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C O N T E N T S

With best complement from

Editorial

The Chikungunya Re-emergence

Gourangie Gogoi*

Introduction :

The name Chikungunya traces its origins to a verb in the Kimakonde language, meaning 'to become contorted', thus eluding to the 'stooped' appearance of those suffering from joint pain, a characteristic clinical feature of the disease[1].

It is an acute febrile illness caused by an arthropod borne virus, Chikungunya virus (CHIKV). A single-stranded RNA virus of family Togaviridae and genus *Alphavirus*; its ICD 10 code is A 92.0[2]. The virus was first recognized as a human pathogen in Tanzania during the 1950s. Since then Chikungunya has shown widespread geographic distribution in more than 40 countries all over the world in Asia, Africa, Europe and North America. This has resulted in significant morbidity and burden to the public health system in these regions[3].

In India, the Chikungunya virus was first isolated in Calcutta in 1963[4]. Thereafter, the virus was not reported from anywhere in the subcontinent[5]. However, in 2006 several states in Southern India had outbreaks of fever caused by Chikungunya virus infection, thus confirming the re-emergence of CHIKV[6].

Epidemiology :

Several studies have confirmed Central/East Africa to be likely the geographical origin of CHIKV. The virus thrived in a sylvatic cycle between the *Aedes* mosquitoes and non human primates of the forests. Sometimes the infection spilled over to the human population giving sporadic cases but outbreaks were uncommon. However, increasing man-animal proximity provided the conducive environment for the initiation and maintenance of the transmission cycle of CHIKV in certain urban areas. Thus, the virus started circulation between mosquitoes and humans in an urban cycle similar to dengue viruses, sometimes even resulting in double infection[7].

Urban outbreaks of Chikungunya were first documented in Bangkok in early 1960s, in India from 1963 to 1973, followed by few minor periodic occurrences over the next 30 years. However, it was not until 2004 that a major epidemic started in Kenya, that spread to many islands in Indian Ocean, to India and to the rest of the South East Asia. Molecular epidemiology gave the evidence that the strain responsible for this outbreak originated in Kenya. It was this genotype of CHIKV which was imported to India where it had never been reported before. Thus, the resulting outbreak that ensued in India continued for more than 3 years leading to millions of cases. The persistence of infection in India is attributable to sustained viral transmission among the vast numbers of immunologically naive population[1].

Certain other factors likely contributing to rapid transmission, included very high attack rates associated with the recurring epidemics, high levels (often >5 log 10 plaque-forming units per mL of blood) of viremia associated with infection in humans, and the worldwide distribution of the vectors *(Aedes aegypti* and *Aedes albopictus*) responsible for transmitting CHIKV.

During its re-emergence in 2006, India witnessed Chikungunya outbreaks from Vellore in Tamil Nadu, Shrirampur in Maharashtra, and both rural and urban areas of Karnataka, Kerala, Madhya Pradesh and Andhra

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Pradesh. Then it moved northwards through Gujarat, Rajasthan to Delhi, to Orissa, West Bengal in the east and down again to Pondicherry , Andaman and Nicobar; covering over 16 states[8]. Over the course of time Chikungunya outbreaks merit are to be kept in the surveillance radar, with documented urban area prevalence of 22.3% and predominantly affecting the 15-44 years age group[9].

In majority (68%) families, there were multiple patients, resulting in clustering of cases. Certain factors associated with vector bionomics have a role to play for the characteristic features of the Chikungunya outbreak. *Aedes* mosquito prefers domestic and peri-domestic artificial accumulation of water for breeding. It has short flight range of not more than 100 meters. It is highly anthropophilic and the females are fearless day biters. During blood feeding, if the host disturbs vectors, then these mosquitoes tend to attempt biting any other person from nearby vicinity[10, 11]. The short incubation period of the virus in vector as well as in host may be another factor for high morbidity in inmates within the house.

Clinical presentation and management :

The incubation period varies from 3-7 days (range 2-12 days), the illness is self-limiting with acute symptoms of fever (100%), headache (82.1%), arthralgia (81.0%), nausea and/or vomiting (62.0%), abdominal pain (34.0%), rash (14.6%) usually involving the limbs and trunk. All individuals infected with the virus do not develop symptoms and sero surveys indicate that 3-25% of persons with antibodies to CHIKV are asymptomatic. Arthralgia or arthritis of multiple joints, when accompanied by oedema, can be debilitating and may prolong morbidity for weeks to several months after the acute phase has long subsided. Haemorrhagic manifestations, commonly observed in dengue are relatively rare[12].

Chikungunya affects both sexes and all age groups but data revealed that maximum cases were recorded in the reproductive age group which was also the economically productive group[13]. Few studies which report more morbidity in females explained the association with daytime and indoor feeding habits of the mosquito vector. Most CHIKV infections occurring during pregnancy do not appear to result in transmission of the virus to the fetus. However, if the pregnant woman is viremic at the time of delivery, there is a risk for mother-to-child transmission with a vertical-transmission rate of 49 %[7].

Serology has been the mainstay for diagnosis of Chikungunya in the past but with the advancement of molecular techniques, viral RNA can be easily detected in serum during the acute stage. Confirmation of diagnosis is done by detection of CHIKV, viral RNA (RT-PCR) or virus specific antibodies. The choice of test is determined by the stage of infection and the volume of samples available[14].

Treatment for Chikungunya is limited to supportive care in the form of rest, fluids, antipyretics and analgesics. Even though these items seem meagre; the opportunity cost due to income forgone as a result of loss of work, person days lost from daily wages, to the patient as well as the family; is quite considerable. In cases with longer morbidity, this cost rises still higher; especially when the economically productive member of the family is affected[15].

Control strategy :

The re-emergence of Chikungunya is due to a variety of social, environmental, behavioural and biological factors. In an immunologically virgin population, the lack of herd immunity within the country may have probably led to its rapid outbreak across several states in India[16].

Integrated vector management is the mainstay of control as it interrupts virus transmission by reducing as well as preventing human-vector contact. This strategy improves efficacy and cost effectiveness, is ecologically sound and sustainable in the long run. The concept of observation of weekly "dry day," at the community level for mosquito larva control has given encouraging results. There is active emptying of water containers, scrubbing and washing, drying, reûlling and covering the containers on ûxed day by all community members.

Behaviour change communication is advocated for individual protection at the household level comprising of covered clothing, use of repellents, coils, aerosols, vaporizers. Insecticide-treated mosquito nets afford good protection for those who sleep during the day (e.g. infants, the bedridden and night-shift workers) [1].

The way forward :

Research should focus into development of therapeutics, such as antivirals, which can treat the disease and stop the high viraemia, thus significantly decrease the morbidity associated with CHIKV infection. Studies are to be undertaken to unmask any hidden angle in the epidemiological triad of Chikungunya. Improved

recognition of the disease, prompt and efficient sharing of epidemiological information among public health experts will control the spread and magnitude of future outbreaks. The estimated economic burden due to Chikungunya, in addition to long term morbidity due to arthralgia can be prevented if appropriate and timely actions are taken. Therefore a robust surveillance system to predict the risk and prevent the outbreak is the need of the hour.

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Original Article

Current Status of Chikungunya in Assam : A Six Month Study

D Raja*, C Phukan*, B Das**

Abstract

Background : **Objectives :** To determine the prevalence of the cases of Chikungunya and to correlate the clinical symptoms of Chikungunya with serological findings in patients attending Gauhati Medical College and Hospital .

Material and Methods : The study was carried out among 1002 clinically suspected Chikungunya cases presenting with fever, headache, retro-orbital pain, back pain and arthralgia. The samples were tested for Chikungunya virus specific IgM antibodies, in the Department of Microbiology, Gauhati Medical College and Hospital. Detection of CHIK V IgM antibodies in serum of all subjects was carried out by ELISA kits procured from NIV, Pune. Age, sex wise distribution and the period of peak incidence of the positive cases was studied. **Result :** In the study, the seroprevalence of Chikungunya among the suspected cases was 13.77%. The prevalence of Chikungunya infection according to clinical symptoms were 98.55% fever, 68.84% headache, 28.98% retro-orbital pain, 27.53% back pain, 18.11% arthalgia. Gender wise distribution showed male and female ratio to be 1.15%.The metro population were infected more than the rural population. The maximum number of seropositive was seen among Kamrup Metro followed by kamrup (R) .The peak season was in the month of October and in the 20-29 years age group. **Conclusion :** Chikungunya is an emerging viral infection which is spreading to new areas in the region.Therefore it is essential to have a proper diagnostic laboratory support, proper surveillance system and public awareness to prevent the spread of the disease.

KEYWORDS: *Chikungunya; Capture linked immunosorbant assay, seropositivity*

INTRODUCTION :

Chikungunya is an arboviral disease which is transmitted by aedes mosquitoes. The virus was first isolated in 1953 in Tanzania. The virus is a member of the genus Alphavirus and the family Togaviridae.[1] Chikungunya virus causes a febrile illness similar to that seen in dengue virus infections. The hallmark feature Chikungunya is a debilitating and prolonged arthralgic syndrome that primarily affects the peripheral small joints. The acute febrile phase of the illness normally resolves within a few days, but the pain associated with CHIKV infection of the joints typically persists for weeks or months causing serious economic and social impact on both the individual and the community.[2] Emergence of severe arboviral hemorrhagic fevers caused by mosquito borne viruses, such as Chikungunya (CHIK) virus, have been frequently reported in the Indian subcontinent in the past few years. There is therefore a need for a means of definitive diagnosis and identification of the viral agent.[3]

The simultaneous isolation of both dengue and Chikungunya from the sera of the same patients has previously been reported, indicating the presence of dual infections. In 2010, a hospital-based study revealed co-circulation of Chikungunya virus and Dengue virus in some areas of West Bengal, India with high morbidity. Further both epidemiological and virological investigations for both viruses are required, as these may create severe effects, particularly in children and young adults who may not possess the antibody.[4] Therefore our aim and objective is to determine the prevalence of Chikungunya cases and to correlate the clinical symptoms of Chikungunya with serological findings.

MATERIALS AND METHOD :

The study was undertaken to know the current status of Chikungunya in patients attending Gauhati Medical College and Hospital during a period of six months from July 2016 to December 2016. The total number of samples were 1002. Each sample was screened for IgM Chikungunya antibodies from the clinically suspected

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cases of Dengue and Chikungunya. The prevalence of Chikungunya was determined in the different districts of Assam. Special interest was given on clinical presentation, duration of illness, age, sex. The month wise distribution of Chikungunya cases from July 2016 to December 2016, which is the peak season of chikungunya infection, was determined. Written inform consent were obtained from each patient. The study was a hospital based cross sectional study. IgM Chikungunya ELISA antibody assay has been done on the serum samples of patients fulfilling the criteria of case definition. Permission was obtained to conduct the study from the Institutional Ethical Committee (IEC), Gauhati Medical College, Assam.

Inclusion criteria were the patients presenting with fever and arthralgia that are not explained by any other etiology , all the patients presenting with retro-orbital pain, rashes, severe headaches, myalgia, backache along with high or low grade fever typically lasting from several days up to a week, samples with clinically compatible illness from new geographical areas without active dengue circulation and meningoencephalitis cases admitted in Gauhati Medical College and Hospital. Exclusion criteria were patients suffering from fever due to other etiological causes, and altered sensorium, seizure, swelling of legs, menorrhagia and pain abdomen which were not associated with Chikungunya infection.

Collection of samples: Under all aseptic and antiseptic condition, 5ml of venous blood was collected from the patients. Blood was allowed to clot and serum was separated by centrifuging at 3000 rpm in a centrifuge machine for 10 minutes. The samples were stored at -20 °C.

Serum samples of 1002 suspected cases were tested for Chikungunya specific IgM antibody by IgM Capture linked immunosorbant assay using IgM Chikungunya ELISA kit procured from NIV Pune and all equivocal samples were tested with NOVALISA IgMμ-Capture ELISA, NOVA TEC kit is produced by Novatech, Germany. The procedure that was followed was according to the kit insert.

Statistical analysis : Data was collected and entered in Microsoft office Excel and analysed by using GraphPad InStat. Description statistics were done for different study variables.

Chi-square test was used for analysis of categorical vartiables. Criteria of significance was used in the study were $p<0.05$.

RESULTS AND DISCUSSION :

Among all 1002 suspected Chikungunya virus infected cases, most of the Chikungunya positive cases presented with symptoms of fever, headache, retro-orbital pain, back pain and arthralgia, of which fever, headache, retro-orbital pain, back pain and arthralgia were the most commonly presented symptoms in Chikungunya positive cases. In our study, among all the 1002 suspected Chikungunya cases 138 (13.77%) were found to be seropositive for Chikungunya by IgM ELISA.

Table 1 shows : Clinical symptoms in Chikungunya seropositive and seronegative cases

Symptoms	Positive cases n=138 (%)	Negative cases n=864 (%)	Total cases n= 1002(%)	p value
Fever	136 (98.55)	805(93.17)	941(93.91)	0.0141
Headache	95 (68.84)	450 (52.08)	545 (54.39)	0.0002
Retro-orbital pain	40 (28.98)	215 (24.88)	255 (25.44)	0.3044
Back pain	38(27.53)	255 (29.51)	293 (29.24)	0.6353
Arthralgia	25 (18.11)	230 (26.62)	255 (25.44)	0.0332
Nausea	12 (8.69)	113 (13.07)	125 (12.47)	0.1479
Vomiting	11 (7.97)	150 (17.36)	161 (16.06)	0.0053
Mucosal bleeding	10 (7.24)	50 (5.78)	60(5.9)	0.5023
Skin rash	5 (3.62)	15 (1.73)	20 (1.99)	0.1411
Diarrhea	4(2.89)	55 (6.36)	59 (5.88)	0.1081
Altered sensorium	0	33 (3.81)	33 (3.29)	0.0196
Seizure	0	10 (1.15)	10 (0.99)	0.2040
Pain abdomen	0	6 (0.69)	6 (0.59)	0.3262
Swelling of legs	0	8 (0.92)	8 (0.79)	0.2564
Menorrhagia	0	7 (0.81)	(0.69)	0.2886

Table 1 shows the 138 seropositive Chikungunya cases with symptoms where 98.55% fever, 68.84% headache, 28.98% retro-orbital pain, 27.53% back pain, 18.11% arthralgia, 8.69% nausea, 7.97% vomiting, 7.24% mucosal bleeding, 3.62% skin rash and 2.89% diarrhea were found. In the study, fever (p value= 0.0141), headache (p value= 0.0002), arthralgia (p value =0.0332),vomiting (p value= 0.0053) and altered sensorium (p value= 0.0196) were found to be statistically significant with Chikungunya infection.

Table 2: Demographic features of the IgM seropositive cases in GMCH from July 2016 to December 2016

	VARIABLE	CHIK POSITIVE (%)	CHIK NEGATIVE (%)
AGE GROUP	Adult ≥ 16 yrs	112(81)	701(81.13)
	Children 0-15 yrs	26(15.47)	163 (18.86)
	p value	0.9944	
GENDER	Male	74 (53.62)	513 (59.37)
	Female	64 (46.37)	351 (40.6)
	p value	0.2027	
PLACE OF RESIDENCE	Metro	117 (84.78)	541 (82.21)
	Rural	21 (15.21)	323(93.89)
	p value	<0.0001	
	Odd ratio	3.326	

The demographic table shows that the prevalence of Chikungunya infection was more among the age group greater or equal to 16 yrs and it was comparatively less among the children below 15 yrs of age (p value=0.9944). The male and female ratio was found to be 1.15. On comparing the occurrence of Chikungunya infection among metro and rural populations, it was found that the metro populations were infected more than rural population 84.7% vs 15.21% and the p value was <0.0001 which is extremely statistically significant.

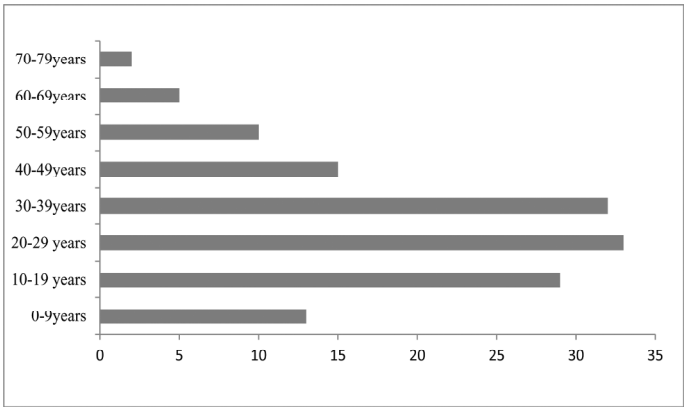

Table 3: District wise distribution of Chikungunya virus infection in Assam.

NAME OF THE DISTRICT	POSITIVE n=138	%	NEGATIVE n=864	%	TOTAL n=1002	%
Kamrup Metro	117	84.7	541	62.6	658	65.6
Kamrup rural	5	3.6	125	14.4	130	12.9
Sivsagar	0	0	10	1.15	10	.99
Golaghat	0	0	12	1.38	12	1.1
Nagaon	4	2.9	28	3.24	32	3.19
Bongaigaon	0	0	11	1.27	11	1.09
Barpeta	1	0.7	31	3.54	32	3.19
Karbi Anglong	0	0	1	0.11	1	0.09
Morigaon	2	1.4	24	2.7	26	2.59
Nalbari	1	0.7	21	2.43	22	2.19
Dhubri	0	0	10	1.15	10	0.99
Lakhimpur	1	0.7	11	1.27	12	1.17
Darrang	3	2.2	22	2.54	25	2.49
Dhemaji	0	0	1	0.11	1	0.09
Goalpara	1	0.7	3	0.34	4	0.39
Dibrugarh	0	0	1	0.11	1	0.09
Cachar	1	0.7	1	0.11	2	0.19
DimaHasao	0	0	8	0.92	8	0.79
Sonitpur	1	0.72	6	0.69	7	0.69
Baksa	1	0.72	2	0.23	3	0.29
Grand total	138	100	864	100	1002	100

Fig 1 shows that highest numbers of positive cases were seen in the age group of 20-29 (23.91%) followed by 30-39 (23.18%) ,10-19 yrs (21.01%), 40-49 years (10.86%),0-9 years (9.42%), 50-59 years (7.24%), 60-69 years (3.62%) and 70-79 years (1.44%)respectively.

The maximum number of seropositive was seen among Kamrup Metro followed by Kamrup Rural. Seropositive cases were not detected from the districts of Dima Hasao, Dibrugarh, Dhemaji, Karbi Anglong, Dhubri, Bongaigaon, Golaghat and Sivsagar districts whereas Barpeta, Nalbari, Lakhimpur, Goalpara , Cachar, Sonitpur and Baksa had detected only single seropositive cases each.

Table 4: Month wise distribution of Chikungunya cases in 2016

Month	No. of Test done	Positive, n= 138 (%)	Negative, n= 864 (%)	p value	χ^2
July	90	3 (2.17)	87(10.06)	0.0026**	9.074
August	117	9 (6.52)	108(12.5)	0.0423**	4.124
September	175	36 (26.08)	139(16.07)	0.0041**	8.253
October	367	47(34.05)	320(37.03)	0.5000	0.4550
November	109	8(5.79)	101(11.68)	0.0206**	5.364
December	144	35(25.36)	109(12.61)	<0.0001**	15.711
Grand total	1002	138	864		

** Significant

Table 4 shows that among a total of 1002 clinically suspected Chikungunya cases, maximum numbers of seropositive cases were seen in the month of October followed by September, December, August, November and July which were found to be 34.05% , 26.08% , 25.36% , 6.52% , 5.79% and 2.17% respectively.

Table 5: Seropositivity in relation to duration of illness

Duration of disease	IgM assay (138)
<5 days	90(65.21%)
5–9 days	45(30.6%)
10–20 days	3(2.17%)

The above table 5 shows that the highest numbers of cases detected were within 5 days of illness which was 65.21% whereas 30.6% and 2.17% were detected within 5-9th days and 10-20th days of illness respectively.

DISCUSSION :

In our study, the seroprevalence of Chikungunya virus infection done by Chikungunya specific IgM antibody

ELISA among the suspected cases were found to be 13.77%. Correlating to studies by Balasubramaniam Sudharsanam M et al[5] and in contrast to the studies by Kumar Narendran Pradeep*et al*[6].The low prevalence rate in our study may be due to the new entry of the virus in this region although the presence of vector was reported earlier from this region. Around 65% of the patients attending the hospital were within three days of illness where the sensitivity of IgM ELISA is comparatively low. ELISA detects IgM in 3.96 days after fever onset.[7]Another reason for low prevalence rate may be due to asymptomatic and mildness of presentation of the disease in the younger age group.

Our study demonstrated fever, headache, arthralgia and vomiting to be significantly associated with CHIKV confirmed cases ($p<0.05$) whereas differences for other symptoms were not found significant. A clinical triad of 'fever, rashes and arthralgia' is suggestive of Chikungunya fever. The clinical features of chikungunya vary from high fever (more than 40°C, rapid in rise and sometimes associated with rigor), severe headache, chills and rigors, nausea and vomiting. The fever may disappear to return in one or two days giving it the name of 'Saddle back fever'.[8] Fever and arthralgia may occur for several months or even years.[9]

Although arthralgia is key to the clinical diagnosis of acute CHIKV infection, Staikowsk y*et al.*[10]Lam *et al.*[11] says that secondary arthralgia or without arthralgia have been described in Asian studies. Chikungunya infection was more frequent in women with a lower educational level. That disadvantaged populations are overexposed to transmissible infectious diseases, including dengue and chikungunya[12].

In our study, the prevalence of Chikungunya infection among the adult above 16 yrs of age showed the seropositivity rate to be 81% and the prevalence was comparatively less among the children below 15 yrs of age which was not found to be statistically significant ($p=0.9944$) Vijayakumar*et al*.[13] found Chikungunya infection more commonly in the adult age group.

Gender distribution for Chikungunya infection was not found to be statistically significant and the male and female ratio was found to be 1:1.5. Based on a study by Ray Pratima et al, AIIMS and SMS had a relatively higher male 6" female ratio. However this could be attributed to the social bias generally observed against females in the north and west India rather than to disease susceptibility based on gender. Various other studies conducted worldwide have shown inconsistencies on gender bias to disease susceptibility with most studies reporting each gender to be equally susceptible.[14]

The maximum number of seropositive cases was seen among Kamrup Metro followed by Kamrup Rural.On comparing the occurrence of Chikungunya infection among metro and rural populations, it was found that the metro populations were infected more than rural population 84.7% vs 15.74%. Debjani Taraphdar*et al*.[15] in their study found that urban populations (74.8%) were mostly infected than rural (25.2%) with a significant p value of 0.001, whose findings are similar to our study.The reasons behind the increased infection rate of Chikungunya in Metro populations may be due to high density of Aedes mosquitoes with increasing urbanization which has lead to an abundance of mosquito breeding sites. Storage of drinking water and other urban water, containers including plant-pot bases, guttering, tarpaulins and tyres and discarded containers can all collect rain water and provide habitat for *Aedes aegypti*. Another point may be due to the highly populated areas along with existence of high density of *Aedes* mosquitoes in metros which helps in easy transmission of Chikungunya virus from one viremic host to another.

In our study maximum seropositivity was found in October followed by September, December, August, November, July which were found to be 34.05%, 26.08%, 25.36%,6.52%, 5.79 and 2.17% respectively. P Dutta et al reported the first evidence of Chikungunya virus infection in Assam, Northeast India during the period of June-September 2008 and the patients did not travel to and from any endemic region confirming indigenous transmission.[16] It was also the maiden report of Chikungunya occurrence in Northeastern part of India. Kalra NL et al in a study indicated that *Aedes aegypti* was endemic in the western plains (Thar desert), northern plains (Punjab and Haryana), Indo-Gangetic plains, eastern plains (Bihar and Bengal basin), Assam valley and the coastal areas of Orissa.

CONCLUSION:

Chikungunya is a newly emerging viral infection which had spread to new areas during this outbreak. Hence it is

essential to have a proper diagnostic laboratory support, proper surveillance system and public awareness in order to prevent future epidemic in this region.

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Original Article

Prevalence of Sepsis among Diabetes Mellitus Patients admitted in a Tertiary Care Hospital

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Abstract

Background : Diabetes is associated with an increased susceptibility to infection and sepsis. The main reason for which diabetes predisposes to infection appears to be abnormalities of the host response, defects in humoral immunity attributable for hyperglycaemia. . The aims of this study were to describe the prevalence of sepsis among diabetes patients both urban and rural population in the Assam Medical College, a tertiary care hospital in the upper Assam.

Methods : This cross-sectional hospital-based study was carried out in the in patients of our unit. The survey was conducted in the period between March 2016 and Feb 2017 for a period of 1 year among the diabetes patients. The subjects were assessed clinically and information were obtained from the routine Diabetic profile.

Results : Total number of diabetics in our study was 171 among which 27(15.78%) were having sepsis. Urinary tract infection (UTI) and Respiratory tract infection (RTI) were found to be the most common source of sepsis.

Conclusions : Infection remains an important cause of morbidity and mortality in diabetics, probably due to abnormalities of the host response, particularly in neutrophil chemotaxis, adhesion and intracellular killing. Hence strict glycemic control and early diagnosis and treatment of infection can prevent sepsis and mortality from diabetes.

KEYWORDS : *UTI, RTI, Infection*

INTRODUCTION :

Diabetes mellitus (DM) is a metabolic disorder of great impact people affected worldwide. Epidemiological data showed that in 2010 there were 285 million with the disease in the world, and it is estimated that in the year of 2030 we will have about 440 million diabetics. Its worldwide prevalence is increasing fast among developing countries. The diabetic patients number has been increasing due to population and urbanization growth, increase in the prevalence of obesity and sedentary lifestyle, and the longer survival of patients with diabetes mellitus. Diabetes is associated with an increased susceptibility to infection and sepsis. The main reason for which diabetes predisposes to infection appears to be abnormalities of the host response, particularly in neutrophil chemotaxis, adhesion and intracellular killing, defects that have been attributed to the effect of hyperglycaemia.[1] Neutrophil defects are solely responsible for the increases in the susceptibility of diabetics to infection is equivocal.There is good evidence that humoral responses in diabetics are poorer and may play a larger role than previously recognised.[2] Cells taking part in the innate and adaptive immune responses in diabetic patients have compromised function favouring micro-organism growth, a process that contributes to sepsis progression[3]. Sepsis and septic shock can result from an infection anywhere in the body, such as pneumonia, influenza, or urinary tract infections. Worldwide, one-third of people who develop sepsis die. Many who do survive are left with life-changing effects, such as post-traumatic stress disorder (PTSD), chronic pain and fatigue, and organ dysfunction (organs don't work properly) and/or amputations.[4]Diabetes patients, relative to non-diabetics, were less likely to develop respiratory failure and more likely to develop renal failure during the course of sepsis.[5]Both sepsis and T2DM are a direct result of the body's inflammatory response causing the body's normal metabolic systems to go haywire. Sepsis is the most common cause of mortality in the non-coronary ICU, as the syndrome can progress to a severe condition, septic shock.[6]

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AIMS AND OBJECTIVE :

To study the prevalence of sepsis among hospitalized diabetic patients.

MATERIALS AND METHODS:

PLACE OF STUDY : Assam Medical College and Hospital.

DIURATION OF STUDY : One year March 2016 to Feb 2017.

DESIGN OF THE STUDY : Observational cross sectional study

STUDY POPULATION :

Case : All Diabetes Mellitus patients admitted in our unit (Medicine 5) at Assam Medical College and Hospital ,who fulfilled American Diabetes Association criteria (2014), were taken up for the study.

Inclusion Criteria :

- All Diabetes mellitus admitted in our unit (Medicine 5) at Assam Medical College and Hospital, who fulfil the American Diabetes Association criteria (2014), were taken up for the study.
- Age more than 12 years.

Exclusion Criteria :

- Age less than or equal to 12 years
- Pregnancy
- Malignancy
- Secondary Hyperglycaemia
- Not giving concern for study

Routine Investigation :

- RBS
- FBS
- PPBS
- RFT
- HBA1C
- Urine R/E
- C/S of urine
- C/S of sputum
- C/S of wound swab
- X-ray chest(PA) view
- USG of W/A

CRITERIA FOR SEPSIS[7]

Systemic inflammatory response syndrome (SIRS) defined by the presence of two or more of

1. Respiratory rate > 20/min
2. Heart rate > 90/min
3. White blood count > 12 × 109/L or < 4 × 109/L
4. Temperature > 38.0°C or < 36.0°C
5. PaCO2 < 4.3 kPa (< 32 mmHg) or ventilated

Sepsis :

Systemic inflammatory response caused by documented infection

Severe sepsis/SIRS :

Sepsis/SIRS with evidence of early organ dysfunction or hypotension.

Septic/SIRS shock :

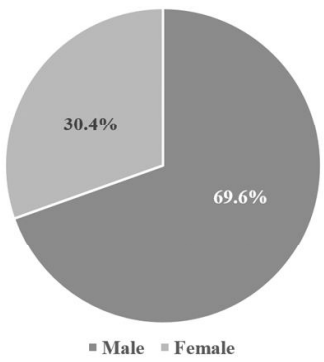
Sepsis associated with organ failure and hypotension systolic BP < 90 mmHg or > 40 mmHg fall from baseline) unresponsive to fluid resuscitation

RESULT :

The total population of the study was 171 individuals aged 12 years and above who gave consent to participate in the study. Among them 119 were males and 52 were females respectively. Mean age of males and females among the participants were 53.78 yrs and 56.93 yrs respectively. Mean duration of diabetes having sepsis in male was found to be 3.6 yrs and in female it was found to be 6 yrs . At presentation of sepsis mean RBS was found to be 339.6 mg/dl.Mean level of HbA1c among the patient with sepsis was found to be 9.66% and 7.71% in males and females respectively. Most common cause of infection are RTI and UTI followed by cellulitis, mastoiditis and cholecystitis. Nephropathy (33.33%) was more common among sepsis followed by retinopathy and neuropathy (14.81% each).

Distribution of Sex

Sex	No of Case
Male	119
Female	52
Total	171



Distribution of Sepsis in Number

Sex	Male	Female	Total
Total	119	52	171
Sepsis	16	11	27
%	13.44	21.15	15.78

Mean Duration of Diabetes in Sepsis:

Sex	Mean Duration (yrs)
Male	3.5
Female	6

Mean RBS at time of Presentation of Sepsis

Sex	Male Mg/dl	Female mg/dl	Total mg/dl
RBS	326	306	339.6

Mean HbA1c Level

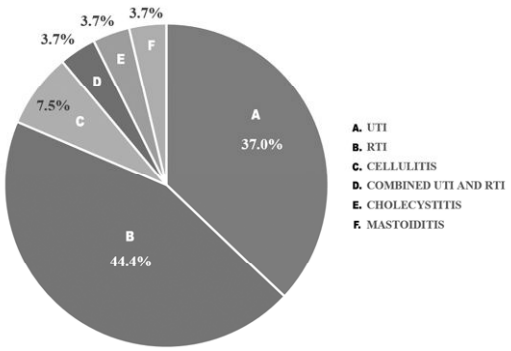
Sex	Mean HbA1c (%)
Male	9.66
Female	7.71
Total	8.83

Distribution of Chronic Complication Among Sepsis

Complication	No of Cases	Percentage
Nephropathy	9	33.33%
Neuropathy	4	14.81%
Retinopathy	4	14.81%

Distibution of Source of Infection

Source	Total Numbres	%
UTI	10	37.0
RTI	12	44.4
Cellulitis	2	7.5
Combined UTI and RTI	1	3.7
Cholecystitis	1	3.7
Mastoiditis	1	3.7



DISCUSSION :

In our study the most common source of sepsis respiratory tract infection which was found to be similar with a study which showed RTI, Genitourinary and soft tissue infection were 27%, 28% and 4% respectively but distribution of sex is different in that study.[8] Another study also showed that people with diabetes who died at 25 to 64 years of age were more likely to have pneumonia and influenza recorded on the death certificate than people without diabetes who died at comparable ages[9] .Level of Hyperglycemia had a positive correlation of prevelance of sepsis in one of the study done by Benfield et al [10] which is in accordance with our study.

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Original Article

Prevalence of UTI and Pattern of Micro-organisms involved in Diabetes Mellitus

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Abstract

Introduction: Introduction: Infections are more common in diabetics than their nondiabetic counterparts and causing frequent morbidity and mortality. UTIs being the most common infections in diabetic patients which is very difficult to treat because of its frequent recurrence and associated burden of medical costs.

Aim of the study: This study was done to determine the prevalence of urinary tract infection in diabetic patients, the various micro-organisms involved and its pattern of sensitivity and resistance to various available antimicrobials in our hospital set up. **Materials and Method:** This is a hospital based prospective, observational study done in a tertiary care hospital for a period of one year. Admitted cases of diabetes mellitus with UTI in medicine wards were taken for the study with the exclusion of pregnant women, renal impairment (CKD and AKI), cases who received antimicrobial drugs during past one month, diabetic patients on wheelchair, with severe psychiatric disorders, under urinary catheterization, and refusal to give their informed consent. Also immunocompromised states like HIV, patients on steroids, malignancy and transplant recipients were excluded. **Results:** In our study, we have included total 151 diabetic patients for study. Among them 107(70.86%) cases were male and 44 (29.14%) were female. Out of 151 patients 65 (43.04 %)had UTI. We encountered 45.45% of female (n=20) having UTI in comparison to 42.05 % of male (n=25). Also, the most common age group that had UTI was 51-60 years of age (45%) in female and 61-70 years of age in male (40%). *E. coli* (64.61 %)was the most common organism causing UTI followed by *Klebsiella pneumoniae* (13.84 %) and *Staphylococcus aureus* (4.61 %). Antimicrobial sensitivity pattern revealed that amikacin, nitrofurantoin and imipenem were most sensitive antibiotics whereas Linezolid, Amoxyclave and Norfloxacin were least sensitive anti-bacterial we encountered. **Conclusion**: *High prevalence of UTI in diabetic patient with female predominance along with significant associations between UTI and glycemic control have been observed in our study. This study will help physician to select empirical antibiotics for UTI in diabetes especially in this part of our country .*

KEYWORDS *: Urinary tract infections, micro-organism, diabetes mellitus, culture, susceptibility test, glycemic control*

INTRODUCTION:

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes mellitus is the most common endocrine disease and presents as a serious public health problem worldwide with virtually every country on the earth reporting a rise in the number of patients .

Diabetes is fast becoming the epidemic of the 21st century. The prevalence of diabetes mellitus has increased over the past decades, and it is now approaching epidemic proportions[1]. Worldwide, 371 million people have diabetes[2] and it is estimated that by 2030 this number will reach 552 millions[3]. Changes in lifestyle, aging of the population and the increasing prevalence of obesity are responsible for this dramatic situation [1].

Type 2 diabetes, which is more prevalent (more than 90% of all diabetes cases) and the main driver of the diabetes epidemic, now affects 5.9% of the world's adult population with almost 80% of the total in developing countries[4].

Diabetes is fast gaining the status of a potential epidemic in India as the World Health Organization (WHO) reports show that 32 million people had diabetes

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in the year 2000[5]. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025[4] .

Diabetics are more prone to infections than their nondiabetic counterparts. In diabetic patients, it is generally accepted that infections are frequent causes of morbidity and mortality. UTIs being the most common bacterial infections in diabetic patients[6]. Although most of the urinary tract infections (UTIs) in diabetic patients are relatively asymptomatic, UTI in diabetes may result to severe complications ranging from dysuria (pain or burning sensation during urination), organ damage and sometimes even death due to complicated UTI (pyelonephritis).

Various impairments in the immune system[7,8] in addition to poor metabolic control of diabetes, [9,10]and incomplete bladder emptying due to autonomic neuropathy[11,12] may all contribute in the pathogenesis of urinary tract infections (UTI) in diabetic patients. Factors that were found to enhance the risk for UTI in diabetics include age, metabolic control, and long term complications, primarily diabetic nephropathy and cystopathy.[13]

The increased risk of UTI among diabetic patients, coupled with the increase in the incidence of type 2 diabetes mellitus worldwide in recent years, may impose a substantial burden on medical costs. In addition, the high rates of antibiotic prescription, including broad-spectrum antibiotics, for UTI in these patients may further induce the development of antibiotic-resistant urinary pathogens. Moreover it is important to recognize and to treat UTIs in diabetic patients because of their possibly severe complications, including renal abscess, bacteremia, renal papillary necrosis. To treat UTI in diabetics is difficult because of its frequent recurrence and involving greater costs.

Considering all these facts we aimed to find out the prevalence of UTI in diabetes ,the pattern of micro-organisms involved with its sensitivity and resistance to various antibiotics available in our hospital set up.

MATERIALS AND METHODS:

This is a hospital based prospective, single centre, observational study done in a tertiary care hospital in Upper Assam. This study was done from September 2016 to August 2017 in Medicine Department, AMCH, Dibrugarh, Assam. We collected patients data in structured proforma including age, sex, duration of diabetes, with or without sign and symptoms suggestive of UTI etc. We have included all diabetes cases (newly diagnosed and old) with age e" 18 years. We excluded pregnant women, renal impairment (CKD and AKI), cases who received antimicrobial drugs during past one month, diabetic patients on wheelchair, with severe psychiatric disorders, under urinary catheterization, refusal to give their informed consent and immunocompromised states like HIV, patients on steroids, malignancy and transplant recipients.

SAMPLE COLLECTION:

A) 5ml of blood was collected into EDTA tubes from all participants and stored at 2 – 8 °C for the determination of glycosylated haemoglobin.B) Midstream Clean Catch Specimen of urine was collected into a clean sterile container and was sent to microbiology laboratory without delay.

Sample analysis :

1) Culture and susceptibility test:

Urine samples were inoculated on Blood agar, Nutrient agar, Mac Conkey agar media for culture using a calibrated loop to determine colony forming units. Semi quantitative method was used for culture and bacterial colony count was done as per standard operative procedure (SOP). All the samples were incubated at 37ºC aerobically for 24hrs. Cultures with colony counts greater than 10^5 (>100,000) CFU/ml for a single isolated uropathogen and colony counts of $>10^4$ (10,000) CFU/ml for more than one isolated uropathogen was considered as significant count. More than three types of bacterial growth was considered as contamination of sample and sample was repeated.

The organisms were identified by using various biochemical test for different phenotypic character. Antibiotic sensitivity test was performed by the disc diffusion (Kirby-Bauer) method and interpretation of sensitivity towards different antibiotics were done by using CLSI-guidelines..

2) Glycosylated haemoglobin determination:

Glycosylated haemoglobin levels were determined using the ion exchange resin method. The results of glycemic control were categorised into three groups such as :"Good control" (HbA1c= <7%), "Fair control" (HbA1c = 7 %< to <9%) and "Poor control" (HbA1c= e" 9%)

RESULTS:

In our study, we have included 151 diabetic patients for study. Among them 107(70.86%) cases were male and 44 (29.14%) were female. Out of 151 patients 65 (43.04 %) had UTI. We encountered 45.45% of female (n=20) having UTI in comparison to 42.05 % of male (n=25) [Table.1].

Table.1 Percentage of UTI in diabetes among both sex

Groups	No of UTI cases in diabetes	%
Total diabetes cases(n=151)	65	43.04 %
Male(n=107)	45	42.05 %
Female(n=44)	20	45.45%

Also, the most common age group that had UTI was 51-60 years of age (45%) in female and 61-70 years of age in male (40%). [Table.2]

Table 2. Age distribution of UTI in diabetes

Years	No of DM cases (n=151)	%	No of UTI in Male, n=45 (%)	No of UTI in Female, n=20(%)
18-30	16	10.59	3(6.66%)	1(5%)
31-40	16	10.59	5(11.11%)	1(5%)
41-50	33	21.85	4(8.88%)	5(25%)
51-60	45	29.8	7(15.55%)	9(45%)
61-70	29	19.2	18(40%)	3(15%)
≥71	12	7.94	8(17.77%)	1(5%)

On analysis of glycemic control, we have found that 44.85 % male and 13.63% female had good glycemic control, 34.57 % male and 59.09% female had fair control and 20.56 % male and 27.27% female had poor control. UTI was encountered in 11.11% male and 10% female patients with good glycemic control, male 40% and female 30% had fair glycemic control and 48.88% male and 60% female had poor glycemic control. [Table.3]

Table 3. Clinical and biochemical characteristics of UTIs in diabetes

Clinical /biochemical characteristics	Male (n= 107)	Female (n= 44)	% of UTI in Male (n=45)	% of UTI in female (n=20)
Duration of diabetes (years) :				
< 1	27(25.23 %)	8(18.18%)	13.33% (n=6)	20% (n=4)
1-5	38(35.51 %)	19(43.18%)	35.55% (n=16)	35% (n=7)
> 5	42(39.25 %)	17(38.63%	51.11% (n=23)	45%(n=9)
HbA1c(%):				
< 7	48(44.85 %)	6(13.63%)	11.11% (n=5)	10% (n=2)
7-<9	37(34.57 %)	26(59.09%)	40% (n=18)	30% (n=6)
≥9	22(20.56 %)	12(27.27%)	48.88% (n=22)	60% (n=12)

We isolated and identified 7 different types of micro-organisms amongst diabetic patient with UTI. *E. coli* (64.61 %) was the most common organism causing UTI followed by *Klebsiella pneumoniae* (13.84 %) and *Staphylococcus aureus* (4.61 %). [Table.4]

Table 4. Microbial pattern in diabetes cases with UTI

Organisms	No of cases (n= 65)	Percentage (%)
E. coli	42	64.61 %
Citrobacter freundii	2	3.07%
Enterococcus fecalis	2	3.07%
Klebsiella pneumoniae	9	13.84 %
Acinetobacter species	3	4.61 %
Pseudomonas	2	3.07%
Staphylococcus aureus	3	4.61 %

Antimicrobial sensitivity pattern revealed that Amikacin, nitrofurantoin and imipenem were most sensitive antibiotics whereas Linezolid, Amoxyclave and Norfloxacin were least sensitive anti-bacterial we encountered. [Table.5]

Table 5. Pattern of highly sensitive antimicrobials found in diabetes cases with UTI

Name of highly sensitive antibiotics	No of cases (n=65)	Percentage (%)
Amikacin	61	93.84%
Ciprofloxacin	19	29.23%
Ofloxacin	55	84.61 %
Levofloxacin	19	29.23%
Nitrofurantoin	57	87.69 %
Pip+Tazo	8	12.30%
Meropenem	18	27.69%
Amoxyclav	8	12.30%
Imipenem	59	90.76 %
Cefuroxime	18	27.69%
Ceftriaxone	18	27.69%
Gentamicin	18	27.69%
Co-trimoxazole	12	18.46%
Norfloxacin	8	12.30%
Linezolid	4	6.15%

Ciprofloxacin, norfloxacin and co-trimoxazole were most resistant antibiotics encountered in *E. coli* infection whereas Amikacin, Nitrofurantoin and Gentamycin were found to be most sensitive [Table: 6]. Also, *Klebsiella*

Table 6. Resistance patterns of micro- organisms to various antibiotics

Organisms	Amikacin	Nitrofurantoi	Ciprofloxacin	Ofloxacin	Levofloxacin	Gentamicin	Imipenem	Co-trimoxazol	cefuroxime	Pip+Tazo	Norfloxacin
E. coli (n=42)	0	0	4	2	2	0	1	4	1	1	4
Klebsiella (n=9)	0	1	3	1	0	0	0	3	1	1	1
Acinetobacter (n=3)	0	0	0	1	0	0	0	1	0	0	1
Citrobacter freundi (n=2)	1	0	1	1	0	0	0	1	1	0	1
Enterococci (n=2)	0	0	1	1	0	0	0	2	0	1	1
Staphylococcus aureus (n=3)	1	1	0	0	1	1	0	1	1	0	2
Pseudomonas (n=2)	0	0	1	1	0	0	0	2	1	0	2

Fig.1. Showing percentage of UTI in diabetes among both sex

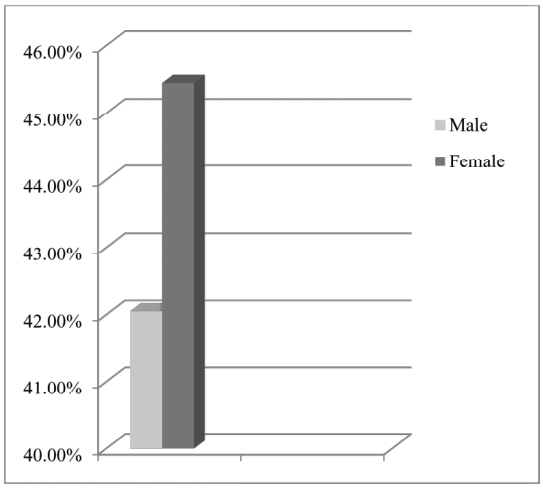


Fig.2. Most common micro-organisms found in UTI with diabetes

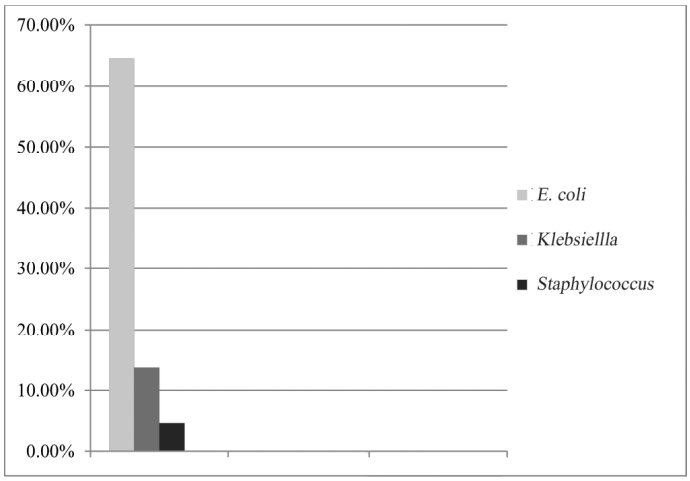
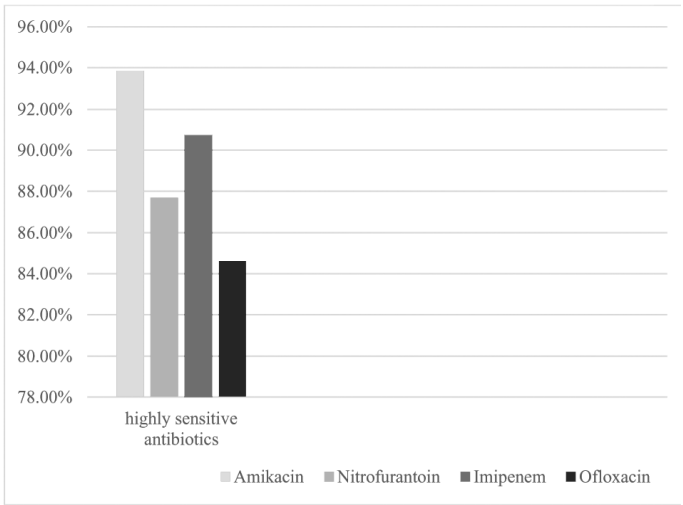


Fig.3. Highly sensitive antibiotics found in diabetes patients with UTI



was more resistant to ciprofloxacin and co trimoxazole but Amikacin, Levofloxacin and Gentamycin were most sensitive [Table:6]. Whereas, *Staphylococcus aureus* was more resistant to Nitrofurantoin, Levofloxacin and Norfloxacin with Piperacillin-Tazobactum, Imipenem were most sensitive antibiotics we have encountered [Table:6]. Piperacillin-Tazobactum,Imipenem,Amikacin and Nitrofurantoin were most sensitive for *Pseudomonas* whereas Ciprofloxaxcin,ofloxacin, co-trimoxazole were resistant to it [Table:6].

DISCUSSION :

In this study, we have included total 151 diabetic patients for the study. We observed that female diabetic patients are more prone to UTI (45.45% of female) in comparison to male (42.05 %).

S. M Ahmed et al.[14] showed the the rate of UTI was higher in females (66.86%) than males (33.14%), which was in concordance with the findings of similar studies done by Khadri et al.[15], Oladeinde B.H et al.[16], Manjunath et al.,[17] and Barate D L et al.[18]. May Sewify et al.[19] found 35% cases were positive for uropathogens and the majority of UTIs occurred in women (88.5%). BV Ramana et al. [20]showed that the prevalence of UTI among female patient was 46% and male was 43% which is consistent with our study.Our study is also consistent with the study done by Bonadio M et al[21]. and Jha N et al.[22] DS Pragash et al[23] showed the overall prevalence of urinary tract infection was 58% and the prevalence rate was higher in females (71%) than males (43%).

Females are more prone to develop UTIs, probably due to their characteristic anatomical and physiological changes - short urethra, its proximity to the anus, urethral trauma during intercourse, dilatation of the urethra and the stasis of urine during pregnancy.

Also, we found the most common age group that had UTI was 51-60 years of age in female (45%) and 61-70 years of age in male (40%). Ishan Hirji et al[24] showed that the the incidence of UTI occurred after the age of 60 years. Syed Mustaq Ahmed [14] et al also found that the highest isolation rate was in the 61-80 years age group. Our study also revealed same result showing the increased vulnerability of the geriatric population to UTIs, probably due to the various age related physiological changes .

May Sewify et al [19]showed that the number of subjects with UTI was clearly higher in the uncontrolled glycemic group (78.2%) in comparison to the controlled glycemic group (21.8%). Aswani Srinivas M[25] et al. have found that majority of the diabetics with UTI (87.14%)

had HbA1c > 6.5 %. Tseng CC et al. [26] also observed that a HbA1c > 8.1 per cent was associated with an increased risk for UTI. Aswani Srinivas M [25] et al also noted that the presence of HbA1c <6.5 per cent significantly decreased the risk of UTI irrespective of whether there was underlying predisposing factor or not. Our study also revealed that the incidence of UTI is more in diabetic patients with poor glycemic control in comparison to good glycemic control [Table.3]. Thus the occurrence of UTI in diabetics seems to be related to the glycaemic control and achieving an HbA1c < 7 % particularly seems to protect those diabetics from UTI .

We isolated and identified 7 different types of micro-organisms amongst diabetic patient with UTI. *E. coli* (64.61 %) was the most common organism causing UTI followed by *Klebsiella pneumonie* (13.84 %) and *Staphylococcus aureus* (4.61 %). Syed Mustaq Ahmed et al[14] studied the UTI prevalence in the north Kerala which revealed that *E. coli* (81.80%) was the predominant organism followed by *Klebsiella pneumoniae* (14.87%), which were similar with the studies done by Supriya et al[27], Pallavi Khanna et al. [28] ,S Baby Padmini et al.[29], Manjunath et al.[17] and Oladeinde B.H et al.[16]. Our study is consistent with these studies [Table 4]. MUHAMMAD NADEEM at el[30] also found that the most common isolated organism was *E. Coli* followed by *Klebseilla*. Varma NC et al[31] in their study have found that *E. coli* was the commonest isolated organism followed by *Klebsiella, S. aureus*, *Proteus* species and *Pseudomonas aeruginosa*. Bajaj JK et al [32] revealed in his study that *Klebsiella* was the commonest organism followed by *E. coli*, *P.aeruginosa* and *S.aureus*. May Sewify et al[19] also observed that *E. coli* was the predominant pathogen isolated from urine samples followed by *Klebsiella*. D S Pragash et al[23] from their study it was clearly found that the pathogens like *Escherchia coli* (54%), *Klebsiella* (21%), *Pseudomonas* (12%), *Proteus* (4%), *Acinetobacter* (1%), *Staphylococcus aureus* (14%), *Enterococci* (1%) and CoNS (8%) were common among the diabetic patients with urinary tract infection.

Antimicrobial sensitivity pattern revealed that Amikacin, nitrofurantoin and imipenem were most sensitive antibiotics whereas Linezolid, Vancomycin and Nalidixic acid were least sensitive anti-bacterial we encountered. Ciprofloxacin, norfloxacin and co-trimoxazole were most resistant antibiotics encountered in *E. coli* infection whereas Amikacin, Nitrofurantoin and Gentamycin were found to be most sensitive antibiotics [Table:6]. Also, *Klebsiella* are more resistant to ciprofloxacin and co-trimoxazole but Amikacin, Levofloxacin and Gentamycin were most sensitive [Table:6]. Whereas, *Staphylococcus aureus* is more resistant to Nitrofurantoin, levofloxacin and norfloxacin with piperacillin-Tazobactum, Imipenem were most sensitive antibiotics we have encountered [Table:6]. Piperacillin -Tazobactum, Imipenem, Amikacin and Nitrofurantoin were most sensitive for Pseudomonas whereas Norfloxacin and co-trimoxazole were more resistant to it [Table:6].

S M Ahmed et al [14] had observed that a majority of the isolates showed a higher sensitivity pattern towards imipenem, piperacillin/tazobactam, and amikacin. Nitrofurantoin, with a resistance of 1.9%, was found to be an effective cure against the *E. coli*. *Klebsiella pneumonia* showed an increased resistance to amoxyclav and cefuroxime and a decreased resistance to ciprofloxacin and norfloxacin as compared to *E. coli*. However, it showed an increased resistance towards nitrofurantoin. *Pseudomonas aeruginosa* showed an increased resistance towards the 3rd generation cephalosporins and a decreased resistance towards the fluroquinolones. Imipenem, piperacillin/ tazobactam and cefoperazone/ sulbactam with 100% sensitivity and amikacin with 87.5% sensitivity, were found to be the most effective drugs for the therapy of UTIs.

D S Pragash[23] also has showed that Amikacin has strong activity against most of the organisms including *Pseudomonas, Acinetobacter* and all the other organisms responsible for UTI in hospital setup. Also they noticed that Amikacin may be prescribed as the empirical treatment for UTI in hospitalised diabetic patients with UTI. It is also shown by D S Pragash that Nitrofurantoin has tremendous effect against other Uropathogens *(E. coli, Klebsiella spp., Proteus spp., Staphylococcus aureus).*

S M Ahmed et al.[14] found that the Enterobacteriaceae family, which showed heavy resistance towards amoxyclav (79.6%), a majority of the fluroquinolones [ciprofloxacin (62.5%) and norfloxacin (71.6%)] and the cephalosporins [cefuroxime (75.9%) and ceftriaxone (71.6%)], was in accordance with the findings of the studies which were

done by Manjunath G N et al[17], Khadri et al.[15] and Barate D L et al.[18].

D S Pragash[23] et al showed that Co-trimoxazole is no more useful against uropathogens as only 17% of the isolates were susceptible for that drug. Previously this antibiotic was used as the drug of choice for empirical treatment of UTI [34]. May Sewify[19] et al in their study they have noted that Gram-negative strains including *E. coli* and *K. pneumoniae* were highly resistant (>45%) to trimethoprim-sulfamethoxazole. Aswani SM et al[12] observed that the isolated *E. coli* strains were resistant at similar rates to ampicillin, cotrimoxazole, norfloxacin and cephalosporins which are in comparison with Bonadio M et al. [21]

CONCLUSION:

In this study we have observed a high prevalence of UTI in diabetic patient with female predominance. Significant associations between UTI and glycemic control have been found. Also the antimicrobials sensitivity and resistance pattern we have encountered in our study will definitely help the physicians in clinical practice to select empirical antibiotics for diabetic patients with UTI which has paramount importance in this part of our country considering the cost and availability of the antibiotics .

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Original Article

Etiological Profile of Patients Presenting with Altered Mental Status : A Hospital Based Study from North-eastern India

C P Thakur*, D Das, K Bhattacharjee****

Abstract

Background : Altered mental status is a common chief complaint among older emergency department patients. Acute changes in mental status are more concerning and are commonly precipitated by an underlying medical illness that can be potentially life-threatening and are associated with a multitude of adverse outcomes. The evaluation should focus on searching for the underlying etiology. The study was conducted to identify the etiological profile and to illuminate the various associated clinical features and their outcomes. **Material and Methods:** A single centered prospective observational study was carried out on patients presenting with altered mental status in the emergency at SMCH, Silchar, Assam from September 2016 to December 2017. **Results and Observations:** In 300 patients with altered mental status recruited, 176 (58.6%) were male and 124 (41.4%) were female. The majority of patients 188(62.7%) were above 60 years of age. Their average age was 58.43±17.11 years. The most common diagnoses accounting for altered mental status were neurological 37.66% (n=113), metabolic 16.33% (n=49), infection 18.67% (n=56), toxicological 10.67% (n=32). Total mortality rate was 16.33% (*n*=49). **Conclusion:** Altered mental status is an important warning signal for ED patients because of its potentially fatal and reversible effects. The most frequently encountered diagnostic categories causing it were neurological, intoxication and metabolic diseases. Prompt evaluation and treatment are essential to decreasing morbidity and mortality associated with altered mental status.

KEY WORDS: *Altered mental status, Emergency department, Demographic characteristics, Clinical feature, Etiology, Mortality.*

INTRODUCTION :

Altered mental status (AMS) denotes an undifferentiated group of disorders of mentation, characterized by impaired cognition, attention, awareness or level of consciousness. Despite the frequency of this complaint, the term "altered mental status" is vague and has several synonyms such as confusion, not acting right, altered behavior, lethargy, disorientation, inappropriate behavior, inattention etc. AMS is a very common emergency case, but the exact etiology of many AMS patients is unknown.[1,2] Patients often manifest vague symptoms, which can be life threatening, thus, AMS diagnosis and treatment are highly challenging for emergency physicians.

AMS is common in older patients admitted to emergency departments (EDs). The incidence of older patients with AMS in EDs is 41%-60%. Whereas the diagnosis of AMS in younger patients is more straightforward and can be attributed to obvious toxicological or organ-specific disorders, diagnosis is more difficult in older patients.[3,4] Moreover, mortality rates are higher in the elderly.

Therefore, such patients require urgent stabilization, accurate diagnosis, and appropriate treatment. An in-depth understanding of the pathogenesis of AMS and complete patient assessment will help increase the diagnosis rate and ensure treatment accuracy. Although the consequences of AMS have been reported in the literature, current epidemiological studies rarely focus on etiology of AMS with very few studies worldwide, especially in this part of the country.

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AIMS AND OBJECTIVES:

1) To identify the etiological profile
2) To illuminate the various clinical features of this diverse group of patients and their outcomes.

MATERIALS AND METHODS:

In this prospective observational study, all patients encountered by physicians who met the inclusion criteria (described below) were enrolled. Patients aged 18 and above with altered mental state (AMS) presenting to the emergency department at Silchar Medical College from September 2016 to December 2017 was included in the study.

AMS was defined as a state of drowsiness, unresponsiveness, sudden behavioral change, disorientation or confusion, agitation or hallucination. AMS was considered to be present if a patient had exhibited any of the following symptoms for less than 1 week at the time of presentation to the ED: Glasgow Coma Scale (GCS) scores below 15, acute change in conscious level, time and/or location disorientation, difficulty remaining awake, inability to respond to verbal or physical stimulation, confusion, irritability or aggressiveness, and any other inappropriate behavior.

Inclusion criteria:-

1) Age e"18 years
2) Presence of altered mental status (AMS).

Exclusion Criteria:-

1) Patients with AMS for > 7 days.
2) Patients with a known chronic abnormal level of consciousness.
3) Patients who had sustained major trauma from motor vehicle crashes or fall from heights.
4) Patients with multisystem trauma.
5) Patients having psychiatric illness (suicidal motive and tendencies, history of mood disorders, anxiety, and psychotic symptoms).
6) Patients referred from another healthcare facility for which their referring physicians had already worked out the cause for AMS were excluded from the study.

As because content features could not be evaluated properly in AMS patients, consciousness assessment was performed according to the GCS score which was evaluated when the patients first presented to the emergency department. Patients were managed by attending emergency physicians and ward specialists. The management and the utilization of specific investigations like computer tomography (CT) scans were based on the discretion of the attending doctors. All the patients diagnosed with AMS were admitted in the hospital. All AMS patients were treated in the emergency department and subjected to observation for at least 24 hours from the time of admission to discharge. The patients who developed AMS symptoms during throughout in the emergency department were also included in the study. Demographic, clinical, radiological and laboratory data of each patient throughout the stay in the hospital from entry into the Emergency department till discharge or demise were collected. Laboratory tests including complete blood count and peripheral blood film, serum urea and creatinine, serum electrolytes, total bilirubin, ALT and AST, serum amylase and lipase, random blood sugar, PT-INR were done. Electrocardiograph (12-lead ECG), cardiac biomarkers, arterial blood gas (ABG) analysis, urinalysis, cerebral spinal fluid analysis, electroencephalography (EEG) were also performed in selected cases. In addition, rapid kit test for malaria antigen, blood smear (thick and thin) for malarial parasites, were also done in selected patients. Radiological tests like chest x ray, CT scan, MRI brain was done as needed. Emergency notes, inpatient medical records, radiology films and reports were collected in a predesigned proforma. The ethics committee of the institution approved the study, and written informed consent was obtained from patient's surrogates.

Statistical analysis was performed using SPSS Version 20. Continuous variables were presented as mean (±standard deviation). Univariate statistical analysis was performed by Chi-square test for comparing proportions. In all analyses, a p-value of <0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS:

Demographic characteristics of patients:

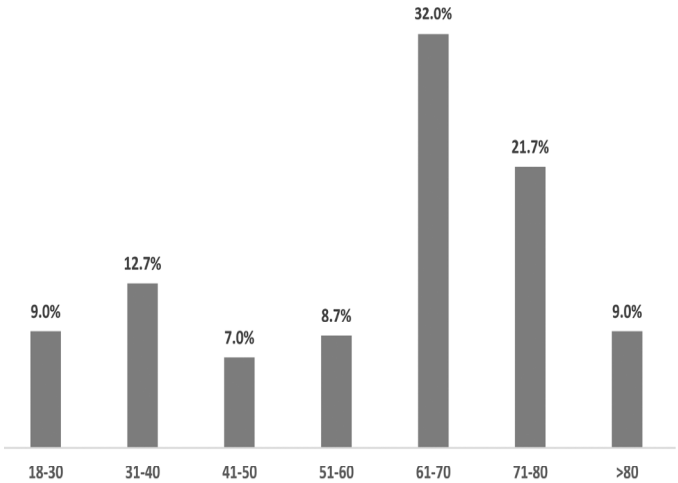
In the present study, 300 patients with AMS were

recruited, out of which 176 (58.6%) were male and 124 (41.4%) were female. The majority of patients 188(62.7%) were above 60 years of age ranging from 18 to 90 years (average age 58.43±17.11 years). 244 (81.33%) AMS patients presented most commonly within the first 24 hour of onset of Symptom. AMS patients presented most commonly 244 (81.33%) within the first 24 hour of onset of symptom. Loss of consciousness was the most common presenting complaint, 222 (74%).

Table 1: Demographics of the study population.

VARIABLES	TOTAL
GENDER	
MALE	176(58.6%)
FEMALE	124(41.4%)
AGE GROUP (IN YEARS)	
18-60	112(37.3%)
>60	188(62.7%)
TYPE OF AMS	
Loss of consciousness	222(74%)
Drowsiness	31(10.33%)
Sudden behavioral changes	18(6%)
Disoriented	11(3.67%)
Hallucination	5(1.67%)
Others	13(4.33%)
DURATION OF AMS (IN HOURS)	
<24	244(81.33%)
≥24	56(18.67%)
GCS SCORE AT PRESENTATION	
13-14	137(45.67%)
9-12	96(32%)
3-8	67(22.33%)

Figure 1: Distribution of patients in different age group:



Etiological analysis of patients:

The most common diagnoses accounting for AMS were neurological 37.66% (n=113), metabolic 16.33% (n=49), infection 18.67% (n=56), toxicological 10.67% (n=32). Cerebrovascular accident (73.45%) was the most common neurological diagnosis followed by seizure disorder (11.50%). In the patients of infectious etiology, the sources of infection included urinary tract infection (25%), sepsis from unknown source (26.78%) and pneumonia (21.42%). Other diagnoses which were seen in a few patients were adrenal insufficiency etc. In 15 patients a confirmed diagnosis could not be established.

Table 2: Etiologic factors of ams in different age groups :

ETIOLOGIC FACTORS	TOTAL NUMBER OF PATIENTS
NEUROLOGICAL(Total):	113
• Ischemic stroke	54(47.78%)
• Intraparenchymal hemorrhage	29(25.67%)
• Status epilepticus/ prolonged postictal	13(11.50%)
• Intracranial mass/shift	8(7.07%)
• Nonconvulsive status	3(2.65%)
• Other(TIA/hydrocephalus)	6(5.3%)
INFECTION:	56
• Pneumonia	12(21.42%)
• Urinary tract infection	14(25%)
• Sepsis from unknown source	15(26.78%)
• Meningitis/encephalitis	9(16.07%)
• Others (gastroenteritis,Cellulitis etc))	6(10.71%)
METABOLIC:	49
• Encephalopathy(uremic/metabolic/hepatic)	19(38.77%)
• Dyselectrolytemia(Hypo-/hyperglycemia, Hypo-/hypernatremia, Hypo-/hyperkalemia, Hypercalcemia)	25(51.02%)
• Other (disequilibrium syndrome etc.)	5(10.2%)
TOXICOLOGICAL:	32
• Drugs overdose	21(65.62%)
• Intoxication/Poisoning (organophosphates)	5(15.62%)
• Alcohol intake	6(18.75%)
ORGAN SPECIFIC INVOLVEMENT:	23
• Lung	7(30.43%)
• Cardiovascular	9(39.13%)
• Kidney	5(21.73%)
• Liver/GIT	2(8.69%)
OTHERS & UNDIAGNOSED	27
TOTAL	300

Clinical outcomes:

The outcomes of these AMS patients were followed up till discharge. The mean hospital length of stay was 11.6 days (median 7 days). Patients with abnormal CT results stayed longer than those whose results were normal (median of 9 days compared with median of 6 days).

Overall, 16.33% (n=49) patients died during hospitalization. The mortality rate of the elderly group (n=35; 18.61%) was significantly higher than that of the non-elderly group (n=14; 12.5%; p=0.003).

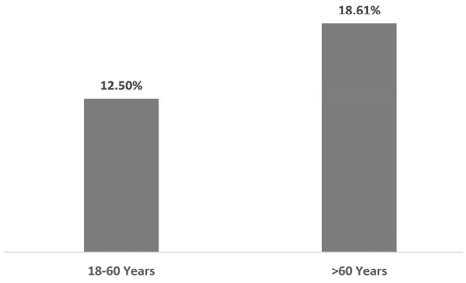


Figure 2: Distribution of Patients According to Mortality:

The causes of mortality between the younger (18–60 years) and older (>60years) subgroups were different. The majority of younger patients died from hemorrhagic stroke, while in older patients, mortality is distributed amongst ischemic stroke (28.44%), hemorrhagic stroke (21.7%) and infections like pneumonia.

DISCUSSION :

Altered mental status (AMS) remains a diagnostic challenge in the Emergency Department. It has a multitude of possible etiologies. Acute onset of AMS within 24 hrs is the most common reason for seeking consultation at the emergency. AMS may be found in 4%–10% of ED patients, this proportion may be higher in special subgroups (such as in the elderly patients).[5] Our data showed that age distribution of AMS patients had two peak segments (the first peak was for patients between 31-40 years, and the second peak was for those aged 61-80 years) as a result of the distinct etiology of AMS among the two age groups. Subsequent analysis revealed that the causative disease of AMS in the elderly group differed from that in the non-elderly group, i.e., metabolic diseases, trauma, and poisoning were often found in young people, whereas cerebral vascular disease, and organ/system failure were frequently seen in the elderly. In acute AMS, this pattern of age distribution was similar to Kanich et al[6] and a study from Xiao et al.[4]

A study[7] showed that the medical history and physical examination are more important than laboratory testing and imaging in the diagnostic evaluation of AMS. Physical examination also helps to determine the development of the condition. The medical history, physical examination, past history, and treatment responses of patients are important in assessing the causes of AMS.

The variety of pathogenic factors that cause several clinical manifestations of AMS results in significantly different clinical treatment. Acute changes in mental status develop within hours and days and require critical care because of life threatening sequelae. Determining the correct diagnosis is crucial for providing proper treatment. Among the various etiologies, neurological causes are the most common. In the present study neurological etiology was present in 37.66% of the patients. Our findings agree with what had been reported by Kanich et al.[6] & Lim Beng Leong et al.[8] A recent study[9] considered neurological events to be the most important factors that cause AMS, and account for about 28% of AMS patients. However in some studies investigating non-traumatic coma causes infection (cerebral malaria) was found to be the most frequent cause in Ethiopia and Zambia (Melka et al.[10], 1997; Sinclair et al.[11], 1989). We also found that in the elderly group, the top three causes of AMS were cerebrovascular disease, systemic and organic failure, and infection. In the non-elderly group, the top three causes were infections, drugs and toxic factors, and metabolic.

In the present study we have demonstrated that AMS is a symptom complex that carries a significant mortality rate (16.33%) and this disagrees with what is reported by a study from Turkey by Zeynep Kekec et al[3] where the mortality was seen in only 11% and Lim Beng Leong et al[8] (8.1%).

CONCLUSION :

The common and important causes of AMS require timely diagnosis, intervention and are largely amenable to treatment. AMS remains a symptom that carries a significant degree of morbidity and mortality, especially in elderly patients with neurological etiologies. The reversibility of diseases and the potentially fatal factors associated with AMS require timely assessment and rapid intervention for the potential causes and conditions of the disease.

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CONSENT FORM FOR CASE REPORTS

For a patient's consent to publication of information about them in a journal or thesis

Name of person described in article or shown in photograph :_____

Subject matter of photograph or article : _____

Title of article : _____

Medical practitioner or corresponding author : _____

I_____ [insert full name] give my consent for this information about MYSELF OR MY CHILD OR WARD/MY RELATIVE [insert full name]:_____, relating to the subject matter above ("the Information") to appear in a journal article, or to be used for the purpose of a thesis or presentation.

I understand the following :

1. The Information will be published without my name/child's name/relatives name attached and every attempt will be made to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - perhaps, for example, somebody who looked after me/my child/relative, if I was in hospital, or a relative - may identify me.
2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
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4. I can withdraw my consent at any time before publication, but once the Information has been committed to publication it will not be possible to withdraw the consent.

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Signature of requesting medical practitioner/health care worker:

_____Date:_____

Review Article

Competency Based Medical Education... in Indian Perspective, an Overview

A Dasgupta*

INTRODUCTION & MCI'S VISION :

Competency of a medical graduate means an observable ability of a health care professional that develops through stages of expertise from novice clinician to master clinician.

Competency based medical education is an approach of designing medical education and training in a way that it focuses on outcomes in the form of abilities to perform the whole range of actions desired from a medical graduate.

The attributes an Indian Medical Graduate needs to acquire while delivering service to the society are –

1) Scholar
2) Professional
3) Communicator
4) Collaborator
5) Manager
6) Health advocate

All these qualities a medical graduate learns during the journey of medical education training and also in the later part of life during practice. The present Indian medical education curriculum does not offer learning on all these aspects and neither there are enough situations to adopt all these qualities during the five year course. But it is expected that an Indian Medical Graduate (IMG) exercise all these qualities the moment he goes to society to offer service. So the present curriculum in India fall short of delivering what is expected to be responsive in certain domains; simultaneously responsible to the Health care needs of the Indian society.

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This has triggered debates for reorientation of medical education in India with reforms which are need based & strengthen the links between medical education & heath care needs.

A proposed amendment to the Graduate Medical Regulations 1997 defines the goal of creating an IMG & it is one of the visions of MCI.

It states-

The goal of Indian undergraduate medical education programme is to create.

'*Indian medical graduate possessing requisite knowledge, skills, attitudes, values and responsiveness, so that he or she may function appropriately and effectively as a physician of first contact of the community while being globally relevant'.*

So the requirement 'competency' comes in.

And competency based learning in any profession signifies the implementation and designing of educational curriculum in such a way that it meets the standards that is expected and an observable ability to perform at the desired level in real life situations.

Characters Unique to Medical Education :

A) Type of medical education existing
   Primary or undergraduate education
   Secondary or post graduate education
   Post-secondary or super specialization education.
B) Accountability of the profession
   To the society
   To the government
   To the employer
   To the profession.
C) The Needs

Explicit about the abilities of the professionals within their own discipline

Ability to function effectively at workplaces that demands intra and inter departmental collaboration Ability to perform integrated practices.

THE BACKGOROUND :

The accountability and needs of medical profession as described was the driving force for competency based medical education (CBME) and a cry from the society for the same. It was the initiative of American Board of Medical Specialists and the Accreditation Council for Graduate Medical Education (ACGME) to establish CBME in all medical schools.

The current medical education system teaches by exposure & experience to specific contents in a specific time.

But to be competent means adoption of complex set of behaviours built on components of knowledge, skills, attitudes & personal ability. In fact there are six defined ACGME behaviours where a medical graduate must show competencies.

In India too, the Medical Council of India in its Vision 2015 document has also recommended a curricular shift from tradition based to CBME and the curriculum is based on teaching of ethics, professionalism, communication skills, integrated teaching and early clinical exposure in addition to traditional existing teaching learning methods. The six competencies as defined by ACGME are more accountable to public particularly in the era of litigations & public funding in health sectors. Policy leaders focused on patient's safety. So in February 1999 ACGME endorsed six general competencies as a foundation for all medical graduates and it holds true anywhere in the globe including India and they are –

1. Patient care
2. Medical knowledge
3. Practice based learning & improvement
4. Interpersonal & communication
5. Professionalism
6. System based practice

TECHNIQUES IN MEDICAL EDUCATION :

In the widest sense the medical curriculum includes content, learning strategies & methods, assessment of students and organisation.

The definition of core curriculum in medical education are the must know activities expected from a medical graduate & it includes basic knowledge, skills and attitudes. The core is now developed with multi-disciplinary approaches and personal interest of individual students so that it encourages problem solving attitudes, critical thinking & most importantly provide environment conducive to continuing professional development.

Integration of multiple disciplines and early clinical exposure from 2nd semester will enhance adoption of clinical and required technical skills. Reaching such goals requires collaboration & co-operation between basic science scientists and clinicians and a major decision making task from college MEU (Medical Education Unit). Conceptual links then can be made between all aspects of learning like didactic lectures, clinical demonstration and tutorials where students acquire an understanding of their relevance to the whole course. This will eliminate Pre, Para-clinical and Clinical divide in medical curriculum and will give birth to a holistic educational TL (teaching learning) method.

There are a number of learning principles that a medical college follows. Traditional approach is system based subject oriented uni-disciplinary, information gathering approach. The SPICES model recommends curriculum change a set of six issues-

i) Student centred
ii) Problem based
iii) Integrated
iv) Community based
v) Electives
vi) Systemic

The most widely used & adopted student centred learning strategy in undergraduate teaching is problem based learning (PBL). PBL are approaches which link basic sciences and clinical experiences and integrate multiple disciplines. Through analysis of problems students identify gaps in their knowledge and set up new learning objectives. They are encouraged to go for self study & apply new found knowledge in problem solving. They are needed to evaluate the information they gathered & remember the experience achieved from problem solving. Earlier it was factual recall.PBL require students to shoulder primary responsibility for their own TL methods.

Hence what is the role for a teacher now?

So the traditional role of teachers must change. Their autonomy as expert in their own disciplines is subsumed to interdisciplinary teams as Integrated Teaching involving

multi-discipline is favoured over traditional single departmental teaching. Loss of authority might be a great disliking for many teachers and may result in loss of confidence for some teachers but gradually they will learn the process of group dynamics; working as a facilitator & guide apart from his usual role of uni-directed information giver. It is essential that all medical teachers are trained and socialized into new roles. Hence MCI is drafting various teacher's training programme with a view to impart new visionary guidelines for medical teachers across India and it is compulsory for all medical teachers to attend and gain competence in this new arena of medical TL methods. So faculty development is critical for successful implementation of curricular reforms and it is accepted globally. The MCI's initiative in 2009 recognized MEU of few medical colleges as regional centres for faculty development.

For acquisition of technical skills ACGME endorsed 'Milestone-Template' planning process is advocated and the student is supervised individually till the required competency is gained and the concerned student himself becomes a supervisor for the said technical skill. It is a time consuming endeavour as each individual student needs to be mapped for competency gain.

So are there any changes needed for assessment & evaluation strategies of students?

Assessments have profound effect in student's learning. Assessment in competence is an insight to performance in real life scenarios & ability for adaptation for a change & generates new knowledge. Various assessment methods are available to assess clinical competence according to model proposed by Miller. Whatever the purpose single assessment methods will not assess all domains of competency; so a variety of assessment methods are utilized to judge competence of medical graduates; Miller's pyramid model of 1999 deals with assessment of clinical competence in all those aspects as described in ACGME endorsed six competencies and it starts with assessment of cognition and ends by going up in the hierarchical model with assessment of behaviour in practice. Assessment of cognition deals with assessment of knowledge & its application and at last it is application of desired performance under controlled environment and also in practice. Along with the usual summative assessment methods like long case, short case presentation, spot case diagnosis now recommendation for mini-CEX, OSCE station with standardized and real patients evaluates knowledge and clinical skills and also communication skills and professionalism.

To conclude let me quote from Frank et.al 2010. This definition says all and clearly focuses the aim of CBME.

'*Competency based education is an approach to preparing physicians for practice that is fundamentally oriented to graduate outcome abilities and organized around competencies derived from an analysis of societal and patient needs .It de-emphasises time based training and promises greater accountability ,flexibility and learner centeredness.'*

CONCLUSION :

We have noticed that there is a change in the whole hospital service system in the past few years. There is change in patient expectation, demographics and awareness. This change created new standards in health care delivery system and the total health care system has become dynamic with introduction of advanced technologies. Presently the system demands that we all physicians should make a quick diagnosis ; offer best treatment with reasonable investigations at low cost and patient also should get cured quickly and all physicians should abide by ethics and be sympathetic to patients and his family needs. And in an era of litigations we all are bound to be competent.

But in India are we producing IMG as society expects and desires? Over the years a palpable gap between health professional education & prevailing learning objectives with societal health needs have raised Govt. & administrative concerns. Hence re-defining the teaching - learning objectives and re-designing our medical curricula with an aim to achieve the well defined six competencies by all individual medical graduates steered by appropriate assessment methods will be our expected goal.

Acknowledgement : *I thank the Medical Education Unit of Sri Ramachandra Medical College & Research Institute Porur Chennai for necessary help and gladly remember their contribution of introducing me to a new dimension of Medical Science, which is Medical Education.*

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Case Report

Two Cases of Langerhans Cell Histiocytosis of the Skull : Good to Review with High Suspicion

G Gogoi[*], D J Kurmi[**], Mondita Borgohain[***], S Gogoi[****], D Konwar[****], R Hazarika[****]

Abstract

Introduction : The term Langerhans cell histiocytosis is applied to a specific , although remarkably variable, clinicopathologic entity characterized and defined by the proliferation of Langerhans cell. Bone is the most frequent site of disease, although skin, lymph node, lung, and other sites may be involved. The peak age at initial diagnosis is from 1 to 3 years, but the disease may manifest at any age. **Case reports :** Two patients came to our tertiary care teaching hospital with complaints of swelling on the scalp with associated pain. These cases were studied in details and were diagnosed as Langerhans cell histiocytosis by histopathology and immunohistochemistry. **Conclusion:** LCH can present as solitary or multiple lesions in one organ system (bone being the most common) or as a disseminated disease. Osteolytic bone lesions are a common manifestation . Histologically, proliferation of Langerhans cells expressing CD1a and S100 admixed with acute and chronic inflammatory cells are consistently reported. By electron microscopy, they contain a highly characteristic and apparently diagnostic organelle: the Birbeck or Langerhans granule. Local treatment with excision, systemic chemotherapy and corticosteroid injection is highly successful in treating this disease and patients have excellent prognosis.

INTRODUCTION :

Langerhans cell histiocytosis (LCH) is a unifocal or,multifocal disorder characterized by a proliferation of distinctive cells with ovoid, reniform, grooved, or highly convoluted nuclei and pale eosinophilic cytoplasm. Bone is the most frequent site of disease, although skin, lymph node, lung, and other sites may be involved. The lesions contain varying proportions of Langerhans cells, macrophages, eosinophils, lymphocytes, giant cells, and, to a lesser extent, plasma cells and neutrophils. Currently, the term *Langerhans cell histiocytosis* is used to include a spectrum of disorders previously designated as eosinophilic granuloma, histiocytosis X, Hand- Schüller-Christian disease, and Letterer-Siwe disease.[1,2]

The disorder was first described on the basis of purely clinical observations more than a century ago, after the Langerhans cell was detected by the medical student Paul Langerhans in 1865[1]. Over the years, the terms *eosinophilic granuloma,Hand-Schüller-Christian disease,* and *Letterer-Siwe disease* were devised to denote the most common clinical manifestations within a broad spectrum of divergent disease patterns (from localized to multifocal involvement) with increasing degrees of severity. In 1953, Liechtenstein observed that the underlying component of all these manifestations was the histiocyte. This observation was followed by the recognition of the many separately defined syndromes as a single disease entity: *histiocytosis X* (*X* being the unknown etiologic factor)[1]. In 1985, the Writing Group of the Histiocyte Society established a histiocytosis classification system based on distinct pathologic criteria and on the clinical evolution of disease. Under the definitive name *Langerhans cell histiocytosis,* the disease was designated as class I of the histiocytic disorders.[3]

The annual incidence of *Langerhans cell histiocytosis* is reported to be between 2.6 and 5.4 cases per million children in the general population. The peak age at initial diagnosis is from 1 to 3 years, but the disease may manifest at any age[1,4,5] . Boys are more often affected than girls[1,6].

Here, we are presenting two cases of Langerhan cell histiocytosis (LCH) of skull which came to our tertiary care teaching hospital in northeast India and were studied

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over a period of 1 year duration. Formalin fixed, paraffin embedded blocks, stained with haematoxylin and eosin (H and E) stain were studied, which were diagnosed histologically as LCH, during this time period. Immunohistochemistry (IHC) was performed using relevant panel of antibodies by horse radish peroxidase in polymer method with pretreatment by microwave heating.

CASE HISTORY :

Case 1

A 34 yr old female presented with swelling over the left side of scalp for 2 months.It was insidious in onset and progressive in nature , associated with headache and pain radiating to left ear. On examination, she had a swelling over left parietal region which was 2x2 sq cm in size and firm in consistency. CECT of brain showed soft tissue swelling with minimal peripheral enhancement on post contrast scan over parietal region, with erosive destructions of outer and inner cortices of underlying bone. CECT showed features suggestive of infective etiology. Craniotomy was done to excise the tumour. During the procedure it was found that the tumour was attached to the bone with the underlying dura slightly thickened. Bone destruction was present with involvement of the overlying scalp. However, the underlying brain parenchyma was normal. The tumour was excised which was of size 3* 3 cm approximately, soft to firm in consistency and moderately vascular (fig 1a, 1b, 1c, 1d) . Histopathological examination and immunohistochemistry were done in a private laboratory where the diagnosis of Necrotizing Granulomatous Inflammation consistent with Tubercular Osteomyelitis was given. However, the specimen was sent for review to our tertiary care centre. In our set up, Histopathology examination on H&E stained section showed characteristic histiocytic cells known as the Langerhans cells having oval nucleus with longitudinal grooves resulting in "coffee bean" appearance which were arranged in clusters and associated with chronic inflammatory cells, predominantly eosinophils and also lymphocytes, macrophages and few giant cells. So it was suggested as LCH (fig 2) .Then it was later confirmed to be LCH monostotic type in the cancer institute where the patient received further treatment.

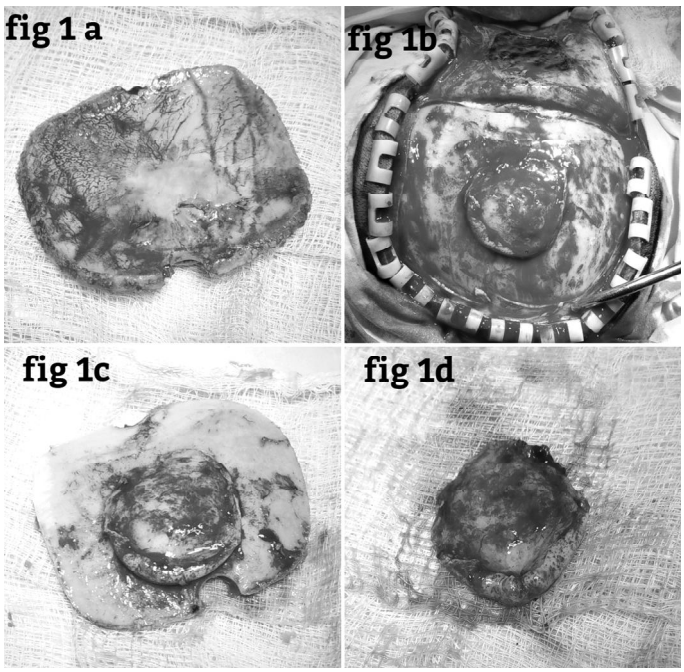

Fig 1 : Gross pictures of (a) inner aspect of bone flap. (b) outer aspect of bone flap, (c) after raising the scalp flap showing tumour in situ over skull, (d) tumour after removal from bone.

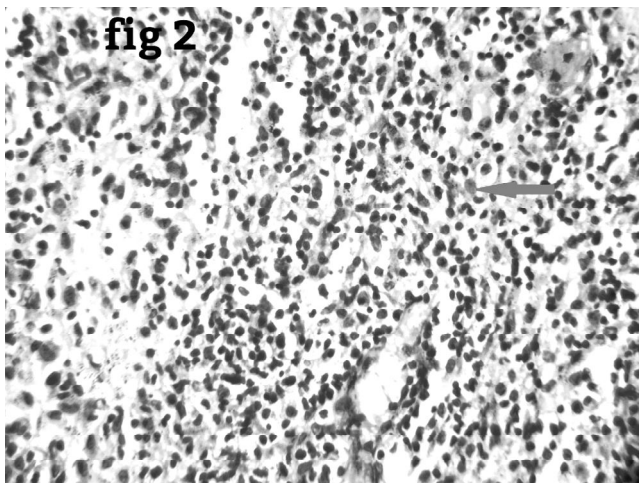

Fig 1 : H&E staining showing langerhans cells (red arrow) with grooved nuclei in a background of inflammatory cells.

Case 2:

A 16 yr old male patient presented with swelling on right side of scalp with associated pain for 3 months. On examination, a swelling over the right parietal area of size 2x3 sq. cm was observed and it was firm in consistency. CECT of brain showed a well defined bony defect in the right parietal bone. CEMRI of brain showed irregular destruction of superior right parietal bone with destruction of both inner and outer cortices associated with T2 hyperintense components in affected bony calvaria; features suggesitve of eosinophilic granuloma.The patient was admitted and had a craniotomy to excise the skull tumor. The specimen was given for histopathological examination. The H & E stained sections showed Langerhan's cells

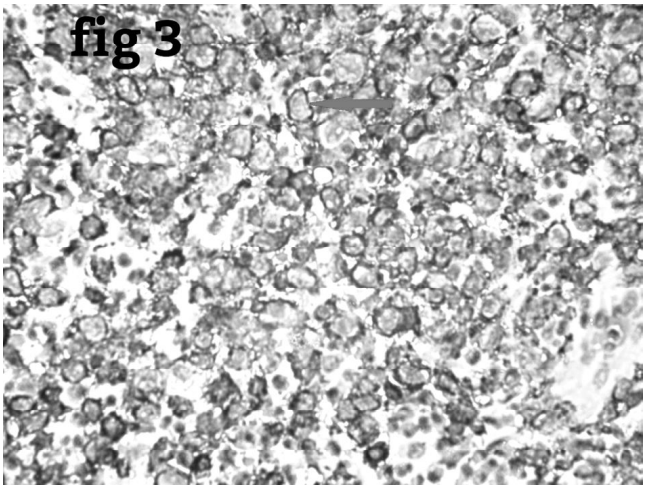

Fig 3 : CD la positivity (red arrow) in Langerhan's Cell Histiocytosis

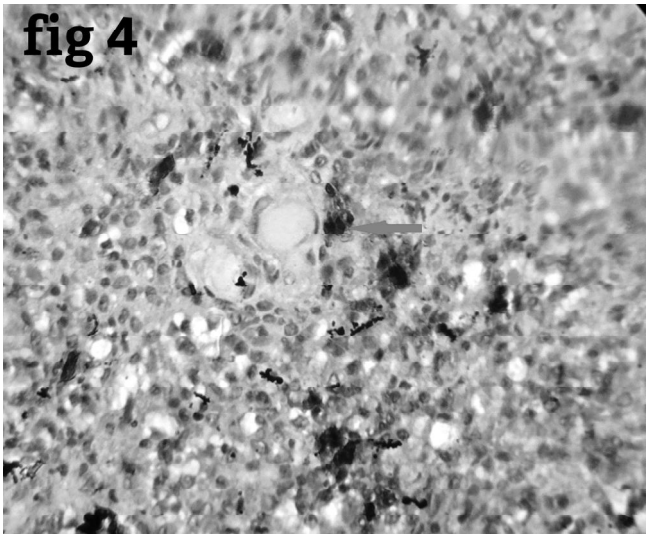

Fig 4 : S-100 positivity (red arrow) in Langerhan's Cell Histiocytosis

arranged in groups or clusters in a background of chronic inflammatory cells. The picture was consistent with langerhan cells histiocytosis (fig 2).

In both the cases, Immunohistochemistry was done for S-100 and CD1a, both of them showed strong positivity, which confirmed the histological diagnosis of LCH (fig 3 and fig 4).

DISCUSSION :

LCH can present as solitary or multiple lesions in one organ system (bone being the most common) or as a disseminated disease[7] .The term Letterer–Siwe disease was used in the past for the systemic form occurring in infants, and Hand–Schüller–Christian disease for the less widespread and more indolent type seen in older children and adults.[8] A self-healing, congenital form is known as Hashimoto–Pritzker disease.[9]

Patients with LCH mainly presents with localized bone pain, dysponea and malaise, and 75% have non-disseminated disease. The skull, femur, pelvis and ribs are most commonly involved. With skull lesions, the orbit and the cranial base are frequently involved and produce the classic triad of bony defects, exophthalmos and diabetes insipidus.[10]

Osteolytic bone lesions are a common manifestation of single system LCH in adults. These lesions tend to be unifocal rather than multifocal, often involving the skull or axial skeleton. Calvarial lesions are normally found incidentally . However they may also present with bone pain, soft-tissue swelling, hearing loss, vertigo and visual disturbances. Histologically, proliferation of Langerhans cells expressing CD1a and S100 admixed with acute and chronic inflammatory cells are consistently reported.[11-16] Immunohistochemical findings in our patient were consistent with these features.

By electron microscopy, they contain a highly characteristic and apparently diagnostic organelle: the Birbeck or Langerhans granule. This is an elongated, zipperlike cytoplasmic structure of unknown function, sometimes continuous with the cell membrane.[17] The differential diagnosis of LCH is wide and to some extent influenced by the site of involvement. It includes RDD, parasitic infections, Kimura disease, hypersensibility reactions, cat-scratch disease, Erdheim–Chester disease, and some types of malignant lymphoma, such as Hodgkin lymphoma and peripheral T-cell lymphoma.[18]

Local treatment with excision, systemic chemotherapy and corticosteroid injection is highly successful in treating this disease and patients have excellent prognosis.[19] Over 90% of patients survive 3 to 5 years post diagnosis.[19,20,21] Age at diagnosis and initial response to therapy affect the prognosis and rate of recurrence of disease.[19]

Recent research supports the notion that LCH is more align with a neoplastic process rather than a reactive one, with a proportion of lesions presenting with *BRAF* or *MAP2K1* mutations. Such mutations may be of some value for risk stratification and prognostication, and immunotherapy with BRAF inhibitors have shown some promise in treatment.[22]

Our patients are classified under category A1 according to the Pathologic Staging of Langerhans cell Histiocytosis (Histiocytic society) as our patients had only monostotic bone involvement with no lymph node or

contiguous soft tissue involvement. Other system involvement was not found.

On follow up, the patients are responding well to the standard treatment of chemotherapy and radiotherapy .

CONCLUSION :

In osteolytic lesions of skull bone, LCH should be kept in common differential diagnosis with a picture of inflammatory lesion which requires ancilliary techniques like immunohistochemistry to support histopathological diagnosis. Correct diagnosis is critical as it requires management as neoplastic lesions and it has potential to transform into lymphoma..

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Case Report

Familial Homozygous Hypercholesterolemia

P K Dutta*, A Ray, S Dey***, R Marak*, S Kakati******

Abstract

Familial hypercholesterolemia (FH) is a genetic disease , a form of primary hyperlipoproteinemia, which is an autosomal codominant disorder characterized by high levels of serum low density lipoprotein (LDL), xanthomas and premature atherosclerosis[1]. The diagnosis of Homozygous Familial Hypercholesterolemia (HoFH) is clinically based, on a family history of elevated cholesterol,persistent high LDL levels and the development of xanthomas and early atherosclerotic cardiac lesions such as aortic stenosis. Homozygous familial hypercholesterolemia is a rare disease that occurs in one in a million in the general population. Here we report a case of homozygous familial hypercholesterolemia in its clinical rarity.

INTRODUCTION :

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder characterized by elevated plasma levels of low density lipoprotein-cholesterol (LDL-C). Familial hypercholesterolaemia comprises of three separate genetic conditions due to mutations in the genes for: (i) the LDL receptor (LDLR), (ii) apolipoprotein B (ApoB), and (iii) pro-protein convertase subtilisin/kexin 9 (PCSK9). The clinical phenotype resulting from these mutations is variable, with, for example, ApoB mutations being the least severe of the three. There are both 'heterozygous' (heFH) and 'homozygous' (hoFH) forms. Heterozygous FH (HeFH) is the widely occurring form of the disease (prevalence of approximately 1 in 500 individuals globally through an autosomal-dominant mechanism)Homozygous FH (HoFH) on the other hand, is a very rare form of the disease (prevalence of 1 in 1 million persons).[2]

The deposition of the Low-density lipoprotein-cholesterol in the tissues cause external manifestations of FH, such as tendinous xanthomas and corneal arcus. LDL-C deposits in arteries can lead to premature atherosclerosis and cardiovascular disease (CVD). HeFH patients if left untreated, may develop CVD by the fourth decade in men and fifth decade of life in women.In contrast, HoFH patients can experience serious cardiovascular events as early as childhood and, on average, in their twenties.[3]

Early lifestyle modification , correction of associated CVD risk factors such as smoking, hypertension, and diabetes are necessary to reduce the mortality and morbidity. HoFH patients may require early medical therapy to reduce sudden deaths due to CVD.

CASE REPORT :

A 13 year old boy presented with chief complaints of multiple, painless, firm small to large yellow to brown lesions all over the body since the age of 5years (since 2010). The lesions appeared initially over the knees and elbow, and subsequently appeared all over his body. Lesions gradually increased in size and number to reach the present state. At the age of 6years (2011), patient was treated by a local doctor and was given a few medicines for a brief period of time but the symptoms did not subside. Since then he is not on any medications. For the past 6 months he complaints of chest pain on exertion and episodes of giddiness as well as fainting.

The patient was born to non consanguineous parents and his developmental milestones were normal. There is no history of hypertension, diabetes mellitus, hypothyroidism or any other chronic illness and he has not been on any medications.

Family history : There is a history of hypertension in

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both the parents of the patient, his mother is also a known diabetic on insulin for the past 14 years. Both his parents developed stroke, his father had a cerebrovascular accident at the age of 48 years while his mother had a history of stroke at around 40 years of age. His maternal uncle had similar skin lesions and had died at an early age (37 years) possibly due to myocardial infarction. There is no similar history of skin lesions in his parents.

General Physical Examination : height - 148cms.,weight 47kg, BMI- 21.46kg/m2 BP- 140/ 90mmHg (on medication ramipril 2.5mg after admission), Fundus examination was found to be normal *Dermatological examination* revealed multiple Tuberous Xanthomas of varying sizes ranging from 1 to 5 cm distributed mainly over the cubital and popliteal fossa, knees, elbows, ankle and wrist. Tendinous Xanthomas were present along the achilles tendon and extensor tendons of hands and Cutaneous Planar Xanthomas with yellowish hue coalescing into plaque like appearance were seen over the dorsum of hands, cubital andpopliteal fossae, around the umbilicus, buttocks, hands,feet and intertrigonous areas were seen. Xanthelasmas were noticed in the medial aspect of both his eyes.

Cardiovascular examination revealed Ejection systolic murmur grade II in the aortic area with bilateral carotid bruit.

Laboratory investigations:

Hematological parameters: within normal limits.

Fasting blood sugar: 98mg/dl.

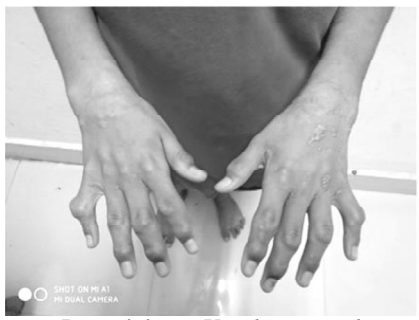
PPBS: 128 mg/dl, HbA1c- 4.9

OGTT after 75 gm glucose done was found to be normal Urea, creatinine, liver function tests and thyroid function tests were within normal limits.

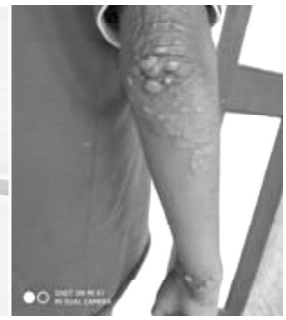
Lipid profile of the patient (Table 1) shows increased total cholesterol, LDL cholesterol and LDL/HDL ratio and normal triglyceride levels. The lipid profile of his elder brothers and parents were also done.

Histopathology of the biopsy specimens confirmed the diagnosis of xanthoma.

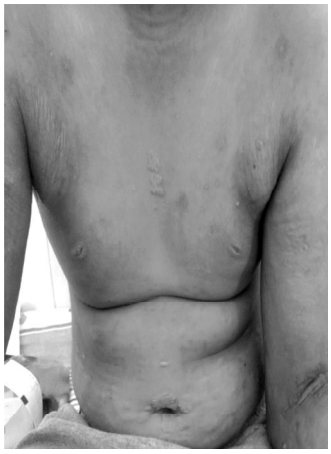
2D-Echocardiography showed aortic leaflet thickening and mild AS *Carotid Doppler* of neck vessels revealed diffuse intimo-medial thickening of bilateral carotid arteries,left internal carotid artery,left external carotid artery and bilateral vertebral arteries with stenotic segment In left vertebral artery at the level of c4-c5 vertebral level



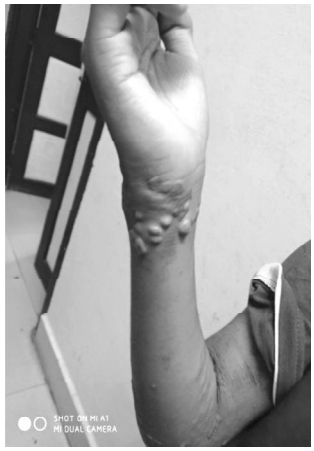
Intertriginous Xanthomas and Xanthomas of Extensor tendons



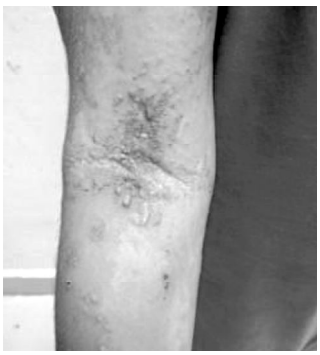
Xanthomas over the elbow joint



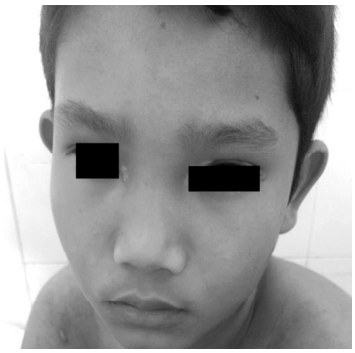
Xanthoma plaques around the umbilicus, and over the chest



Nodular Xanthomas over the wrist



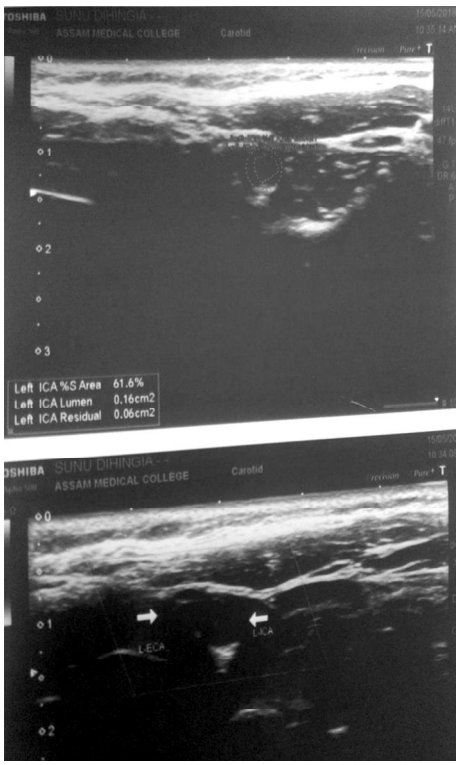
Plaques of xanthomas in the cubital fossa



Xanthelasmas around the medical aspect of the eyes.

Table 1: Lipid profile of the patient and family members

	Patient	Elder brother	Mother	Father
Total cholesterol (mg/dl)	549	266	156	143
Triglycerides (mg/dl)	96	143	199	150
LDL (mg/dl)	528	193.4	95.2	78
HDL (mg/dl)	30	32	21	35
VLDL (mg/dl)	19.2	40.6	39.8	30
LDL/HDL ratio	17.6	6.04	4.5	2.2



Intimo-medial thickening and narrowing of left internal and external carotid artery.

Lipid profile of the patient and family members (table1)

Lipid profile of his elder brother shows hypercholesterenemia that could be a possible FH heterozygous.

With the available laboratory data and clinical findings,it was established that the patient had Homozygous FH (type II a Frederickson's Hyperlipoproteinemia), with echocardiographic,doppler and MRI evidence of extensive atherosclerosis with aortic stenosis.He was advised low cholesterol diet, treated with Tab Atorvastatin 40 mg HS and was asked for reular follow up.

DISCUSSION :

Familial hypercholesterolemia is as an autosomal - dominant disorder of lipid metabolism. This genetic disorder is characterized by high cholesterol levels, particularly very high levels LDL that leads to early onset of cardiovascular disease (as early as 1st decade of life).

There is mutation in the LDL receptor gene that is present on the chromosome 19 that encodes the LDL receptor protein, which normally removes LDL from circulation. Apolipoprotien B (ApoB mutation may also be present), which is the part of LDL that binds with the receptor.

Increase LDL levels in blood result in atherosclerotic changes in arteries.[13,14] Furthermore, patients may develop accumulation of cholesterol in other parts of the body leading to the development of cutaneous xanthomas of various types like xanthelasma, Tendon xanthomas, and Tuberous xanthomas.

There are two types of FH: the heterozygous form in which the patient has one normal allele and one mutated allele. This is the most common form with an incidence of 1:500. The other form is homozygous form in which the patient has two mutated alleles, considered an autosomal codominant disorder. This is rare with an incidence of approximately one in a million[2] Patients with heterozygous FH are usually diagnosed as adults and usually respond well to medical therapy. On the other hand, patients with HoFH are often diagnosed early in childhood, do not respond well to medical therapy, and can progress rapidly to premature coronary artery disease.

Xanthomas are the characteristic cutaneous manifestation of hyperlipidemia particularly that of Familial Hypercholesterolemia. The term "Xanthoma" was first coined by Smith in 1869.[4]

The manifestations of the severe form of hypercholesterolemia was noted in the early descriptions of the condition Xanthelesma multiplex in 1879[5]. Muller and Harbitz described the first familial examples of tendon or subcutaneous xanthomas associated with sudden death in young people, giving the name Muller–Harbitz disease for FHs[6]. In 1964, FH was defined as an autosomal dominant disease and a clinical distinction was made based on the phenotype severity of a heFH(mild) and hoFH (severe) form.

Fredrickson et al.[7], classified primary hyperlipoproteinemia on the basis of electrophoretic lipoprotein phenotype, into five major types (types I–V).

Type	Synonym	Defect	Serum abnormality	Clinical Features	Treatment	Serum appearance
Type 1	Familial Hyperchylomicronemia	Low LDL Altered ApoC2	Chylomicron ↑	Pancreatitis, Lipemia retinalis, skin eruptions, Xanthoma, Hepatosplenomegaly	Diet	Creamy top layer
Type IIa	Familial Hypercholestrolemia	↓LDL receptor	LDL↑	Xanthelasma, Arcus senilis, Tendon xanthomas	Cholestyramine or Cholestipol, Statins, Niacin	Clear
Type IIb	Familial Combined Hypercholestrolemia	↓LDL receptor & ↑Apo B	LDL & VLDL↑		Statins, Niacin, Fibrate	Clear
Type III	Familial dysbetalipoproteinemia	Apo E2 synthesis defect	IDL↑	Tubo-eruptive xanthomas, palmar xanthoma	Fibrate, Statins	Turbid
Type IV	Familial Hyperlipemia	↑VLDL production, ↓elimination	VLDL↑		Statins, Niacin, Fibrate	
Type V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Niacin, Fibrate	Creamy top layer & Turbid bottom

A Xanthoma (Greek= yellow) is a deposition of yellowish Cholesterol-rich material that can appear anywhere in the body in various disease states. Xanthoma is not a disease but a cutaneous manifestation of lipidosis in which cholesterol accumulates in large macrophages to form Foam cells within the skin.

Apart from xanthomas, familial hypercholesterolemia results in an almost 100-fold increased risk of coronary artery disease (CAD). Homozygous FH patients also develop symptomatic CAD in early childhood.

The consequences of LDLR gene mutations are high total serum cholesterol and high serum LDL-C. The levels of these lipoprotein particles in the plasma are significant determinants of the initiation of changes in vascular endothelial damage, of monocyte differentiation into macrophages and foam cell formation,leading to the development of atherosclerotic lesions, premature coronary artery disease (CAD), peripheral arterial disease, and valvular disease (predominantly aortic stenosis).

Familial hypercholesterolaemia often leads to accumulation ofcholesterol in the skin, where xanthomas can occur .Xanthomas particularly affect the tendons: elbows, Achilles tendon, and hands. Xanthelasmata are lipid depositions around theeyes. Deposition of lipid can also occur in the cornea, leading to presenile corneal arcus. Xanthomas and corneal arcus are pathognomonic for heFH and hoFH and their presence is associated with a three-fold higher risk of CVD in patients with FH. Compared with heFH, these symptoms are much more severe and occur earlier in patients with hoFH. For example, xanthomas may be observed at birth or develop during early childhood in those with hoFH.

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele and occur in 1 in 500 persons.Patients have 2–3 fold elevation in LDL cholesterol (200–400 mg/dl), normal triglycerides, development ofmainly tendon xanthomas during III–VI decades and premature atherosclerosis leading to coronary heart disease. Untreated patients with heterozygous FH have about 50% chance of having MI before age 60[8]. In comparison patients with Homozygous FH are prone to develop significantly higher levels of LDL cholesterol, and thereby a much earlier manifestation of CVD. These subjects may be unaware of the relevance of the xanthomas and are also known to have sudden deaths.

Apart from LDL receptor mutations, Familial defective apolipoprotein B-100 (FDB), Autosomal Recessive Hypercholesterolemia (ARH) and sitosterolemia have phenotypic similarities with homozygous FH.

There is no single internationally accepted set of criteria for the clinical diagnosis of FH. The most commonly used are the US (Make Early Diagnosis to Prevent Early Death) MEDPED, the UK (Simon Broome), and the Dutch Lipid Clinic sets of criteria that have been statistically and genetically validated.

From detailed, history, clinical assessment, investigations and literature search, the diagnosis of the rarehomozygous hypercholesterolemia was done in our patient.

The diagnosis of homozygous FH in our patient was based on the presence of

1. Serum cholesterol levels [549 mg/dl with normal triglyceride levels after ruling out secondary causes such as hypothyroidism, diabetes, nephritic syndrome etc.

2. Appearance of xanthomas in the first decade of life.

3. Documentation of hypercholesterolemia in both parents and in one of the siblings.

4. evidence of presence of premature atherosclerosis in carotid Doppler and echocardiogram evidence of aortic stenosis and aortic leaflet thickening.

5. The presence of rare pathognomonic intertriginous xanthomas, which have been described as a marker ofthis homozygous type.[9]

LDL receptor studies and genetic analysis could not be done in our patient.

CONCLUSION :

Homozygous Familial Hypercholesterolemia is a rare, often underdiagnosed disease which is often missed by the clinician as a probable dermatological entity due to the presence of xanthomas in the early stages. As the patients remain asymptomatic, besides the cutaneous manifestations, they tend to overlook subtle signs such as chest heaviness or presyncopal episodes which infact are predictors of underlying atherosclerosis of the coronary and carotid vessels. It is imperative to identify such patients and intervene early as they are very prone to develop early CAD and perhaps even sudden death. A genetic workup of the family members is also important as this is an Autosomal dominant disease and early treatment may

prolong the life.

Hence early diagnosis, dietary modifications and drug therapy with statins and bile acid sequestrants is very important in these patients. Drug therapy may be less effective in homozygous FH as compared to heterozygous FH , in whom other treatment modalities like liver transplantation, LDL apheresis can be considered.

This case study highlights that despite huge medical advancement FH remains seriously under-diagnosed, with a delay in the treatment. With early diagnosis and prompt treatment these patients can live longer and more productive lives. The diagnosis of FH is important not only for the prognosis of the patient but also has implications for thefamily members who may have inherited the same disorder.Therefore genetic counseling and screening of first degree relatives and extended family members plays an important role in early detection and treatment.

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