.(6.67%) cases. This result is consistent with another study conducted by Gbarek Z et al in 1992 where they studied 316 diabetic patients with a prevalence of 42% involvement of rheumatic diseases, comprising both inflammatory and degenerative disorders. Although musculoskeletal manifestations are more commonly associated with long standing Type-1 Diabetes Mellitus patients, many studies conducted by different authors have

shown that there is increase involvement of musculoskeletal system in Type-2 Diabetes Mellitus patients rather than Type-1 Diabetes Mellitus (Gozdzile J. et al, 1987)

In our study total number of Type-2 Diabetes Mellitus patients were 70, out of which 49 patients presented with rheumatological manifestations in contrast to 100% involvement in Type-1 Diabetes Mellitus.

In our study out of 49 Type 2 patients, ADC was noticed in 8 (14.81%) cases, which comprises about 10.67% among diabetic patients. This result is similar with the study conducted by Bridgman et al (1972)7, where they have found 10.8% involvement of musculoskeletal system among diabetic population. Involvement of shoulder hand syndrome was found in 4 cases among all diabetic patients, which comprises 5.33% among the diabetes. This result is similar with the study of Douery et al (1981)8, where they had found SHS in 7.4% of diabetic patients.

Diabetic hand syndrome (LJM) was found in 10 cases of which 7 patients belong to Type-2 Diabetes Mellitus, where only 3 patients in Type-1 Diabetes Mellitus. Among all diabetic patients this involvement was found to be 13.33%. Schuyer M.R. et al (1976) found diabetic hand syndrome with a prevalence of 8—53%. This study correlated well with our present study.

Involvement of flexor tenosynovitis was noticed in 4 patients among all diabetic patients (5033%). McKenzie et al in the year 1975 studied 63 patients with a reported involvement of about 10% of flexor tenosynovitis among diabetic population. Similar study conducted by Tosipovilith et al (1990) also showed similar results.

DISH was found in 7 patients in our study, all of which belongs to Type-2 Diabetes Mellitus patients. The exact percentage of DISH involvement was 9.33%, which is similar to the study conducted by Karave et al9, in 1996 with a reported incidence of about 13% involvement among diabetes.

About 6 cases in our study presented with CPPD (Calcium Pyrophosphate Dihydrate) arthropathy, which comprises about 8% involvement in diabetes. Similar study conducted by Crisp AJ et al in 1994 found the prevalence of CPPD arthropathy in between 8—73 patients.

Dupuytren's contracture and gouty arthritis and hyperuricemia were found in 3 cases respectively with an involvement of 4% of all diabetes. Backett et al in 1994 reported a prevalence of 1.62—63% involvement of Dupuytren's contracture among all diabetics. Similar study conducted by Boyle J. et al in 1969 10 showed 10% involvement of gouty arthritis and hyperuricemia and diabetic population.

Dermatological involvement in the form of thickening of skin was found only in 2 patients. Therefore patients were later diagnosed as having progressive systematic sclerosis and thought to be not directly correlated with diabetic complications. We thought this that this was an association between diabetes and PSS rather than a primary manifestation of diabetes.

Carpel tunnel syndrome was found in 3 cases with a prevalence of 4% involvement of all diabetes, which is similar to the study conducted by Jung Y. et al 11 in 1971 where they found involvement of 5—8% patients with carpel tunnel syndrome.

Neuro-osteoarthropathy, osteopenia, osteolysis and osteoarthritis were found in 1 case respectively with a prevalence of 1.33%. Similar studies conducted by different authors showed similar results.

In our study the predominant involvement was found among male patients but in some diseases females are equal to male and even more than male. In our study 53.7% of patients duration of onset of rheumatological manifestations was more than 5 years (duration). So, rheumatological complications depend on the duration of the disease. Longer the duration of the disease, the manifestations are more prominent.

From the present study it is evident that 68.52% of patients with rheumatological manifestations presented with complications 27.72% of patients presented with neuropathy, retinopathy and nephropathy all together, 25.93% of patients presented with neuropathy.

HbA1C values were found to be elevated in those patients who presented with rheumatic involvement. So this finding implies poor glycaemic control among these patients.

Conclusion : "Rheumatological manifestation of Diabetes" is an ignored entity for last decades despite of the fact that it posed significant morbidity hampering quality of life. But this can be preventable by good glycemic control to some extend. So, Rheumatological examination of a diabetic patient should be routinely done for early detection of this problem.

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Review Article

Sudden Unexpected Death in Epilepsy (SUDEP)

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People with epilepsy have a 2.6 fold increased risk of premature death compared with the general population[1]. The risk of sudden death in young adults with epilepsy is increased 24 fold[2]. Sudden unexpected death in epilepsy (SUDEP) is the most frequent cause of epilepsy related death with incidence rates up-to nine per 1000 person years in people with pharmacoresistant epilepsy[3,4]. In children with epilepsy, the cumulative risk of dying suddenly is 7% within 40 years[5]. Because of the magnitude of this problem, there is an urgent need to understand the mechanism of SUDEP and to develop preventive measures.

Definition :

Sudden unexpected death in epilepsy can be defined as the sudden, unexpected, witnessed or un-witnessed, non traumatic and non drowning death of a person with epilepsy with or without a seizure, excluding documented status epilepticus and in whom postmortem examination does not reveal a structural or toxicological cause of death[6].

Definite SUDEP :

All such death which fulfil the above criteria in whom an autopsy has been done.

Probable SUDEP :

Sudden death in which there has been no postmortem examination, but for which no other compelling cause is evident, is designated as probable SUDEP.

Possible SUDEP :

There are many cases that, because information is scarce or because there are plausible explanation for death, sometimes considered as possible SUDEP.

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Risk factors :

1) Type of Seizure: Evidence from epidemiologic, observational, clinical and pathological studies strongly suggest that in most cases, sudden, unexpected death in epilepsy occurs after a seizure, usually generalized tonic clonic seizure[7].
2) Increased frequency or recent history of seizure – among patients who have had more than three tonic - clonic seizures in preceding year, the risk of sudden unexpected death is increased by a factor of more than eight (8).
3) Lack of treatment with antiepileptic drugs (AED).
4) Subtherapeutic levels of AED.
5) Antiepileptic drug polytherapy.
6) Frequent changes in antiepileptic drugs.
7) Early adulthood.
8) Epilepsy of long duration.
9) Mental retardation.
10) Use of psychotropic drugs.

Mechanism :

Among fifteen cases of sudden, unexpected death in epilepsy that were witnessed in the community, "difficulty in breathing" was observed in 80%[3]; 70% patients were found in prone position[8] suggesting that suffocation contributed to their death. Seizure can cause apnoea or arrhythmia without convulsive activity.

In separate case reports of 13 patients in epilepsy monitoring units, 8 died suddenly and 5 were resuscitated after a life threatening episode. Patients who were successfully resuscitated were younger than who died (29 years v/s 48 years), older patients may be more vulnerable to seizure induced cardio pulmonary or brain dysfunction. Respiratory problems predominated in 8 patients who underwent post ictal hypoventilation, apnoea, cyanosis, respiratory stridor, laryngospasm, pulmonary edema or suffocation[4].

Respiratory factors:

Seizure induced respiratory changes can be lethal and may involve pulmonary dysfunction and suppression of brain stem respiratory and arousal centers[10]. Some serotonergic neurons stimulate respiratory nuclei in the brain stem, where as others, activated by hypercapnia, contribute to the involvement of ascending arousal system. Post ictal depression of serotonergic activity can impair respiration and reflexive repositioning if the mouth and nose are obstructed by beddings[7].

Cerebral shutdown :

Seizure and post ictal state can affect brainstem respiratory centers. Central apnoeas or hypopneas complicate most seizures[11]. Respiration depends on brain stem activity; prolonged suppression of activity stops respiration. Post ictal hypercapnoea and hypoxemia can occur despite increased respiratory effort possibly from ventilation perfusion inequality, which is caused by right to left pulmonary shunting or neurogenic pulmonary odema. Post ictal hypercapnoea can cause severe acidosis that is arrhythmogenic[12]. The effects of prolonged post ictal EEG suppression, apnoea, pulmonary shunting and edema, suffocation in the prone position, impaired arousal to hypercapnia, laryngospasm and respiratory acidosis probably combine and cascade with cardiac factors to cause many cases of sudden unexpected death with epilepsy.

Cardiac factors:

Hypoxemia can lower threshold for cardiac arrhythmias during seizure, especially in patient with channelopathies affecting both brain and cardiac tissues eg: long QT syndrome, Type – II[13]. Interictal and ictal cardiovascular changes occur in patients with epilepsy including prolongation of QT interval corrected for heart rate (QTc) during the ictal and interictal periods and shortening of QTc interval post ictally. Sympathetic cardiac regulation using Radiotracer ^{123}I – metaiodobenzylguandine (MIBG) has shown reduced uptake of MIBG in people with chronic epilepsy compared to control suggesting impairment of post ganglionic sympathetic innervation possibly as a consequence of neuronal loss in patient with long standing temporal lobe epilepsy[14]. This reduction in sympathetic innervation could lead to increased sensitivity to adrenergic stimulation, which might predispose the individual to the arrythmogenic effect of catecholamine release during seizure.

Impaired myocardial contractility can also decrease oxygen supply and facilitated sudden death. Takotsubo cardiomyopathy (found in epileptics) is charectarized by stress induced transient impairment of cardiac wall motion with sudden chest pain, dyspnoea and ECG features similar to those found in acute coronary syndrome[15]. It has been reported in some people with epilepsy mainly after a convulsive seizure or status epilepticus. Takotsubo cardiomyopathy can lead to cadiogenic shock and cardiac arrhythmia suggesting it could be a potential cause of SUDEP.

Adenosine has also recently attracted attention. Over stimulation of adenosine receptors can cause cardiac and respiratory collapse and yet release of adenosine plays a role in seizure termination. It has been hypothesized that prolonged seizures causing metabolic instability in addition with decreased adenosine clearance might be a mechanism leading to SUDEP in some cases[16].

Antiepileptic drugs: (AED)

Antiepileptic drugs exert variety of effects that could predispose to sudden death. Carbamazepine and phenytoin slow cardiac conduction, probably through their affect on sodium channels. Carbamazepine, rufinamide and primidone has been shown to lengthen the QT interval, which could predispose to cardiac arrhythmias. Lamotrigine, which is known to inhibit potassium channels has also been reported as risk factor of SUDEP[17].

There are other drug affects that might contribute to the risk of SUDEP. AED have been reported to reduce the number of red cells, which may lead to impaired oxygen supply to the tissues[18]. In edition fatty acid levels can be affected by AEDs[19]. As these compounds play important role in the regulation of cardiac and neuronal cell wall function, it is possible that any alteration in their serum concentration can adversely affect cardiac excitability.

Prevention:

- The treating physician must ensure good control of seizures
- The patient in turn must perfectly adhere to treatment.
- All efforts should be made for supervision at night (nocturnal supervision) .
- The family members must be trained about cardio pulmonary resuscitation.
- Before labeling a case as refractory seizure, a 12

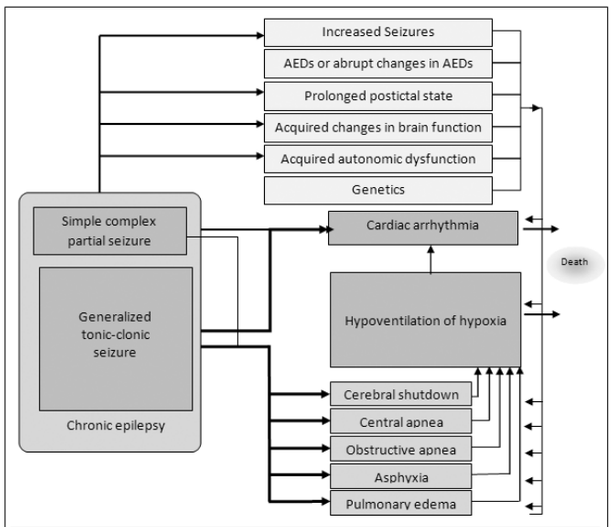

Table -1. Mechanisms of Seizure-Induced Death[7].

in Europe. Further research of SUDEP should also include genetic testing. The affect of nocturnal supervision needs to be examined to see if it is really protective and additional studies of the epilepsy surgery in the prevention of SUDEP are needed.

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Case Report

Hemophagocytosis in Dengue

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ABSTRACT :

Hemophagocytic syndrome or Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening condition arising out of immune dysregulation and characterized by fever, splenomegaly and uncontrolled maturation of macrophages and lymphocytes, leading to pancytopenia. This condition may be familial or arise secondary to infective, neoplastic or immunological diseases in genetically susceptible individuals. Dengue as a cause of HLH is rare in the literature. We report a case of Dengue Shock Syndrome precipitating HLH.

Key words: *Hemophagocytic lymphohistiocytosis (HLH), Dengue*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an unusual syndrome characterized by fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors) in bone marrow and other tissues (1). HLH may be diagnosed in association with viral, malignant, genetic, or autoimmune diseases.

The case

A 22 year old lady from Kolkata presented with fever, headache, myalgia, rash, anorexia and retroorbital pain for 7 days. Physical examination revealed temperature of 102ÚF, BP 100/70 mmHg, mild pallor, pedal edema, morbilliform rash involving trunk and limbs, and just palpable liver and spleen, both of soft consistency. Blood examination on the day of admission showed Hb 8.7 gm/dl, platelets 80,000/cumm and total leucocyte count of 4600/cumm, with 64% neutrophils and 31% lymphocytes. The NS1 Antigen was reactive and dengue IgG & IgM antibodies were negative(pre admission report), as was the malarial dual antigen. Renal and liver function tests were in normal range. The patient was put on IV crystalloids and antipyretics, and was allowed soft diet with plenty of oral fluids. The clinical scenario and blood counts continued to remain same on the next day.

The patient developed pain abdomen 2 days after admission. This pain was more on right upper quadrant of the abdomen, and was accompanied with nausea, vomiting, high colored urine, breathlessness on talking and minimal bilateral ankle swelling. The fever was continuous, varying between 100ÚF to 103ÚF, although the rash had subsided by this time. Over the next day, the pallor worsened, icterus appeared, pedal edema increased, the liver was enlarged, palpable 3cm below right costal cartilage at right mid clavicular line and was soft , tender and the splenomegaly persisted, no lymph nodes were palpable during the course of the illness.

Repeat blood counts on day 3 revealed pancytopenia with Hb 7.7gm/dl, total count 3,900/cumm, and platelets 60,000/cumm. Dengue IgM was positive on Day 4 of hospitalization, while LFT was deranged: Total Bilirubin 3.4mg/dl, (direct 1.9 and indirect 1.5), AST 428IU/ml, ALT 435IU/ml, ALP 205IU/ml, total protein 7.0 gm/dl, albumin 4.0 gm/dl and globulin 3.0gm/dl. The Prothrombin Time was 27.5 seconds and INR was 2.5. LDH was

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markedly elevated (986U/l). Renal parameters and electrolytes were normal. USG abdomen revealed mild bilateral pleural effusion, mild ascites, hepatosplenomegaly and no retroperitoneal lymph nodes. The chest X-ray and ECG were unremarkable. Output was adequate and IV Ceftriaxone and Amikacin were added in view of progressive neutropenia.

We entertained a working diagnosis of dengue fever with capillary leakage and hepatic dysfunction. The patient was transfused with 6 units of fresh frozen plasma and intensive clinical monitoring was instituted. The lady continued to deteriorate and on the 7th day of hospitalisation, patient became irritable with altered sensorium, headache and vomiting. The BP was 80/60 mmHg and the output was around 15ml/kg/hour. The counts dropped further and platelets were transfused. CT scan of brain was normal and bone marrow aspiration was performed.

The bone marrow histopathology report was available on day 9 of admission and suggested dyshematopoiesis involving all lineages, adequate stainable iron, increased numbers of reticulo-endothelial cells and evidence of hemophagocytosis. We diagnosed a case of secondary Hemophagocytic Syndrome, also known as Hemophagocytic lymphohistiocytosis (HLH) due to Dengue fever, complicated with the features of Dengue Shock Syndrome. IV dexamethasone as per HLH 2004 protocol was instituted and supportive measures boosted with IV Co-amoxyclav and IV Clindamycin, along with inotropic assistance. Lab tests on day 9 were: bilirubin 5.5mg/dl, (direct 3.0, indirect 2.5), AST 1109 IU/ml, ALT 3343 IU/ml, ALP 205IU/ml, total protein 7.2 gm/dl, albumin 2.5 gm/dl, globulin 4.70 gm/dl, LDH 2800u/l, serum ferritin 6700 ng/ml and fasting serum triglyceride measured 809 mg/dl ,fibrinogen 130 mg/L. HBsAg, anti-HCV, ELISA HIV 1 and 2, VDRL and ANF by the Hep-2 methods were all negative. There was a single episode of GTCS on the 10th day of hospital stay but the patient clinically improved over the course of the next 12 days. She was discharged after 3 weeks of admission in an afebrile, well oriented state with blood counts in the normal range.

Discussion :

Haemophagocytic lymphohistocytosis (HLH), also called "Haemophagocytic Syndrome" (HPS), is a reactive proliferative disorder that affects the antigen-processing macrophages which results in uncontrolled haemophagocytosis (1). The initial diagnostic criteria set forth by the Histiocytic Society for inclusion in the international registry for HLH is as follows (I) Fever as high as 38.5°C for 7 days or more. (II) Splenomegaly – 3 cm below left costal margin (III) Cytopenia involving at least 2 lineages: Absolute Neutrophils < 1000/iL, Platelets less than100,000/iL, Hemoglobin < 9 g/dL (IV) Fibrinogen < 150 mg/L or fasting triglyceride >3 mmol/L (265mg/dl) (V) Hemophagocytosis in spleen, lymph node or Bone Marrow. In 2004, three additional criteria were introduced: (VI) Serum Ferritin > 500 ìg/L (VII) sCD25 > 2400 U/L (VIII) Decreased or altered NK cell activity (2). Altogether five of these eight criteria must be fulfilled, unless family history or molecular diagnosis is consistent with HLH.

The therapy of HLH includes etoposide, dexamethasone, cyclosporine A. Steroids suppress the sever hyperinflammation and dexamethasone is preferred as it crosses the blood brain barrier. Cyclosporine A inhibits T cell activation. Etoposide is effective in killing the over – stimulated macrophages. This must be combined with treating the triggering infection or neoplasm. If the defect lies in the genetic background, allogenic stem cell transplantation is advocated (3).

HLH is not a single disease and may be encountered either as a familial trait or in association with a variety of

Classification of Haemophagocytic lymphohistocytosis (HLH) (3)

1. Inherited HLH
■ **Familial HLH (Farquhar disease)**
▪ Known genetic defects (perforin, munc 13-4, syntaxin 11)
▪ Unknown genetic defects.
■ **Immune deficiency syndrome**
▪ Chediak Higashi syndrome
▪ Griscelli syndrome
▪ X- linked lymphoproliferative syndrome
2. Acquired HLH
■ **Exogenous agents (infectious organisms, toxins)**
▪ Infection – associated hemophagocytic syndrome (IAHS)
■ **Endogenous products (tissue damage, metabolic products)**
▪ Rheumatic diseases
▪ Macrophage activation syndrome (MAS)
Malignant disease

underlying diseases that leads to highly stimulated but inactive immune response (Table 1) (3). Although initial reports suggested that viruses alone contribute to infection associated HLH, subsequently it was clear that HLH may be associated with bacteria, fungi, mycobacteria and parasites as well. As a result, the term Viral Associated Hemophagocytic Syndrome (VAHS) was redesigned as Infection Associated Hemophagocytic Syndrome (IAHS) (4). HLH in association with malignant disease is well known entity in adults but rare in children, with lymphoma being the most common asociation. In a recent Japanese review of patient with lymphoma associated hemophagocytic syndrome (LAHS), EBV genome was detected from more than 80% of T/NK cell lymphoma but rarely from B cell lymphoma (5).

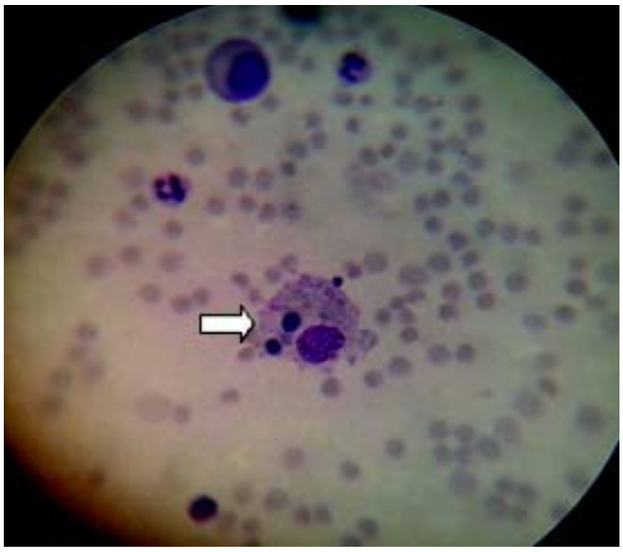

Figure 1: Bone marrow aspiration showing hemophagocytosis

Several infections have now been associated with HLH. Occasional reports have associated falciparum malaria as a cause of HLH (6). Association of dengue with HLH is even rarer (7). A study from Thailand found HLH in 2 out of 157 cases of Dengue hemorrhagic fever (8). A case report from Kolkata, India in 2011 is possibly the latest in the published literature till date (9). Our case is worth reporting because it highlights the possibility of HLH in cases of classic dengue fever and also adds to the small global list of documentations where dengue has been incriminated as the precipitant of this life threatening inflammatory condition.

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Case Report

A Case of Varicella Zoster Vasculopathy Induced Acute Stroke

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ABSTRACT :

Arterial ischemic stroke (AIS) during childhood frequently causes significant long-term morbidity. The etiologies of AIS during childhood are multifactorial and differ from adults. Varicella has been identified as one potential risk factor for AIS during childhood. Vasculopathies caused by Varicella zoster virus (VZV) are indicative of a productive virus infection in cerebral arteries after either reactivation of VZV (shingles) or primary infection (chickenpox). VZV vasculopathy can cause unifocal, multifocal, superficial and deep-seated infarctions. Lesions at the grey–white matter junction and involvement of both large and small arteries on imaging are a clue to diagnosis which is best confirmed by the presence of anti-VZV IgG antibody and mononuclear pleocytosis in the cerebrospinal fluid.

We report a two-year and six-month-old immunocompetent boy who developed aphasia and right hemiparesis three months after Varicella zoster infection (rash).

KEY WORDS: Arterial ischemic stroke, Varicella zoster virus, vasculopathy

Introduction

The aetiologies of childhood strokes are multiple; heart disease whether congenital or acquired, metabolic, hematological disorders, infections and vasospastic conditions being the common etiologies. Varicella has been identified as one potential risk factor for AIS during childhood.VZV vasculopathy results after either reactivation of VZV (shingles) or primary infection (chickenpox).In children, VZV vasculopathy has been proposed to account for 31% of all arterial ischemic strokes;[1] moreover, stroke was preceded by chickenpox in 44% of children with transient cerebral arteriopathy.[1], [2]

Case history

A 2.6 year-old full term male child, with normal developmental mile stones was admitted with acute onset right hemiplegia with aphasia.He had history of generalized vesicular rash suggestive of chicken pox, three months prior to present episode. There was no history of convulsions, loss of consciousness .Maternal history for zoster infection during pregnancy was negative. On examination, the boy was found to be conscious and alert. He had right UMN facial palsy. Motor power in the right upper and lower limbs was grade 3 with hypertonia. Reflexes were exaggerated on the right side. Right plantar was extensor. There were no signs of meningeal irritation. Cardiac examination was normal.

On investigations his routine blood examination suggested Hb 13.2 g; TC 8600; and DC P56 L34 E7 B3. Peripheral blood smear was normal. Blood VDRL and HIV serology was negative. CT scan head showed left capsuloganglionic infarct (Figure 1).MRI brain with MRA revealed, acute cerebral infarct in left MCA territory (Figure 2), with marked attenuated caliber of left ICA and nonvisualization of left MCA (Figure3).CSF examination revealed protein 21.3 mg/dl, sugar 69 mg/dl, 8 cells/mm^3 (all lymphocytes).CSF /Serum quotient for Varicella zoster antibody was 1.97 (significant) , CSF VDRL was non reactive. ECG and ECHO were normal.

The child was treated with intravenous acyclovir for

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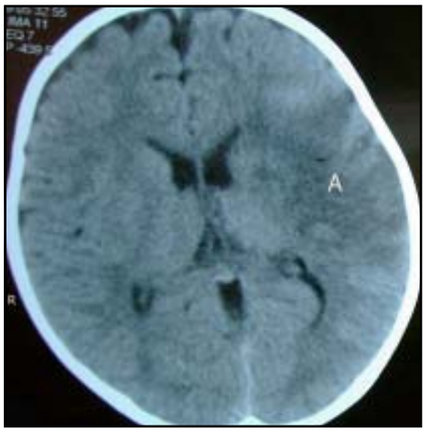

Figure 1. *CT scan head showing left capsuloganglionic infarct (A).*

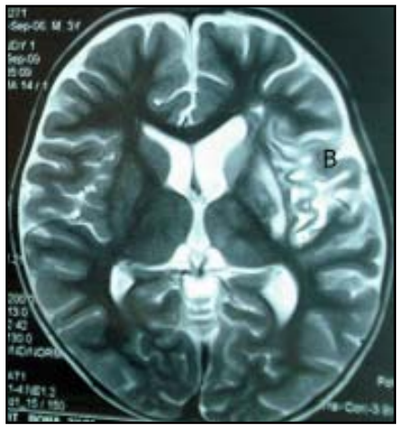

Figure 2. *MRI showing acute cerebral infarct involving the left MCA territory (B).*

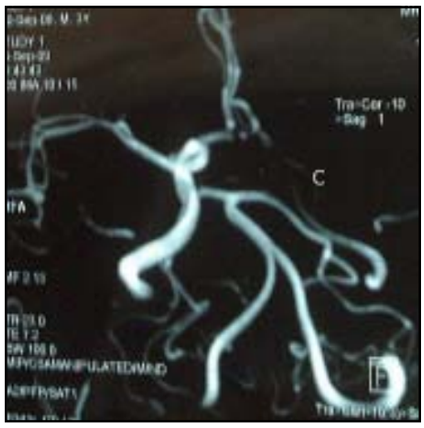

Figure 3. *MRA showing marked attenuated caliber of left ICA and nonvisualization of left MCA (C).*

14 days which resulted in near-complete neurological recovery.

On follow-up at 1 month, the patient could walk independently. Motor power was grade 4 with hypertonia on right side. At two and half month, he was completely normal with normal motor power, mild hypertonia on right side, with no aphasia.

Discussion

Chicken pox is mostly observed in pre-school and school-age children .Neurological complications caused by chicken pox are estimated to be approximately 0.01-0.03%. Cerebellar ataxia and encephalitis are seen frequently, while transverse myelitis, aseptic meningitis, Guillain Barre Syndrome, meningoencephalitis, ventriculitis, optic neuritis, post-herpetic neuralgia, herpes zoster ophthalmicus, delayed hemiparesis, peripheral motor neuropathy, cerebral angitis, Reye's syndrome and facial paralysis are observed rarely. [3],[4],[5] A recent study of Neurological complications of chickenpox has reported a single case of stroke post-chickenpox with normal MR angiography among total 18 cases. [6]

Varicella zoster virus (VZV) vasculopathy produces stroke secondary to viral infection of cerebral arteries. Vasculopathy typically involves one or more cerebral arteries. The clinical diagnosis of VZV vasculopathy is usually based on a history of recent zoster followed by neurologic symptoms and signs; imaging abnormalities indicating cerebral ischemia, infarction, or haemorrhage; angiographic evidence of narrowing or beading in cerebral arteries; and a CSF pleocytosis .Neurologic disease often develops weeks and sometimes months after zoster and not all patients with pathologically and virologically verified disease have a history of zoster rash or chickenpox[7].

Brain imaging reveals abnormalities in most cases, abnormalities are both cortical and deep; and occur in both the grey and white matter and at grey–white matter junctions in particular[8] (—a clue to the cause of disease). Gangliocapsular infarcts as seen in our case is commonly observed.[9] Vascular studies show involvement of both large and small arteries in 50%, pure small-artery involvement in 37% and pure large-artery disease in 13% patients.[7] Typical angiographic changes include segmental constriction, often with poststenotic dilatation. Abnormalities in the CSF are common. A modest pleocytosis, generally of fewer than 100 cells and predominantly mononuclear, is seen in two-thirds of patients with VZV vasculopathy,[7] clearly the absence of CSF pleocytosis does not rule out VZV vasculopathy.Virologic analysis is often limited to a search only for VZV DNA in CSF, which is negative in most cases of VZV vasculopathy,in contrast to this ,the detection of anti-VZV IgG antibody by enzyme immunoabsorbent assay (EIA)in CSF, is the virologic test of choice to diagnose the disease .[10] In every patient in whom anti-VZV IgG antibody is detected in the CSF,a increased CSF to serum ratio of anti-VZV IgG antibody is consistent with intrathecal synthesis of VZV IgG antibody.[11] All patients are typically treated with intravenous acyclovir on the basis of category 3 evidence with or without steroids.[7]

KEY MESSAGE: Although rare the clinical diagnosis of VZV vasculopathy should be strongly suspected in child with a recent history of varicella with stroke because of its potential treatability.

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Case Report

A Case of Solitary Fibrous Tumour Presenting with Hypoglycemia

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ABSTRACT :

Solitary Fibrous Tumour (SFT) is a rare primary tumour arising from mesenchymal cells in the areolar tissue adjacent to the mesothelial lined pleura. The association of paraneoplastic hypoglycemia and finger clubbing with pleural solitary fibrous tumour is rare. A 70 years old male with long history of "early morning light headedness and occasional blackouts", was found to have hypoglycemia. He was having digital clubbing and decrease breath sounds in the Right lower chest but no other significant clinical findings. Chest radiograph and CT Scan revealed a heterogeneously enhancing mass lesion in the Right chest which was diagnosed to be SFT in histology.

Introduction:

SFT is a rare neoplasm with fewer than 800 cases reported in literature. It arise from submesothelial mesenchymal cells in the areolar tissue subjacent to the mesothelial lined pleura[1]. Predominant age presentation is sixth and seventh decades of life with a fairly equal frequency in both sexes. These are mostly asymtomatic. Symptomatic patient present with cough, chest pain , dyspnoea, fever. Paraneoplastic syndromes may occur but are more likely seen in patients with larger tumours. Hypertrophic Osteoarthropathy is the most common paraneoplastic syndrome in SFT patients reported in up to 22% of patients (especially in tumours greater than 7 cm in diameter) compared to a 5% incidence in lung Carcinoma[2]. Others are presenting with clubbing, gynaecomastia or galactorhoea. Incidence of severe symptoms like hypoglycemia in SFT patients is as low as 3-4%[2].

Case report:

Ours' is an interesting case of 70 year old Hindu resident of Tripura presented in medicine department with history of cough and chest pain for 2 years and early morning clinical features suggestive of hypoglycemic attacks relieved after taking food for 4 months with no past history of haemoptysis or T.B. No history of similar illness in the family. On examinaton, patient looked cachetic with a pulse rate of 80/min., B.P. 126/74 mm of Hg, RR-16/min, temperature - 98.8 degree F, clubbing. Icterus, pallor, edema were absent. Respiratory system examination revealed decrease breath sound in right lower chest, but no other significant clinical finding. Cardiovascular System, Nervous system Examination examination,Gastrointestinal examination were normal.

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Investigation:

TLC-: 9,000 / cu mm
Hb: 9.8 gm/ dl.
ESR: 15 mm AEFH
FBS: 13 mg/ dl.
Serum urea: 28 mg/dl
Serum Creatinine : 1.2 mg/dl
Serum Na+ : 136 mmol/L, Serum K+ - 4.1mmol/L
Urine examination : Protein - trace.

Chest X-Ray P. A. View - Dense homogenous opacity is noted in mid and lower zone of right lung silhouetting the right hilum, right heart border ,right hemidiaphragm ,right cardiophrenic angle and displacing the mediastinum towards left side.

CT SCAN OF THORAX - (Fig.- 1-4)

Serial axial sections of the THORAX were studied using HRCT protocol (with IV contrast) from apices to bases.

Study reveals:-

Heterogeneously enhancing mass lesion of size 15 X 14 X 13 cm is noted in the right hemi thorax extending

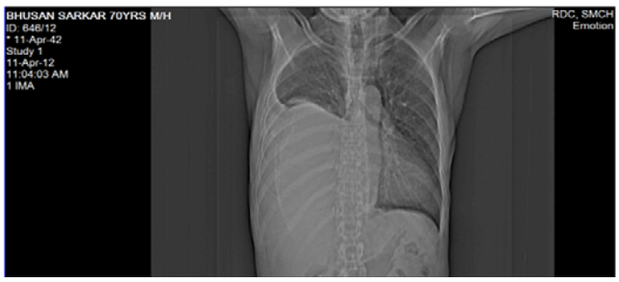


Fig. 1

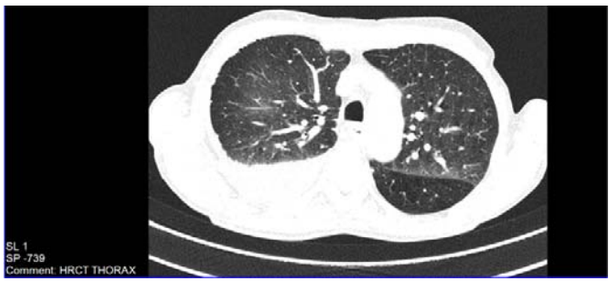


Fig. 2

Fig. 3

Fig. 4

from lateral chest wall to mediastinum. The mass has displaced the lung superiorly and medially the mass has extended up to the mediastinum with loss of fat plane at few places. Laterally the mass has broad based attachment to the pleura & has extended to lateral chest wall with possible extension to intercostal space. The mass has displaced the diaphragm inferiorly.

Suggestive of Pleural based tumour.

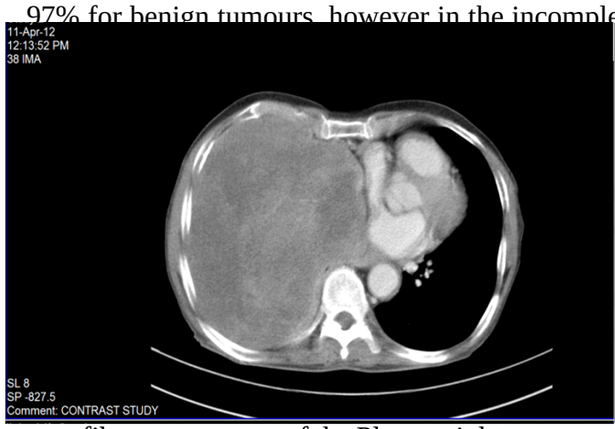
USG guided FNAC smear :- Shows few dispersed and clusters of spindle cells in a clear background.

Serum Insulin estimation could not done as the facility is not available in Silchar Medical College and Hospital and nither the patient could afford it from outside.

Patient was managed conservatively and referred to higher centre for resection of tumour and further management.

Discussion:

SFT tends to affect mainly adults during the sixth and seventh decades of life. Most patients are asymptomatic and lesion is discovered incidentally on chest radiographs. Systematic patients may report dyspnoea, cough or vague chest or shoulder discomfort. Symptoms are usually related due to local mass effect of large lesions or to associated Paraneoplastic phenomenon. They range in size from 1-36 cms with a mean 6 cms. Extrathoracic manifestations include clubbing of fingers with HPO and hypoglycemia. HPO is reported in up to 22% of patients, especially in tumours greater than 7 cm in diameter[3]. Both Paraneoplastic syndrome are more common in tumours larger than 7 cms in size and resolve with surgical resection of tumour. Recommended treatment for SFT is complete resection of tumour[4]. Five year survival rate is as high as 97% for benign tumours, however in the incomplete



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Case Report

Vertebral artery dissection in young male: leading to Opalski syndrome - Case Report

S Choubey* D K Boruah R Patil, S Mali*****

ABSTRACT :

Vertebral artery dissection is uncommon cause of stroke. Lateral medullary infarction (Wallenberg syndrome) is a relatively common vertebrobasilar vascular syndrome in VAD which is usually not associated with paralysis. However, ipsilateral hemiparesis as part of lateral medullary infarction is known as Opalski's syndrome which is very rare.. We had a young male patient with symptoms typical of vertebral artery dissection and weakness that was specific of this rare syndrome. It was confirmed by specific investigations like MRI brain and CT angiography and treated conservatively with antiplatelet agents.

Vertebral artery dissection is area lead to focal neurologic signs attributable to ischemia of the brainstem or cerebellum ultimately develop in 85% of patients; however, a latent period as long as 3 days between the onset of pain and the development of CNS sequelae is not uncommon. When neurologic dysfunction does occur, patients most commonly report symptoms attributable to lateral medullary dysfunction (ie, Wallenberg syndrome).

Patient history may include, ipsilateral facial dysesthesia (pain and numbness), dysarthria or hoarseness (cranial nerves [CN] IX and X), contralateral loss of pain and temperature sensation in the trunk and limbs, vertigo,nausea and vomiting, diplopia or oscillopsia,dysphagia (CN IX and X), disequilibrium, unilateral hearing loss. Rarely, patients may manifest contralateral weakness or paralysis (Lesion of pyramidal tract in medulla above the level of dicussation)

However, ipsilateral hemiparesis as part of lateral medullary infarction below the level of dicussation is rare, and is known as Opalski's syndrome. Hence the case with vertebral artery dissection with Opalski's syndrome is quite notable case.

Introduction :

Vertebral artery dissection is a rare condition but is an increasingly recognized cause of stroke in patients younger than 45years. Although its pathophysiology and treatment closely resemble that of its sister condition, carotid artery dissection (CAD), the clinical presentation, etiology, and epidemiological profile of VADs are unique.

Lateral medullary infarction (Wallenberg syndrome) is a relatively common vertebrobasilar vascular syndrome in VAD which is usually not associated with paralysis. Combined lateral and medial medullary syndrome leads to contralateral paralysis of arm and leg. However, ipsilateral hemiparesis as part of lateral medullary infarction is known as Opalski's syndrome. Some pathologic and neuroradiologic reports have shown that the lesion is located lower than in Wallenberg syndrome, and the ipsilateral hemiparesis seen in this syndrome is attributed to the involvement of corticospinal fibers caudal to the pyramidal decussation.[1] And also, Opalski's syndrome with cerebellar lesion is rare.

Case Report: A 32 year old male shopkeeper non-diabetic, non hypertensive came to our hospital with history of severe left sided neck pain and same sided occipital headache followed by weakness of left side of body. He was suffering from that neck pain and headache for 15

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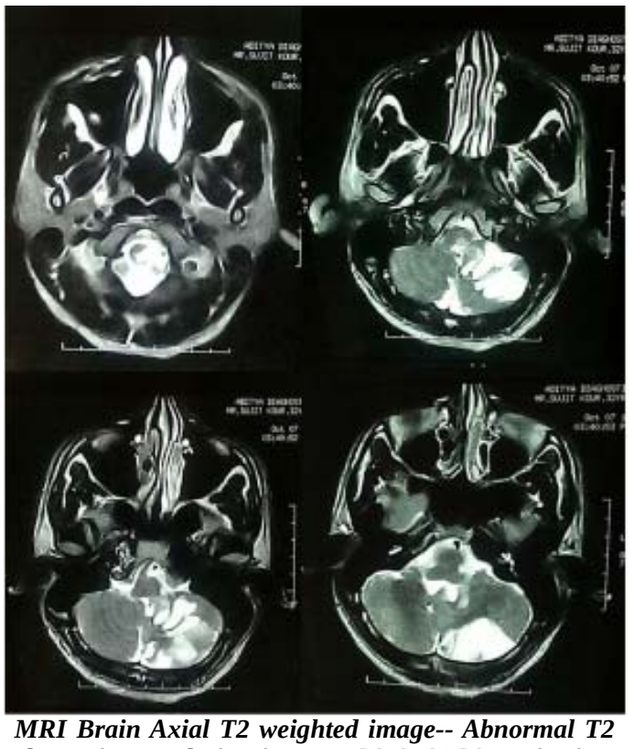
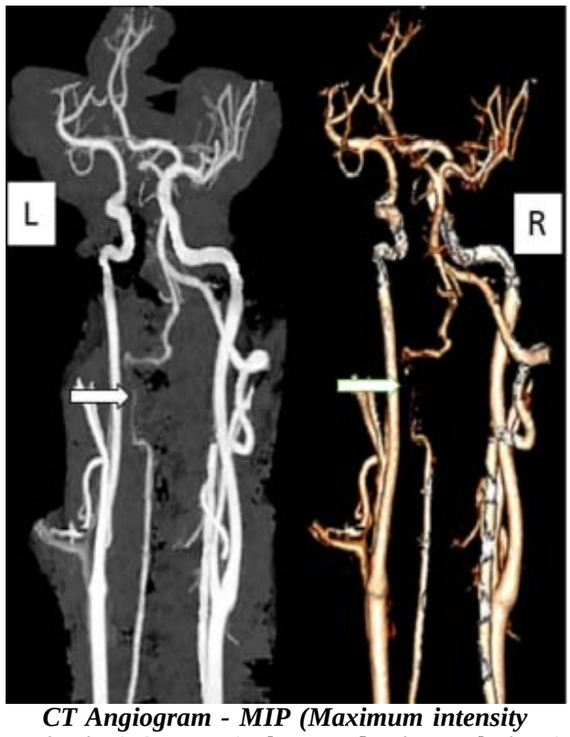


MRI Brain Axial T2 weighted image-- Abnormal T2 hyper intense lesion in Lt PICA & AICA territories



CT Angiogram - MIP (Maximum intensity projection) & VRT (Volume reduction technique) images showing Lt vertebral artery dissection

days in low intensity. On the day of admission his pain was sharp shooting type and radiating to ward head aggravated by Left lateral neck movement. His weakness had started after 6 to 8 hrs after aggravation of pain and progressed over 1-2 hr to complete immobility of left side of body. He was also complaining of diplopia for 2-3 hr, giddiness, nausea and one vomiting, hiccups, slight difficulty in eating. There was no h/o trauma to spine or any chiropractic neck movement. There was no significant past or family history. He was occasional alcoholic and nonsmoker.

On thorough clinical examination he was conscious and well oriented, his pulse was 70/min, BP was 130/80 mmHg. He was having mild ptosis and constricted pupil in his left eye, and we also noticed decreased sweating on his face after 2-3 days suggesting that he had left sided horners syndrome. Nystagmus was present in left lateral gaze. He had 8 to 11 cranial nerve palsies. He had hypotonia and 0/5 power in left UL and LL. His reflexes were brisk and planar extensor on left side. His pain and temperature sensation over left side of face were decreased. He had posterior column sensory loss on left side body. Only abnormality on right side was decreased pain and temperature sensation. These were features of Brown-Séquard syndrome. His CT brain was normal, MRI brain and upper cervical cord was done on second day showing Infarct in left PICA & AICA territories involving cerebellum, left posterior-lateral portion of medulla and spinal cord up to lower part of C2. CT angiography done on next day showing left vertebral artery dissection in its third part. He was given antiplatelet agents. Patient improved and was able to eat and move his limbs at the time of discharge.

Discussion: Although a PICA occlusion can be the cause of Wallenberg's (lateral medullary) syndrome, this syndrome is more often caused by an intracranial vertebral artery occlusion. This syndrome produces an ipsilateral Horner's syndrome; loss of pain and temperature sensation in the face; weakness of the palate, pharynx, and vocal cords; and cerebellar ataxia.

Involvement of the ipsilateral posterior spinal artery that arise from the VA or PICA may account for ipsilateral sensory loss from infarction of the ipsilateral dorsal column nuclei as a component of the lateral medullary wedge syndrome.[2]

Contralateral to the lesion, there is hemibody loss of pain and temperature sensation.

The medial medullary (Dejerine) syndrome is less common and may be caused by occlusion of the distal vertebral artery, a branch of the vertebral artery, or the lower basilar artery. Vertebral artery dissection, dolichoectasia of the vertebrobasilar system, and embolism are less common causes of the medial medullary syndrome. The findings with this syndrome include an ipsilateral lower motor neuron paralysis of the tongue and contralateral paralysis of the arm and leg. The face is often spared. In addition, there is contralateral hemibody loss of tactile, vibratory, and position sense. Occlusion of the intracranial vertebral artery can lead to a total unilateral medullary syndrome (of Babinski-Nageotte), a combination of the medial and lateral medullary syndromes. [3]

The Babinski-Nageotte syndrome is caused by hemimedullary infarction and combines the medial medullary and the lateral medullary syndromes.[4]

The submedullary syndrome of Opalski is caused by VA occlusion with extensive infarction of the cervicomedullary junction. The patient has the lateral medullary wedge syndrome plus ipsilateral hemiplegia because of infarction of the pyramidal tract after its decussation.[5]

The lesion also may affect the ipsilateral dorsal column nuclei.

Our paient had symptoms of lateral medullary syndrome that is ipsilateral nystagmus, vertigo, nausea, vomiting due to involvement of inferior cerebellar peduncle and vestibular nuclei.

He had decreased pain and temperature on left side of face due to involvement trigeminal nucleus and tract, decrease pain and temperature sense on right side due to involvement of spinothalamic tract. Left sided Horners syndrome due to involvement of descending sympathetic tract fibres. Dysphasia due to involvement of nucleus ambigus, left sided taste sensation loss due to involvement of nucleus tractus solitaius, left sided posterior column sensation loss due to involvement of dorsal column nuclei as described above.

Along with that he had left sided hemiplegia due to involvement of lateral corticospinal tract upto cervical second segment (pyramidal tract after its dicussation – cervicomedulary junction.)

Conclusion: Spinal hemiplegia (Brown-Séquard syndrome) due to other causes can be confused with hemiplegia due to cervicomedullary junction infarction but good history of neck pain and clinical examination of cranial nerve involvent will differentiate the diagnosis from vertebral artery dissection. Vertebral artery dissection in young adult is common but extensive involvement of lateral medulla and inferior cerabellum with upper part of spinal cord can occur.

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Case Report

In-Stent Restenosis in the Drug-Eluting Stent Era: A Case Report from Gauhati Medical College and Hospital

B Dutta*, C Modak**

ABSTRACT :

Unlike BMS in stent restenosis (ISR) of Drug Eluting Stent is a rare entity and its management strategy is not yet clear. We are, therefore, reporting this case. A 47-year-old diabetic, hypertensive and dyslipidemic man, who underwent coronary angioplasty with Endeavor stent of 3mm × 20 mm across the proximal left anterior descending artery lesion in April, 2010 presented with unstable angina in August, 2011. Coronary angiography revealed ostial to proximal LAD 70% type 2 In Stent Restenosis which was successfully treated with Endeavor Resolute 3mm × 24 mm stent achieving TMI-3 flow. He was on regular follow up and vigilant attention was paid to risk factor modification. At 9 months post PTCA, check angiography showed no evidence of late lumen loss.

Key words : *In Stent Restenosis(ISR), Drug Eluting Stent*

INTRODUCTION

Restenosis, or reduction in lumen diameter after percutaneous coronary intervention (PCI), is the result of arterial damage with subsequent neointimal tissue proliferation. Binary angiographic restenosis is defined as e™ 50% luminal narrowing at follow-up angiography (1). The most widely accepted definition of clinical restenosis, assessed as a requirement for ischemia-driven repeat revascularization, was proposed by the Academic Research Consortium (2).

The initial pivotal randomized trials comparing DES and BMS were conducted in patients with de novo native coronary artery lesions, and ISR was observed at follow-up in < 6% of patients (3, 4). Subsequently, restenosis rates increased to the double-digit domain (>10%) in randomized head-to-head DES comparisons and registries including more complex patients and lesions (5, 6, 7, 8).

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Reports on the presentation of BMS ISR have shown that unstable angina is a frequent manifestation of ISR (26% to 53%). The presentation of DES ISR is similar to that of BMS ISR with approximately 16% to 66% of patients presenting with unstable angina and 1% to 20% with MI (9, 10).

Possible mechanisms include biological factors (drug resistance, hypersensitivity), mechanical factors (stent underexpansion, nonuniform stent strut distribution, stent fracture, nonuniform drug elution/deposition, duration of drug delivery, polymer peeling), technical factors (barotrauma outside stented segment, stent gap, residual uncovered atherosclerotic plaques) (13).

Predictive factors for DES restenosis, such as diabetes mellitus, complex lesions (B2/C), small vessels, longer stents, and stent underexpansion, identified from real-world data seem to be similar to those for BMS restenosis (11,12,).

A very recent randomized trial has concluded that in the focal DES restenosis, repeat Sirolimus Eluting Stent (SES) implantation is more effective for reducing late loss and subsequent angiographic restenosis than cutting balloon angioplasty. However, in the diffuse type DES restenosis, the second-generation Everolimus Eluting Stent (EES) is not

more effective than the first-generation Sirolimus Eluting Stent (SES) in improving angiographic or clinical outcomes (14).

CASE REPORT

A 47-year-old diabetic, hypertensive and dyslipidemic man was a diagnosed case of coronary artery disease presented with unstable angina and he underwent coronary angioplasty in Pune with Endeavor stent of 3mm × 20 mm across the proximal left anterior descending artery lesion in the month of April, 2010. After that he was not on regular follow up and he again became symptomatic at 3 months after the procedure. Angina was gradually increasing in severity and he presented with unstable angina and admitted into the Cardiology department, Gauhati Medical College in the month of August, 2011.

ECG revealed LAFB and QS complexes in V1 and V2. Echocardiography showed regional wall motion abnormality in the left anterior descending coronary artery territory with mild left ventricular systolic dysfunction. Left ventricular ejection fraction was 45% as measured by Simpson's method.

Blood investigation revealed dyslipidemia, poor glycemic control and normal renal function tests and electrolytes.

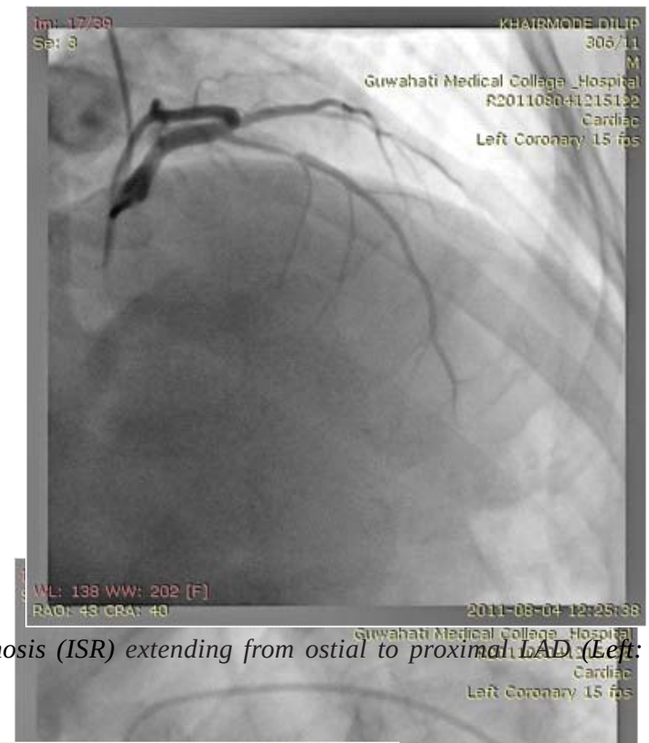

Figure 1. *Angiography showing diffuse in-stent restenosis (ISR) extending from ostial to proximal LAD. (Left: LAO caudal view; Right: RAO Cranial view)*

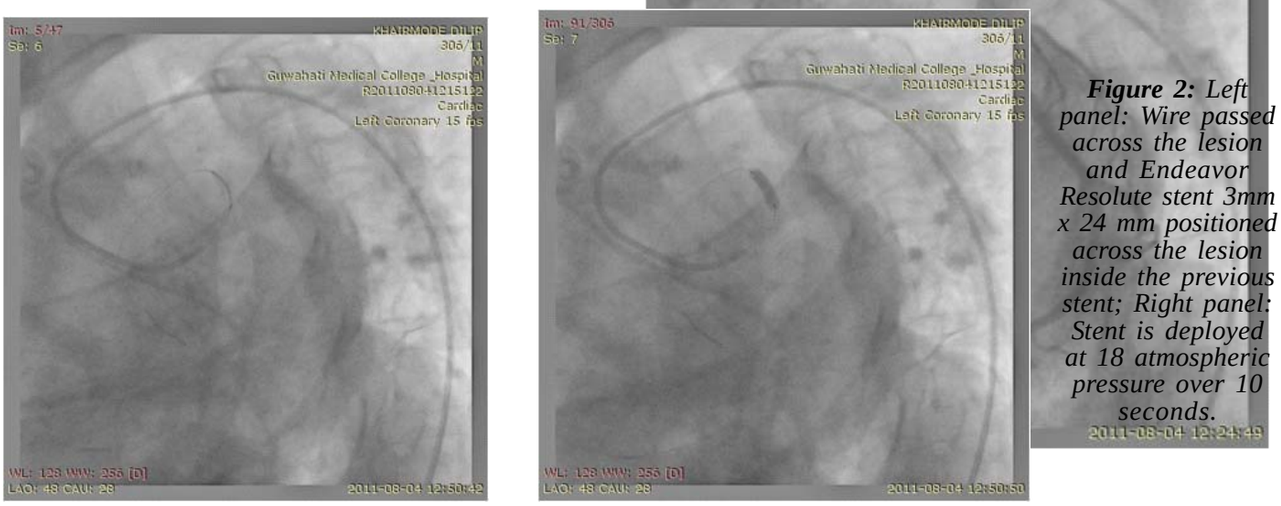

Figure 2: *Left panel: Wire passed across the lesion and Endeavor Resolute stent 3mm x 24 mm positioned across the lesion inside the previous stent; Right panel: Stent is deployed at 18 atmospheric pressure over 10 seconds.*

His biomarkers were negative.

Coronary angiography revealed left dominant coronary circulation with ostial to proximal LAD 70% type 2 In Stent Restenosis of the previous Endeavor Stent (Figure1). He was taken up for PCI. Left coronary artery was hooked with JL 3.5 guiding catheter. Lesion crossed with Zinger medium J-tipped wire. Another Endeavor Resolute 3mm × 24 mm stent was deployed across the restenosis segment of left anterior descending coronary artery at 18 atmospheric pressure for 10 seconds (Figure 2). TIMI-3 flow was achieved and there was no periproceedural complication (Figure 3).

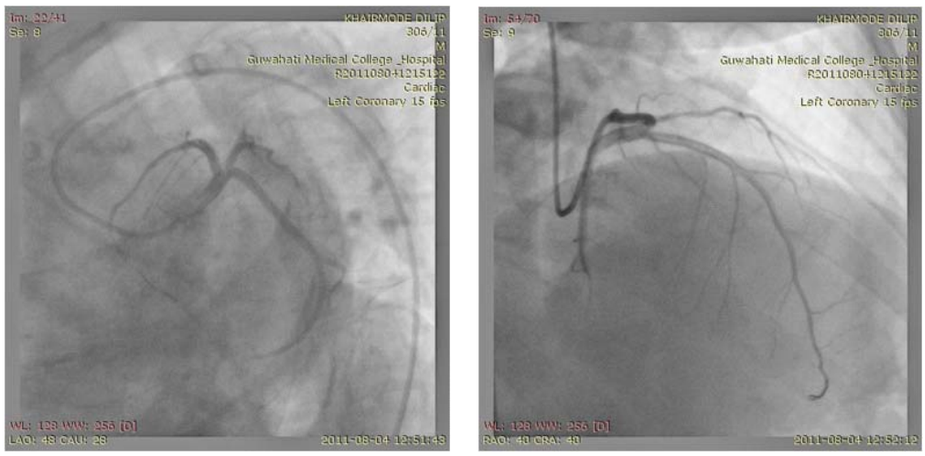

Figure 3: *Final angiographic result after stent deployment – TIMI 3 flow achieved. (Left panel - LAO caudal view; Right panel- RAO cranial view.*

He was prescribed triple antiplatelet therapy including aspirin, clopidogrel and cilostazole, insulin, high dose statin (Atorvastatin 80 mg) and antihypertensive medications.

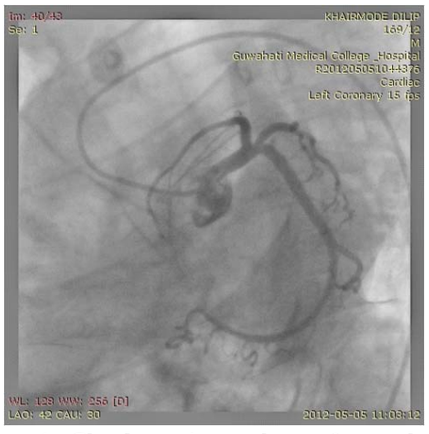

Figure 4: *Check angiography at 9 months of follow up reveals normal epicardial coronaries.*

He was on monthly follow up for 3 months and then 3 monthly follow up till 9 months. During all the follow up visits he was completely asymptomatic and he was having good BP, lipid and glycemic control. His HbA_1c was < 7 and LDL was <70 mg/dl.

At 9 months post PTCA, check angiography showed no evidence of late lumen loss (Figure 4).

DISCUSSION

There were several risk factors for developing In Stent Restenosis in this patient. Firstly, the patient is diabetic which itself is a strong predictor of restenosis. Diabetes part was not taken care of adequately and so patient has uncontrolled hyperglycemia. After second Angioplasty patient was on insulin and had good glycemic control. Secondly, the first stent implanted was an Endeavor stent which has its inherent drawback of delivering zotarolimus for shorter duration as compared to Endeavor resolute stent. We therefore decided to implant a Endeavor resolute stent this time. Though some mechanical and technical factors which are unknown in this case may be the primary reason for ISR in this patient, biological factors like drug resistance and hypersensitivity may also contribute to it. Third factor which may significantly affect the outcome of PCI using drug eluting stent is patient's compliance to antiplatelet drugs and statin. This patient was not on any follow up after the first angioplasty which may indicate that patient may not be compliant to any of the medicines or advices regarding risk factor modification. We therefore kept the patient on triple antiplatelet regime throughout the follow up period and kept the patient under regular and frequent follow up.

CONCLUSION

Although DES result in reduced rates of restenosis compared with BMS across all lesion and patient subsets, this rate increases in subset of patient with multiple risk factors. Angiographic success immediately after PCI may not always predict in stent restenosis and future cardiac

event. Regular follow up and vigilant attention to risk factor modification is equally important to prevent future coronary event and late lumen loss.

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Journey of a young multiple myeloma patient

Tapan Saikia*

M.H., a 33-yr old male presented to us with severe pain in dorsal spine in early 2005. An x-ray of dorsal spine revealed wedge fracture of the D7 vertebra. Detailed work up with CBC, biochemistry, urine analysis, MRI spine, bone marrow aspirate/trephine biopsy, serum immunofixation with free light chain ratio (FLC), serum beta 2 microglobulin level, confirmed the disease to be Multiple Myeloma, IgGKappa type, ISS, IIA. He had normal cytogenetic pattern.

His disease was managed with thalidomide and dexamethasone for 4 months. He also received bisphosphonate therapy with monthly zoledronic acid. The response at this point was a very good partial response (GVPR by EBMT criteria). Being a transplant eligible case, he was offered high-dose melphalan (HDMel) followed by autologous blood stem cell rescue. Post HDMel, the response was near complete response(nCR). Maintenance therapy with thalidomide continued for 3 years.

In late 2009, the myeloma relapsed with bone pain from lytic lesions in ribs and pelvic bones. Following a full work up, he received treatment with bortezomib (proteasome inhibitor), liposomal doxorubicin and dexamethasone x 6 cycles. A VGPR was attained. The way from this point,1.To wait & watch or,2.Bortezomib maintenance or,3. An allogeneic blood stem cell transplant (SCT). He had two sisters who were HLA identical with him. He chose allogeneic SCT after a detailed discussion. In late 2010, he received conditioning chemotherapy with fludarabine and melphalan followed by peripheral blood stem cell transplantation from one of the sisters. Donor cell engraftment occurred within 4 weeks. He experienced grade II acute GVHD which responded to a short course of prednisone. Seven months post-transplant while the myeloma was in complete remission, he developed limited stage chronic GVHD involving muco-cuteneous areas, mouth & skin. Prednisone was reinstituted along with mycofenolate mofetil. The response was rapid, but waxing and waning of GVHD continued. Four months later, he developed high-grade fever and dysuria. Viral investigations revealed an adenoviral cystitis. It responded completely to a high dose and long course of ribavirin. Most recently, he came down with a bilateral community acquired viral infection that responded rapidly to moxifloxacin and high dose trimethoprim. Sputum and BAL cytology& cultures were negative for any specific infection.

Currently, he is in excellent health with mild recurrent episodes of oral chronic GVHD. He continues do his normal daily activities and myeloma remains in complete remission.

This case brings the full trysts and travails of multiple myeloma. One aberration is he is too young to have myeloma. The incidence at this age is 5% of all myeloma. The response to initial induction therapy was favorable, VGPR, which happens in about 60% of newly diagnosed patients treated with thalidomide and dexamethasone. Consolidation therapy with high-dose melphalan, 200 mg/sq.m and autologous blood stem cell rescue (a standard of care) produced an nCR, which is expected in such a case. Thalidomide maintenance is known to offer improved progression free survival but not overall survival.

Second line therapy using novel agents like bortezomib, liposomal doxorubicin and dexamethasone in combination can produce effective response in about 80% cases. The trickiest part was allogeneic SCT. In myeloma this procedure can cause severe acute GVHD and fatal outcome may happen in more than 50% cases.

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Therefore, it remains an investigational approach. He had been fortunate not to have severe acute GVHD. Development chronic GVHD, if extensive, could be debilitating for many and may even succumb to opportunistic infections. He has limited stage chronic GVHD, opportunistic infections are occurring but have not affected vital organs or immune system badly yet. However, his immune system is yet to mature due to GVHD. This has not happened despite re-vaccination program.

Complete and sustained response of myeloma to sibling donor allogeneic stem cell transplant proved the graft versus myeloma (GVM) effect.

This case brings about each and every aspect of myeloma – disease behavior (response and relapse), adequate response to HDMel with autologous SCT but relapse at about 5 years. Novel agents in myeloma at relapse are very effective and it helped him. Finally, he had the benefit of an allogeneic SCT with eradication (most probably) through GVM but experiencing limited stage chronic GVHD. A review of literature shows that benefit from total therapy could be possible in a subset of myeloma patients offering an opportunity of a cure (1,2).

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Article Submission

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