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Editorial

Computed Tomography in Acute Ischemic Stroke

Binod Sharma*

Introduction :

Stroke is a global health problem. It is the second most common cause of death after coronary artery disease and fourth leading cause of disability worldwide. However, while stroke threatens humankind all across the globe, stroke is becoming an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors. According to the estimates from the GBD study in 2001, over 85 per cent of the global burden of stroke was borne by low- and middle-income countries and the number of disability-adjusted life years in these countries was approximately seven times that in high-income countries. A global systematic review of population-based stroke studies has documented that the incidence rate of stroke in low and middle-income countries has increased from 56/100,000 person-years during 1970-1979 to 117/100,000 person-years during the period 2000-2008[1]. India has been experiencing significant demographic, economic and epidemiological transition during the past two decades. These have resulted in an increase in life expectancy and consequently an increase in ageing population. Currently in India, the estimated age adjusted prevalence rate of stroke range, 84-262/100,000 and age-adjusted, annual cumulative stroke incidence is 141-152/100,000 persons[2]. Further, mortality from stroke in India is significantly higher (35-42%) than that seen in the industrialized Western countries(17-33%)[3]. High stroke related case fatality in India is mostly due to inadequacy of prompt medical care in many areas and lesion severity. Ischemic stroke by far the commonest type of stroke accounting 80% to 85% of strokes and the remaining 15 to 20% are hemorrhagic. A third main type of stroke, cerebral venous thrombosis generally causes only <1% of all strokes. The most important treatment aspect of acute ischemic stroke is early revascularization therapy by thrombolytic agents. Noncontrast Computed Tomography head (NCCT) is the first-line diagnostic test for emergency evaluation of acute stroke due to its speed of imaging, widespread availability, and low cost. The evaluation of a patient with suspected stroke is incomplete without a CT scan of brain. The first diagnostic step is to distinguish between a vascular and a nonvascular lesion, stroke-mimicking conditions such as subdural haematoma, abscess, or brain tumour (which are the underlying lesions in about 4% of patients presenting with a stroke syndrome) can usually be distinguished from a vascular lesion by a combination of clinical assessment and CT scan. After excluding a nonvascular cause, the major reason for performing a CT brain scan is to differentiate haemorrhage from infarct which cannot be done reliably by clinical examination alone. According to the AHA guidelines[4], the first aim of global assessment of a patient with suspected stroke is to exclude another possible cause of symptoms (such as hemorrhage). On the other-hand, signs of acute neurological dysfunction referable to stroke can be caused by a number of conditions. These so-called stroke mimics can be caused by a number of conditions such as epilepsy, brain tumors, or even infections/inflammatory diseases of the central nervous system. The aims of neuroimaging specially CT are manifold : (1) to rule out hemorrhage, (2) demonstrate

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the presence of ischemia, (3) extent of ischemia and infarction, (4) to demonstrate the presence of ischemic penumbra by CT perfusion, (5) demonstrate the underlying cause (vascular occlusion) by CT angiography, (6) to demonstrate success by showing reperfusion or demonstrating failure and or complications such as emboli or bleeding and, finally, (7) to allow follow-up imaging that correlates well with clinical status.Thrombolysis is the mainstay of treatment of acute ischemic stroke. The time window for intravenous thrombolysis from stroke onset is 4.5 hours. Every second from stroke onset to thrombolysis is crucial and early the thrombolysis, better the outcomes of interventions. An unenhanced CT scan of the brain (5 mm slices through the posterior fossa, 10 mm slices throughout the rest of the brain) takes only 5 min. CT is superiror than MRI because, CT takes few minutes to complete the scanning and it is readily available in many hospitals.

CT features in Acute Ischemic Stroke :

In the past, CT was thought to be insensitive to ischemic changes in the first 24 h . Even now, an infarct may never be seen in up to 50% of patients[5]. The likelihood of seeing a relevant infarct depends on time to scanning, and the stroke severity. The later the patient is scanned, and the more extensive the clinical syndrome, the greater the chance of seeing an infarct. Signs of infarction on CT within the first six hours of stroke are often subtle but become more obvious and better demarcated over the first few days. When visible, an established infarct (i.e. one that is a day or so old) appears as a wedge-shaped or rounded hypodensity within a recognized vascular territory. Swelling may be seen within the lesion, reaching its peak around the third to fifth day. In the International Stroke Trial (IST),[6] an infarct was visible in 33% of patients scanned within 6 h, and in 58% of those scanned 24–48 h after onset. Overall, 61% with an extensive clinical syndrome (total anterior circulation infarct) had a visible infarct, compared with 41% of those with lacunar clinical syndromes. With the advances in modern CT technology, and more patients presenting for early assessment, signs of infarction may be seen on a scan within a few hours of stroke onset. Unfortunately, these signs are subtle and may be missed. The characteristic changes are a loss of tissue density, resulting in loss of distinction between grey and white matter, and swelling. The pathological process that explains the CT signs is an influx of water into affected ischemic cells. The grey matter is affected first, as neurones are more sensitive to ischemia than other cells. It is necessary to recognize very early CT signs of ischemia. A suggested approach to the evaluation of early signs of infarction is to look systematically at the scan for the typical change, comparing parts of one hemisphere to the opposite hemisphere. There are numbers of early CT findings on NCCT which may help in the decision making in thrombolysis at early stage of ischemic stroke.

Loss of insular ribbon sign :

Loss of insular ribbon sign is defined as decreased precision in delineation of grey-white matter interface at lateral margin of insula. It is a most common early sign of ischemia of the MCA (or internal carotid artery) territory and reported to be present in 75-100% of the cases[7]. The insular segment of the MCA and its branches supplies the insular ribbon. In MCA (or internal carotid artery) infarction, with cessation of flow, the insular ribbon becomes the region most distal from the anterior and posterior cerebral collateral circulation. Consequently, the insular ribbon effectively becomes a watershed arterial zone. Loss of insular ribbon sign hardly ever appeared alone and more than half of the patients with this sign also had obscuration of basal ganglia and effacement of the hemispherical sulcus. The concomitant presence of these three signs seemed to have a strong correlation with internal carotid artery occlusion and showed poor arterial recanalization after thrombolysis[7].

Loss of basal ganglia (lentiform nucleus) outline :

This is one of the earliest sign that can be seen in acute stroke patient, in some, as soon as one hour after clinical onset. Loss of definition of grey matter is most obvious at the interface of grey and white matter in the basal ganglia. The distinction between caudate nucleus and anterior limb of internal capsule, globus pallidus and genu of internal capsule, and putamen and external capsule, is blurred or lost . Within the first few hours, the ischemic grey matter becomes a similar density to the adjacent white matter. Later, the grey and white matter becomes more hypodense, so that the whole area is darker than surrounding brain tissue. Swelling is seen as compression of the adjacent ventricle. In a study, this important early sign of ischemia

was found in 73-92% of cases when scan was obtained within 6 hours of stroke onset[8]. Lentiform nucleus of basal ganglia is fed by the lenticulostriate arteries from M1 segment of MCA without collateral flow from cortical anastomoses, thus this sign is seen in patient with M1 or ICA infarction.

Hyperdense middle cerebral artery sign (HMCAS):

This is not strictly a sign of early infarction, but reflects occlusion of the middle cerebral artery (MCA) by acute thrombus or embolism. The hyperdense MCA sign has been reported to have high specificity and positive predictive value for thromboembolic occlusion of the MCA. It is associated with severe neurological deficit, extensive brain damage and poor clinical outcome. The CT appearance is an increased density of part of the MCA, compared with other parts of the vessel or its contralateral counter-part (not attributable to calcification). Although most frequent in the MCA, any artery may appear hyperdense when it contains fresh thrombus, even the lenticulostriate arteries. In the distal MCA, it has been called the hyperdense sylvian fissure 'dot'sign. The incidence of hyperdense MCA sign greatly varies and reported to be ranging from 5%-41% in patients with acute ischemic stroke[9]. However, MCA may appear hyperdense without intraluminal thrombosis in few conditions such as in patients with raised hematocrit, partial volume averaging artifact from vascular wall calcification and due to relative hypodensity of adjacent parenchymal hypodensity.

Cortical sulcal effacement :

Swelling of the cortex results in effacement (loss of visibility) of the sulci in the territory of the involved artery, most easily seen by comparing sulci in corresponding parts of each hemisphere. Loss of definition between grey and white matter may be seen at the boundary between cortex and white matter, in particular involving the insular cortex. It reflects cortical ischemia and isolated sulcal effacement was highly indicative of branch occlusion and a partial superficial infarct. This sign in isolation is a good indicator for intravenous thrombolysis with 47% rate of recanalization[7].

Focal hypodensity

Subtle changes of cerebral ischemia include hypoattenuation in CT, due to increase tissue water content by cytotoxic oedema. Slight hypo- attenuation of grey matter may manifest as loss of the distinction between gray and white matter, more marked hypoattenuation may appear as tissue hypodensity. This is observed on CT scan as increased radiolucency of brain structures relative to other parts of the same structures or to contralateral counterpart. This sign is found in 20% to 60% of acute stroke cases[10].

ASPECTS score

Extent of early ischemic changes is an important predictor for the response to thrombolysis. Thrombolysis benefits patients with a small (less than 1/3 of the MCA territory) hypoattenuation area on NCCT scan. However, volume estimation with this one-third rule is difficult in routine practice. The Alberta stroke program early CT score (ASPECTS) was developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes (4.5 hours from symptom onset) on pre-treatment CT studies in patients with acute ischemic stroke of the anterior circulation

.This CT score is simple and reliable and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment. ASPECTS is a topographic scoring system which divides the MCA territory into 10 regions. These 10 regions are subdivided into 2 levels. The upper level involves all axial cuts above the ganglionic structures and the lower level all ganglionic and infraganglionic cuts. The individual regions include subcortical (lentiform and caudate nucleus, posterior limb of internal capsule) and cortical structures (insula, M1 through M6). A normal CT scan will have an ASPECT score of 10-points. To compute the ASPECTS, one point is subtracted from ten for an area of early ischemic change, such as focal swelling or parenchymal hypoattenuation, for each of the defined region. A score of zero indicated diffuse ischemic involvement throughout the MCA territory. Baseline ASPECTS score correlates inversely with the severity of NIHSS and with functional outcome. In small ischemic changes ASPECTS score is usually more than 7 and scores of 7 or less, indicating more extensive MCA involvement and are correlated with both poor functional outcome and symptomatic intracerebral haemorrhage on thrombolysis[11].

CT angiography :

Computed tomography angiography (CTA) uses an injection of iodine-rich contrast material and CT scanning

to help diagnose and evaluate blood vessel disease or related conditions, such as aneurysms or blockages. CT angiography (CTA) can rapidly provide useful information that may influence management and may indicate infarct size, location, and extent of vessel occlusion and collateral integrity, all of which can influence clinical outcome and recanalization in ischemic stroke. CTA accurately localizes thrombus and quantifies clot burden, both provide prognostic information in ischemic stroke and may guide management. CT angiography also demonstrates success or failed thrombolysis.

CT perfusion imaging

Perfusion imaging allows investigating the presence or absence of alterations in cerebral perfusion in patients with suspected stroke. It can be performed immediately following NCCT and has advantages of accessibility and speed. Differentiation of salvageable ischemic penumbra from unsalvageable core of infarct may help to identify patients most likely to benefit from thrombectomy or thrombolysis. In order to quantify and more precisely detect brain perfusion, several standard flow parameters are calculated. Mean transit time (MTT) represents the mean time required for a volume to clear the capillaries, while the time-to-peak (TTP) reflects the time required for a volume to reach peak concentration. Both MTT and TTP are very sensitive to local perfusion disturbances, but less specific to ischemia or infarction. Cerebral blood volume (CBV, ml/100 g brain) represents the volume of blood in a volume of tissue, and reflects autoregulation. As perfusion pressure decreases, autoregulatory mechanisms are activated, locally resulting in vasodilatation and recruitment of supporting capillary networks to increase perfusion of the ischemic region. The results of these changes are increased CBV, MTT and TTP. Within the ischemic core there is a failure of autoregulation, and CBV is ominously decreased in this region. Cerebral blood flow (CBF, ml/100 g brain/min) represents the delivery of blood to tissue per unit time and is calculated by dividing the CBV by MTT. CBF is decreased in all hypoperfused regions, including both the penumbra and ischemic core. On perfusion CT, CBV has been shown to correlate with infarct volume, and the subtraction of CBF and CBV is the usual way to detect the penumbra. In CT, a mismatch between CBV and MTT defines the ischemic penumbra. Almost all cases with an anterior circulation stroke show mismatch within the first 3 h. This declines to 75% within the first 6 h and to 50% 12–18 h after onset [12]. Perfusion imaging allows investigating the presence or absence of alterations in cerebral perfusion in patients with suspected stroke. Development of CT perfusion techniques based on flat panel CT should allow combining all axial imaging modalities (CT, CT angiography, CT perfusion) with the interventional techniques in order to facilitate and combine diagnostic and interventional procedures.

Conclusion :

The CT scan is the unquestioned ‘cardiogram of the brain’. It is widely available, not very expensive, and applicable to the majority of stroke patients. Computed tomography has remained at the forefront of imaging in acute stroke because it is slightly faster than MRI, and patient handling is simpler and more secure because there are no concerns regarding claustrophobia and magnetic fields. It can exclude haemorrhage immediately and establishes infarct in around 50% of patients with ischemic stroke. Early, subtle signs of infarction may be detected in patients scanned within six hours, and help to confirm the diagnosis of ischemia. Due to its wide availability, rapidity in excluding the haemorrhage, CT is the gold standard for the treatment of acute ischemic stroke in the stroke care units.

References :

1. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol* 2009; *8* : 355-69.
2. Ray BK, Hazra A, Ghosal M, Banerjee T, Chaudhuri A, Singh V, *et al.* Early and delayed fatality of stroke in Kolkata, India: Results from a 7-year longitudinal population-based study. *J Stroke Cerebrovasc Dis* 2013; *22* : 281-9.
3. Brown RD, Whisnant JP, Sicks JD, O’Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: Secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373-80.
4. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ, Stroke Council of the American Stroke Association (2003) Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 34(4):1056–1083
5. Wardlaw JM, Dennis MS, Warlow CP & Sandercock PA (2001) Imaging appearance of the symptomatic perforating artery in patients with lacunar infarction: occlusion or other vascular pathology? *Annals of Neurology*, 50, 208–15

6. International Stroke Trial Collaborative Group. (1997) The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischemic stroke. *Lancet*, 349, 1569–81.
7. Koga M, Saku Y, Toyoda K, Takaba H, Ibayashi S, Iida M. Reappraisal of early CT signs to predict the arterial occlusion site in acute embolic stroke. *J Neurol Neurosurg Psychiatry 2003; 74: 649-53*.
8. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri B, Norman D. Loss of the insular ribbon: another early CT sign of acute middle cerebral artery infarction. *Radiology* 1990; 176: 801-06.
9. Liebeskind DS, Sanossian N, Yong WH, et al. CT and MRI early vessel signs reflect clot composite in acute stroke. *Stroke* 2011; 42: 1237-43
10. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction: obscuration of the lentiform nucleus. *Radiology* 1988; 168: 463-67.
11. Weir NU, Pexman JH, Hill MD, Buchan AM. How well does ASPECTS predicts the outcome of acute stroke treated with IV tPA? *Neurology* 2006; 67: 516-18.
12. Leary MC, Kidwell CS, Villablanca JP, Starkman S, Jahan R, Duckwiler GR, Gobin YP, Sykes S, Gough KJ, Ferguson K, Llanes JN, Masamed R, Tremwel M, Ovbiagele B, Vespa PM, Vinuela F, Saver JL (2003) Validation of computed tomographic middle cerebral artery "dot" sign: an angiographic correlation study. *Stroke* 34(11):2636–2640

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Original Article

Evaluation of Ischemic Stroke with Computed Tomography in Adult Indians : A Single Centre Experience

S Latchamsetty*, K K Prabhakar*

Abstract

Objectives : Documenting findings fo Computed Tomographic (CT) scan in patients with ischemic stroke (IS) was primary objective. **Methods :** Comprehensive medical examination, Clinical and laboratory investigations were done,risk factors were assessed. CT findings were analysed. **Results :** Out of 50 patients, 33 were men; mean age was 58.56±10.26 years. 52% were smokers and 46.0% consumed alcohol. There were 76.0% hypertensives; family history of hypertension (20.0%) and diabetes mellitus (12.0%) were high. Gradual onset of symptoms (90.0%) was common. Cardiac complaints (12.0%), palpitations (8.0%) and palpitations along with breathlessness (4.0%); respiratory abnormality (22.0%) were also present. Left and right hemiplegia noted in 60.0%, and 36.0% of patients, respectively. Hyperlipedemia was reported in 48.0%. ECG was normal in 84.0% patients; abnormalities (16 %) included ischemic changes due to coronary artery disease (4.0%), atrial Fibrillation due to Chronic Rheumatic heart disease, and left ventricular hypertrophy due to hypertension (n=03); anterior and inferior lateral wall ischemia in one each. Infarct in the middle (94.0%), posterior (4.0%), anterior (2.0%) cerebreal artery territory were seen on CT. Infarct on right side (62 .0%) was common. **Conclusion :** Carotid atheroembolism is major cause for IS. Hypertension, Diabetes mellitus, smoking, alcoholism, dyslipidemia were risk factors. CT scan is a sensitive parameter in the assessment.

Keywords : *Cerebral infarcts, Computed tomography, Diabetes Mellitus, Hypertension, Ischemic stroke.*

Introduction :

Stroke is a medical emergency and is the third most common cause of death after Coronary heart disease and Cancer in the World. Stroke caused by ischemia from thrombo embolic events due to atherosclerotic disease at the carotid bifurcation or flow limiting stenosis is one of the leading causes of morbidity and mortality. When cerebral infarction occurs, the immediate goal is to optimize cerebral perfusion of the ischemic area. Attention directed towards preventing common complications of bed ridden patients namely infections (pneumonia, Urinary Tract Infections, skin) and deep vein thrombosis with pulmonary embolism.

Most strokes are ischemic (88%), while the rates of intra cranial hemorrhage and sub - arachnoid hemorrhage are 9 % and 3 % respectively.[1] Stroke incidence rates ranged from 0.2 – 2.5 per 1000 population 2 % of all hospital cases are from stroke.[2]

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Accurate diagnosis of carotid stenosis is important as it is associated with increased risk of cerebral infarction. Lesser degree of carotid stenosis is clinically important as a source of emboli that may cause cerebral infarction, can be treated medically with drugs that inhibit platelet aggregation and thrombus formation.

There are non modifiable & modifiable risk factors that can be controlled with numerous options for intervention. O'Donnell MJ et al have identified the common risk factors, global variation.[3] It has been identified that modifiable factors contribute large to the disease burden of IS. People at risk need to be identified in order to institute stroke prevention strategies. The prevalence of stroke in India occurs at a much younger age than in well developed countries and therefore is a source of great socio economic burden. There is tremendous progress in the diagnosis of stroke with the advent of better imaging techniques like CT scan. A number of these ischemic events can be prevented by accurate diagnosis and management of patients with carotid stenosis.

Developing countries including India are still focussing mainly on the infections and communicable diseases; in midst diseases due to ischemic events which were once considered restricted to older age group, are on the rise, more in the younger patient groups. With this backdrop

we attempted to identify the prevailing risk factors and etiology in patients with ischemic stroke (IS), its influencee on management and treatment outcomes that describes the current scenario in our country. With the availability of improved diagnostic methods radiology has pivotal role; noninvasive techniques in computed tomography (CT) and Magnetic resonance imaging (MRI) have proved its role in early detection of ischemia in stroke patients, help the physicians in early recognition and plan treatment strategies.

Materials & Methods :

This prospective clinical study was conducted on hospitalised patients in a tertiary care, teaching hospital, after obtaining institutional ethics committee clearance and patients were screened after obtaining a written informed consent.

Documenting the Computed Tomographic (CT) scan findings and patients presenting with ischemic stroke was the primary objective. In addition, we studied the mode of presentation, clinical features, common risk factors that contributed to ischemic stroke; apart from this, we also performed comprehensive patient assessment that included initial neurological and cardiopulmonary examination to establish the cause for the event. Detailed physical examination was done to note the injuries, any occular signs, peripheral vascular involvement and Cardiac arrhythmia (if any).

If patients had recent, sudden onset of focal neurological deficit a probable diagnosis of ischemic stroke was made. We included patients with sudden onset of loss of consciousness in whom CT was suggestive of Ischemic stroke, those with hemiparesis with or without loss of consciousness with CT scan showing Ischemic changes and those with recent onset of other focal neurological deficits with CT scan evidence of Ischemic stroke.

Complete history & examination of these patients were documented. At admission, complete hemogram, blood sugar, electrolytes, renal function tests, lipid profile, CT scan, Chest X-ray and ECG were done. These tests were done within 1hour of admission repeat tests were done after 2days except for CT scan and lipid profile.

All were treated with supportive therapy & anti platelet agents. These patients were followed up for six months.

Results :

We included 50 patients (male =33, 66%, female= 17, 34.0%) meeting inclusion/exclusion criteria. Figure 1 depicts the age distribution of patients, 38.0% (n=19) were in the age group of 51-60 years followed by 26.0% (n=13) in the age group of 61-70 years. Mean age of the patients were 58.56±10.26 years with a range of 36 -80 years. (Fig 1)

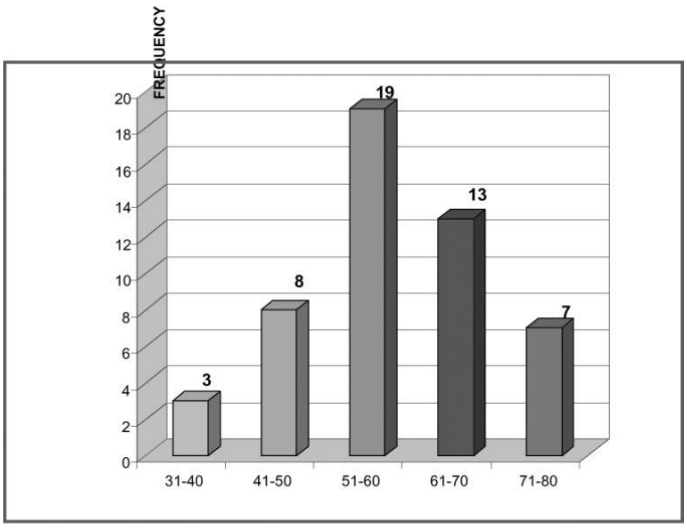

Figure 1. Age –range among the study population

There were 26 (52%) smokers and 23 (46.0%) consumed alcohol. There were 38 (76.0%) hypertensive patients. (Fig 2).

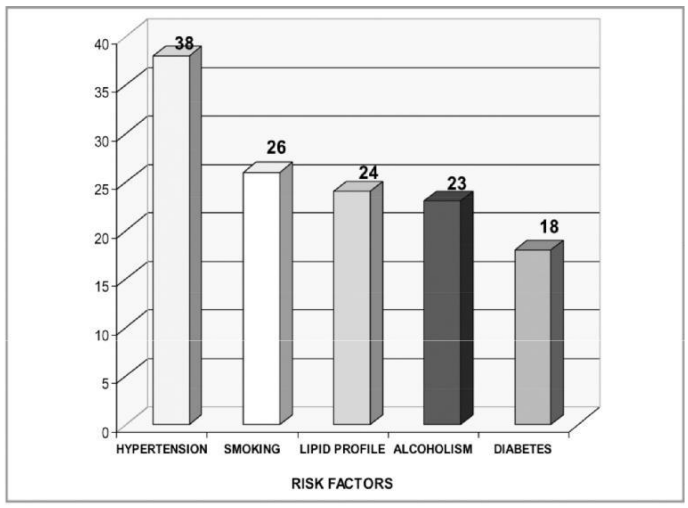

Figure 2. Risk factors for Ischemic stroke among the study population.

Family history of hypertension (n=10, 20%), and diabetes mellitus (n=06, 12%) were common (Table 1).

Table 1. Family History of illness

Family history	n (%)	Cumulative n (%)
CHD	2 (4.00)	2 (4.00)
CVA	2 (4.00)	4 (8.00)
DM	3 (6.00)	7 (14.00)
HTN	7 (14.00)	14 (28.00)
HTN & DM	3 (6.00)	17 (34.00)
NO	33 (66.00)	50 (100.00)

Gradual onset of symptoms was seen in 45 (90.0%) patients; only five patients had sudden onset of symptoms.

Six (12%) patients presented with cardiac complaints. Four patients (8.0%) had palpitations and two had palpitations along with breathlessness. Respiration was normal in 39 (78.0%) patients, while respiratory abnormality was seen in 11 (22.0%) patients.

Our patients presented with altered sensorium, speech defect; all had limb weakness. Twenty (40.0%) patients had altered sensorium 40% (20) which varied from mild confusion to coma, while the remaining 30 were conscious. Speech defect was seen in 40 (80.0%) patients, of which six (12%) were aphasic, 33 (66%) had dysarthria and one was in coma. In nine (18 %), no defect in speech was observed. Seventh cranial nerve was affected in 26 (52.0%); cranial nerves were not involved in 19 (38.0%) while could not elicit in five (10.0%). Higher intellectual functions were abnormal in 20 (40.0%).

Table 2. CT findings of Ischemic stroke among the study populaiton

CT SCAN Findings	Frequency (%)	Cum frequency	Cumulative %
Acute infarct in Lt. Internal capsule	6 (12.00)	6	12.00%
Infarct in Rt internal capsule	4(8.00)	10	20.00%
Acute infarct in Rt mca territory	10(20.00)	20	40.00%
Acute infarct in Lt. MCA territory	4(8.00)	24	48.00%
Acute infarct in posterior limb of Lt Internal capsule	1 (2.00)	25	50.00%
Acute infarct in post limb of Rt Internal capsule	1(2.00)	26	52.00%
Acute infarct in Rt Int. Capsule & chr. Infract in Lt PCA	1(2.00)	27	54.00%
Acute infarct in Rt. ACA territory	1(2.00)	28	56.00%
Hyper mature infarct in Rt occipital area	1(2.00)	29	58.00%
Infarct in Rt Internal capsule	1(2.00)	30	60.00%
Infarct in lentiform & caudate nucleus	1(2.00)	31	62.00%
Infarct in Lt anterior limb of Internal capsule	1(2.00)	32	64.00%
Infarct in Rt internal capsule & corona radiata	1(2.00)	33	66.00%
Infarct in Rt ant. Limb of Int capsule	3(6.00)	36	72.00%
Infarct in Rt MCA & thalamus	1(2.00)	37	74.00%
Infarct in the anterior limb of Lt internal capsule.	2(2.00)	39	78.00%
Ischemic infarct in Rt occipital area.	1(2.00)	40	80.00%
Lacunar infarct	2(4.00)	42	84.00%
Lacunar infarct in the Lt thalamus, dif cereb atrophy	1(2.00)	43	86.00%
Large infarct in Rt MCA territory	1(2.00)	44	88.00%
Large Lt MCA territory	1(2.00)	45	90.00%
Multiple ischemic infarcts	4(8.00)	49	98.00%
Periventricular isch. Changes & diff cereb atrophy	1(2.00)	50	100.00%

The weakness pattern included hemiparesis, hemiplegia. Right side hemiplegia was observed in 36 % (18) of the patients, left side hemiplegia was observed in 60 % (30), left brachial monoplegia and coma was observed in one patient each (hence not elicited).

Investigations :

Laboratory investigations

We observed anemia in 16 % (n=08), raised erythrocyte sedimentation rate (ESR) in 20 % (n=10), elevated blood sugar in 36 % (n=18) patients. Blood urea and serum creatinine was high in 8 % (n=04) of the patients. Abnormal lipid profile (hyperlipedemia) was seen in 48 % (24) of patients; of which total plasma cholesterol was high in 18 patients and six patients had high total plasma cholesterol plus LDL with low HDL.

ECG Interpretation :

ECG abnormalities were noted in 16 % (n=08) of the patients; ischemic changes due to coronary artery disease (CAD) were seen in 4 % (n=02) of patients. Atrial Fibrillation due to Chronic Rheumatic heart disease (Mitral Stenosis), and left ventricular hypertrophy (LVH) due to hypertension was noted in three patients. Anterior wall ischemia and inferior lateral wall ischemia was seen in one patient each. ECG was normal in 42 (84.0%) patients.

Radiological investigations

CT Scan

CT scan brain is the main investigation in our study. Infarct in the middle cerebral artery (MCA) (n=47, 94%) territory, posterior cerebral artery (n=02, 4.0%), anterior cerebreal artery (n=01, 2.0%) were seen. Infarct on right side was seen in 62 %(n=31). The infarcts were ranging from the lacunar infarct to the large infarcts. Patient's CT findings are given in table 2 and figures 3, 4,5, 6 & 7.

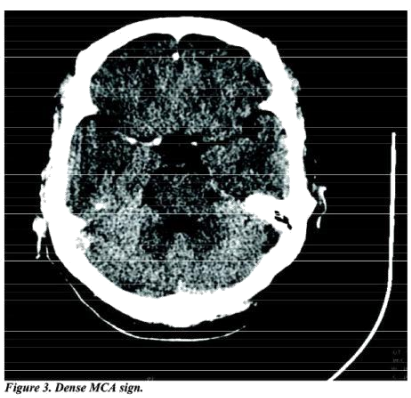

Figure 3. Dense MCA sign.

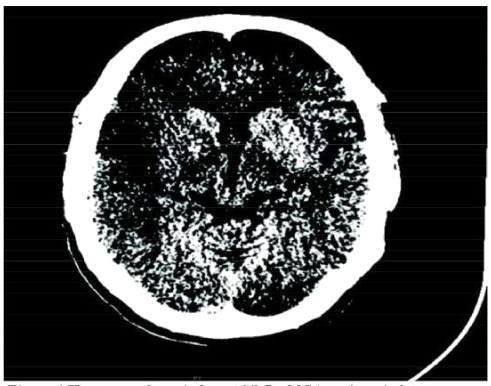

Figure 4.Hyperacute large infarct >1/3 Rt. MCA territory infarct.

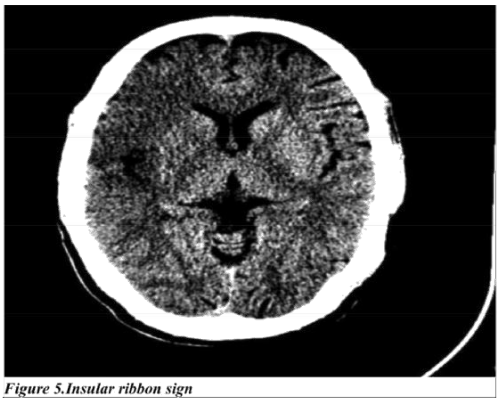

Figure 5.Insular ribbon sign

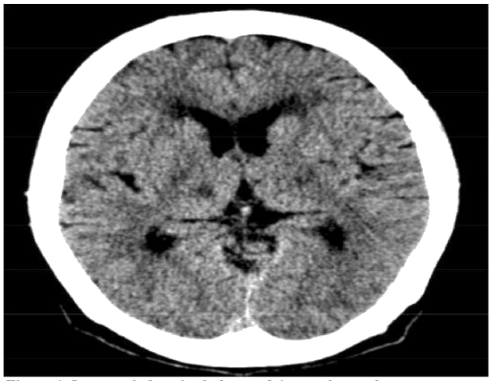

Figure 6. Lacunar infarct in thalamus & internal capsule

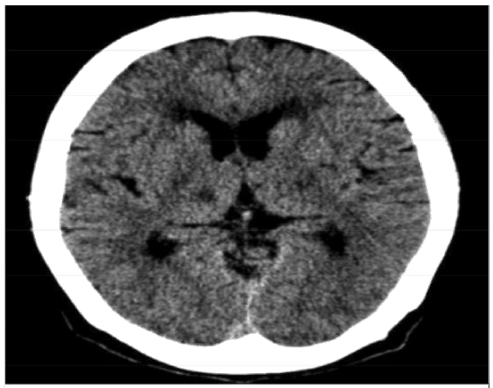

Figure 6. Lacunar infarct in thalamus & internal capsule

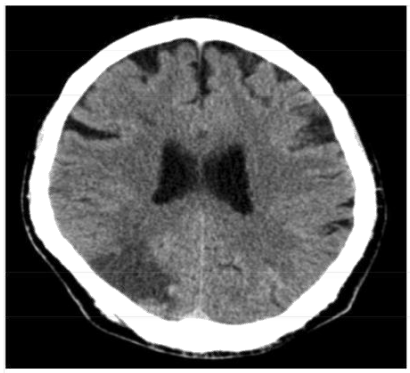

Figure 7. Wedge shaped RT MCA territory infarct invol. Both gray & white matter

Treatment :

All were treated with anticoagulants (low molecular weight heparins), anti-platelets, Intravenous (IV) fluids and supportive care (oxygen, measured to prevent bed sores). Active and passive physiotheapy of limbs were advised. Dietary measures to maintain adequate nutrition was followed. During their stay in the hospital, monitoring & good control of blood glucose, blood pressure, prophylaxis for peptic ulcer, control & treatment of secondary infections (if any) with appropriate antibiotics were maintained.

Outcome :

The patients were monitored daily during their hospital stay. After discharge from the hospital, they were followed up once in 15days for 3 months.

Complete recovery was seen in 18 % (n=09) of the patients in 7 days, residual weakness was found in 64 % (n=32) of the patients and mortality occurred in one patient due to aspiration pneumonia. There were no TIAs or RIND. Other 8 pts did not come for follow up.

Discussion :

There is increase in the incidnce of stroke indicated by epidemiological data (16.9 million people suffer a stroke each year, and a global incidence of 258/100,000/year). The increase is more in females.[4] There is significant difference between high- and low-income countries. Increase in prevailing risk factors, change in the life style in the latter has contributed in additon to the epidemiological shift and transition in these coutnries. Of the various causes of stroke, ischemic stroke is more common (90%) and increasing over the years.[5]

Of 50 cases of Ischemic stroke in our study, males (66 %) outnumbered females (34 %) revealing that men are more affected than women.

Ischemic stroke is common after the age of 50 years and the risk increases with age. Uddin MJ et al have reported the mean age of 63.58+/-10.22 years in their study. Mean age has remained around 64 years across the globe.[4,5] Mean age of patients in our study was slightly lower (58.56±10.26 years) with higher proportion of patients belonging to 51-60 years age group (38.0%). These observations are similar to the previous reports. Katsanos AH et report mean age as 57.6 ± 13.5 years in their study[6] similar to that by Farah R et al.[7] Slightly higher age (mean age of 64.4±11.5 years) was reported by Saeed E, et al. [8]

Men are more prone with an age-adjusted incidence 1.5 times higher than women. In contrast, Farah et al

reported female preponderence. Risk factors have been different for men and women. Modifiable risk factors (smoke and alcohol) were predominant in men while women had coronary artery disease and AF contributing to the gender difference. There were difference in the site affected and pathological process involved.

Classical sudden onset of symptoms were seen in minority of our patients (10%). Hence, physician should not deviate from arriving a diagnosis in those presenting with symptoms of gradual onset. CNS symptoms were predominant with speech deficit being common presentation (80.0%); aphasia was seen in 12.0% of our patients with speech deficit. Our patients had varied level of consciousness while being hospitalised, from mild confusion to coma (n=01) while 60% were conscious. The weakness pattern included hemiparesis, hemiplegia with the latter being common. These are similar to the text book descriptions. We did not find any significant deviation in the clinical presentation.

There is a discussion on the impact of family history of IS in these patients but the data available has failed to show a positive relationship between the two. Similarly, number of patients with positive family history of IS were less in our study, thus eliciting doubts over the existing concept among clinicians. Family history of IS per se may not contribute significantly, but presence of other risk factors (ex smoking, alcohol, cardiovascular disease) may play a major role in these patients.

Various risk factors have been identified to be associated with ischemic stroke. Smoking, dyslipidemia, hypertension, diabetes mellitus are well proven risk factors. Hypertension is another independent risk factor for IS.[9] and carries the high lifetime risk of IS.[10] In the present study 76 % (38 patients) presented with high blood pressure. It correlated with the observation of Sare GM et al who reported high blood pressure in 80% of patients.[11] Gorelick PB et al too reported hypertension as an independent risk factor.[12]

Diabetes Mellitus is a well documented risk factor for ischemic stroke and contributes significantly to mortality. Larsson SC et al suggest that diabetes mellitus may have a role in the development of large artery stroke based on the radiological evidences in their study.[13] Pathological processess that occur in DM contribute to IS; hence, better disease management in terms of tight glycemic control can result in preventing or minimising the development of IS in these patients, provided, the other risks are not contributing. Muñoz-Rivas N et al reported that DM doubles the risk of stroke. Poor outcome in women with type 2 DM in terms of higher mortality, hospital readmissions and considered as an independent risk factor.[14] Higher blood glucose result in poor outcome and longer hospital stay.[15] High blood glucose levels were seen in 18 (36%) of our study population; Woo D et al reported that Diabetes mellitus was encountered in 33% of the patients with Ischemic stroke and Diabetes mellitus is a clear risk factor for stroke.[16]

Smoking is an important contributing factor in those with ischemic stroke with data suggesting a positive association between the two. We found that smoking and hypertension to be independent risk factors.

Hyperlipidemia has been linked to the developent of stroke since long. However, Saeed et al stated that hyperlipidemia can not be considered as a major risk as the mean cholesterol levels were 4.16±1.1 mmol/l in the patients with confirmed ischemic strok emphasizing the need to focus on other major risk factors to prevent and better management.[8]

In the study conducted by Putaala J et al,[17] it was found that the most frequent risk factors were dyslipidemia 60% and smoking 44%, which correlated with the present study wherein Dyslipidemia and Smoking were found to be important risk factors. Smoking, hypertension and hypercholestrolemia are the leading risk factors that are modifiable, in additon to diabetes. Hence, these factors have to be tackled successfully. In contrast, incidence of DM, hyperlipidemia were reported by Katsanos AH et al.[6]

Atrial fibrillation is a strong risk factor for ischemic stroke. Patients with AF are 4-5 times more prone of ischemic stroke and also have high death rate. Coronary artery disease is a contributing factor for IS. The positive association has been supported by studies. It also affects the long term outcome, survival, hospital readmission, re stroke.

Observations of Al-Hashel JY et al[18] too are in similar lines, in terms of risk factors (hypertension, CAD, age). Younger the age, less neurological complications and outcomes were observed. Presence of these common risk factors have been well documented in the literature. In many occassions, it is observed that more than one risk factor is present in these patiens. Hyperlipidemia, impaired glucose control, hypertension are frequent; in addition, low levels of high density lipoproteins have their contribution. Presence of these risk factors in those with family history of IS is associated with higher chance of IS in them.

Radiological evidences are important in distinguishing not only different types of strokes but also in those with atypical presentation. Imaging in IS helps us to establish the cause, precise location, size of the infarct, the underperfused area, treatment option, prognosis and outcome in these patients. Middle cerebral artery is frequently involved in IS. With diagnostic clinical features, a simple non-contrast study is a valuable tool to confirm the diagnosis and decide therapeutic management. Nedeltchev K et al assessed the risk factors for mortality in acute stroke and report that apart from comorbidities, hyperglycemia and atrial fibrillation, radiological evidences of early signs of ischemia, dense artery sign, proximal vessel occlusion are poor prognostic factors. [19] Initial CT findings can be abnormal in significant proportion (86.5%) and these findings are useful for risk adjustment. In our study, infarcts at internal capsule and Lt Middle cerebral artery was the common finding on CT.

Treatment protocols in IS aim to prevent immediate life threatening conditions, restore circulation, minimise the neuronal damage, prevent complications, improve/ achieve favourable therapeutic outcome. Our patients were treated with anti coagulants (LMWH), Anti platelets (aspirin), IV Fluids and supportive care (Oxygen sos .prevention of bed sore)

Residual neurological deficit was seen in 64% while total recovery was seen in 36.0%. Only one patient died of aspiration pneumonia. There were no other complications in our patients. This indicates that with appropriate treatment, IS can be well tackled. Early intervention, may help to minimise residual neurological complications.

Women need careful evaluation and support as outcome is poorer, but Dehlendorff C et al concluded that women presented with severe form of IS than men, but have better survival.[20] Severity at initial presentation, older age and presence of multiple associated risk factors in them need physician's attention. Metabolic syndrome, which is more common in women is also a risk factor for IS.

Focus on the modifiable risk factors in the developed countries resulted in the reduction in the IS. With a contrasting scenario in developing countries, the epidemiological shift from infections to chronic diseases, challenges still exist in the early diagnosis as the access to health care is still not available to many. Delayed symptoms and atypical symptoms have to be identified and correlated. Advanced imaging techniques is not only less invasive, but also helps in precise location of in occult lesions of ischemic focus. CT angiography and CT perfusion should be made available at all referral centres. MRI is often useful in determining the clot burden, active bleeding and the state of collaterals.Use of mobile imaging equipments (in ambulance) will help in the diagnosis during pre hospitalization. Apart from controlling these risk factors, life style modifications, we suggest to minimise the delay in reaching the hospital, to increase the awareness among the general public and general practioner to identify these initial symptoms. Patient should be trained adequately to identify symptoms of re stroke and high risk patients should be educated to identify the symptoms of stroke and seek medical assistance at the earliest for better treatment outcome. A regular follow up is required for all patients with IS.

Study on the influence of socio-economic status of the individual during the life suggested that the effect during childhood has positive association with IS. Since most of our patients belong to middle and lower income groups studying this factor would have an impact on the management and outcome.

Conclusions :

Ischemic stroke can occur due to diverse clinical settings and present with protean clinical manifestations. Carotid atheroembolism is the major cause for the Ischemic cerebrovascular accidents. Hypertension, Diabetes mellitus, smoking, alcoholism, dyslipidemia have profound association with ischemic stroke. Cardiac embolus is one of the major cause for the development of IS. Proper treatment of the underlying cardiac condition will prevent the further cerebrovascular accidents.

CT scan brain is an important sensitive, parameter in the evolution of stroke. MCA territory stroke was the commonest stroke. Immediate and proper management measures are to be instituted for the recovery of the patients and for their early ambulation and rehabilitation.

Acknowledgement

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References :

1. Thorn T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart diseases and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.[Published corrections appear in Circulation 2006; 113: e 696 and Circulation 2006 ; 114: e630] . Circulation 2006 ; 113 : e 85 – e 151.
2. Dalal PM. The first Asian Pacific symposium of stroke. Japanese circulation 1981; 46: 621 – 4.
3. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761-75.
4. Aziz ZA, Lee YY, Sidek NN, Ngah BA, Looi I, Hanip MR et al. Gender disparities and thrombolysis use among patient with first-ever ischemic stroke in Malaysia. Neurol Res. 2016;38:406-13.
5. Olamoyegun MA, Akinlade AT, Fawale MB, Ogbera AO. Dyslipidaemia as a risk factor in the occurrence of stroke in Nigeria: prevalence and patterns. The Pan African Medical Journal. 2016;25:72.
6. Katsanos AH1, Fiolaki A1, Markou S1, Markoula S1, Kosmidou M2, Kyritsis AP et al. Ischemic stroke risk factors during Greek economic crisis. Atherosclerosis. 2016;245:118-22.
7. Farah R, Zeidan RK, Chahine MN, Asmar R, Chahine R, Salameh P et al. Prevalence of stroke symptoms among stroke-free residents: first national data from Lebanon. Int J Stroke. 2015;10 Suppl A100:83-8.
8. Saeed E, Ali R, Jalal-ud-din M, Saeed A, Jadoon RJ, Moiz M. Hypercholesterolemia in patients of ischemic stroke. J Ayub Med Coll Abbottabad. 2015;27:637-9.
9. Guerrero-Romero F, Rodríguez-Morán M. Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. Stroke. 1999;30:1787–91.
10. Turin TC, Okamura T, Afzal AR, Rumana N, Watanabe M, Higashiyama A et al. Hypertension and lifetime risk of stroke. J Hypertens. 2016;34:116-22
11. Sare GM, Geeganage C, Bath PM. Cerebrovasc Dis. 2009;27 Suppl 1:156-61
12. Gorelick PB, Rodin MB, Langenberg P, Hier DB, Costigan J. Weekly alcohol consumption, cigarette smoking, and the risk of ischemic stroke: results of a case-control study at three urban medical centers in Chicago, Illinois. Neurology 1989;39:339–43
13. Larsson SC, Scott RA, Traylor M, Langenberg CC, Hindy G, Melander O, et al. Type 2 diabetes, glucose, insulin, BMI, and ischemic stroke subtypes: Mendelian randomization study. Neurology. 2017;89:454-60.
14. Muñoz-Rivas N, Méndez-Bailón M, Hernández-Barrera V, de Miguel-Yanes JM, Jiménez-García R, Esteban-Hernández J et al. Time Trends in Ischemic Stroke among Type 2 Diabetic and Non-Diabetic Patients: Analysis of the Spanish National Hospital Discharge Data (2003-2012). PLoS One. 2015;10:e0145535
15. Osei E1, Fonville S2, Zandbergen AA3, Koudstaal PJ2, Dippel DW2, den Hertog HM. Glucose in prediabetic and diabetic range and outcome after stroke. Acta Neurol Scand. 2017;135:170-5.
16. Woo D, Gebel J, Miller R, Kothari R, Brott T, Khoury J, et al. Incidence rate of first – ever ischemic stroke sub types among blacks : a population – based study. Stroke. 1999;30:2517–22.
17. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 Consecutive Patients Aged 15 to 49 With First-Ever Ischemic Stroke: The Helsinki Young Stroke Registry. Stroke. 2009;40:1195-1203.
18. Al-Hashel JY1, Al-Sabah AA2, Ahmed SF3, Al-Enezi M2, Al-Tawheid N2, Al Mesailekh Z, et al. Risk Factors, Subtypes, and Outcome of Ischemic Stroke in Kuwait: A National Study. J Stroke Cerebrovasc Dis. 2016;25:2145-52
19. Nedeltchev K, Renz N, Karameshev A, Haefeli T, Brekenfeld C, Meier N, et al. Predictors of early mortality after acute ischaemic stroke. Swiss Med Wkly. 2010;140:254-9.
20. Dehlendorff C1, Andersen KK1, Olsen TS2. Sex Disparities in Stroke: Women Have More Severe Strokes but Better Survival Than Men. J Am Heart Assoc. 2015;4. pii: e001967.

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Original Article

Pathogenic Bacterial Isolates from Burn Wound Infection & Their Antimicrobial Susceptibility Pattern in Assam Medical College & Hospital, Dibrugarh

A K Borah[*], K Punam[**], M E Hussain[***], M Kataki[*]

Abstract :

Introduction: Colonization and infection by multidrug resistant microorganism is a major cause of morbidity & mortality in burn patients as mostly they are nosocomial to know. **Objective:** To study the bacteriological profile of burn wound and their antimicrobial susceptibility pattern**. Materials and Methods:** A retrospective study was conducted from July 2015-December 2017 in order to meet the objectives. A total of 190 specimens were received from burn patients from the Department of Plastic Surgery and were processed aerobically. Isolates were identified based on standard microbiological methods and antimicrobial susceptibility testing was done by Kirby Bauer's disc diffusion methods as per CLSI guideline. **Results and Observations:** In the present study, a total of 184 bacterial pathogen were isolated from 190 samples. Most frequent isolates were Mixed bacterial flora (43 %) followed by predominant isolates of *Pseudomonas* (39%); *Klebsiella* (24%); *Proteus* (10%); *Acinetobacter* (6%); *Citrobacter* (5%). MRSA (4%); CONS (2%) ; *Escherichia* coli (2%); Enterococcus (1.6%) & MSSA (1%) of the total sample and 3% showed no growth . High level of drug resistance was observed with Ceftriaxone, meropenem and amoxicillin – clavulinic acid among the Gram negative bacterias and Penicillin, Erythromycin and Cefoxitin among the Gram positive bacterias. Lower drug resistance with Azithromycin, Gentamycin & Ampicillin- sulbactum was observed among Gram negative bacterias whereas, among the Gram positive it was Linezolid, Clindamycin & Ciprofloxacin. **Conclusion:** *Pseudomonas* are the major cause of infection in burn wound showing high level resistance to antimicrobials, emphasizing the need for strengthening the infection control practice and regular & periodic surveillance activities to contain the upward trend of resistance.

Key Words : *Burn; Infection; Patients ; wound; Antimicrobial*

Introduction :

Infection is an important cause of mortality in burns. It has been estimated that 75% of all deaths following thermal injuries are related to infections[1]. Infections remain the leading cause of death among patients who are hospitalized for burns. The risk of burn wound infection is directly correlated to the extent of the burn and is related to the impaired resistance resulting from disruption of the skin's mechanical integrity and generalized immunosuppression. In India, majority of accidental burns are domestic in nature. The rate of nosocomial infections are higher in burn patients due to various factors like nature of burn injury itself, immunocompromised status of the patient, invasive diagnostic and therapeutic procedures and prolonged ICU stay[2].Colonization and infection by multidrug resistant microorganism is a major cause of morbidity & mortality in burn patients causing delayed healing due to formation of multispecies biofilm on wound within 48-72 hours of injury resulting in bacterimia, sepsis and MODS[6]. Burn infections are largely nosocomial, so isolates & antibiogram is necessary for adequate and effective identification.

A retrospective study was undertaken from July 2015-December 2017 to know the bacteriological profile of the burn wound and their antimicrobial susceptibility pattern.

Aims & Objective :

The present study is undertaken with the following aims and objectives:

1. To find out the bacterial profile for post burn infection in pus
2. To evaluate the antibiotic sensitivity of organisms cultured and isolated.

Materials & Methods :

A total of 190 specimens were received from burn patients from the Department of Plastic Surgery and were

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processed aerobically. The age of the patients ranged from one year to over (50) years old. Isolates were identified based on standard microbiological methods and antimicrobial susceptibility testing was done by Kirby Bauer's disc diffusion methods as per CLSI guideline. The specimen swabs were taken from patients in the surgical ward and sent to Department of Microbiology which were cultured directly on blood agar and MacConkey agar aerobically overnight at 37^0C for 24 - 48 hours.. Gram stain ,biochemical tests were done to identify and diagnose the colony morphology of the causative pathogens[3-5].Antimicrobial susceptibility was performed on Mueller-Hinton agar by the standard disk diffusion method recommended by the antibiotics tested for gram-positive cocci were: Ampicillin (10 mg), Cefoxitin (30 mg), Ciprofloxacin (5 mg), Erythromycin (15 mg), Vancomycin (30 mg), Linezolid (30 mg); For gram negative bacilli: Ampicillin (10 mg), Amikacin (30 mg), Gentamicin (30 mg), Ciprofloxacin (5 mg), Piperacillin/Tazobactum(30/10 mg),Imipenem (10 mg) and for non-fermenters ceftazidime, (30 mg), piperacillin (100 mg), cefepime (30 mg), amikacin (30 mg), gentamicin (30 mg), ciprofloxacin (5 mg ,Piperacillin / Tazobactum(75 /30 mg), Meropenem (10 mg) and Imipenem (10 mg) were used.

Result :

This study showed that 136 (71.6 %) were females and 54 (28.4%) were males. The highest number of patients was 80 (42.1%) at age group (20-29) years. The lowest frequently affected was 5(2.6%) and 6(3.1%) at age group (Ã50) and (1-9) years. Out of 190 bacterial isolates; 104 (54.7 %) were isolated in pure culture while 80 (42.1%) showed mixed bacterial growth and 6(3.1%) did not show any growth of organism. The most dominant bacteria among Gram negative bacteria were *Pseudomonas* 72 (37.9 %) followed by *Klebsiella* 45 (23.6%) and *Proteus* 18 (9.5%) and among the Gram positive bacteria were Methicillin resistant *Staphylococcus aureus* 8 (4.2%), Coagulase Negative *Staphylococcus* species 4(2.1%) Enterococcus 3(1.7%). Among the gram negative bacteria highest resistance to drug is with ceftriaxone , Aztreonam, ciprofloxacin, Meropenen & Imipenem and least resistance is shown by Gentamycin & cefotaxim. Colistin is highly sensitive to gram negative bacteria particularly to *Pseudomonas*. Among gram positive bacteria higher resistance is with Penicillin, followed by Erythromycin, Cotrimoxazole, Cefoxitin, Clindamycin and least resistance was with Vancomycin, Linezolid & Tetracycline.

Table 1: Sex-wise distribution of patients

Sex	No. of patients	Percentage
Female	136	71.58
Male 54	28.42	

Table 2: Age-wise distribution of patients

Age in years	No. of patients	Percentage
1-9	6	3.16
10-19	15	7.89
20-29	80	42.11
30-39	63	33.16
40-49	21	11.05
>50	5	2.63

Figure1: Bar diagram showing age-wise distribution of patients

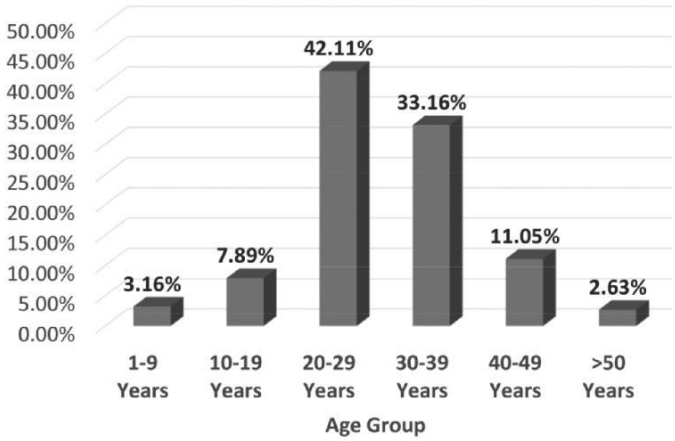

Figure1: Pie-chart showing percentage of isolates for patients

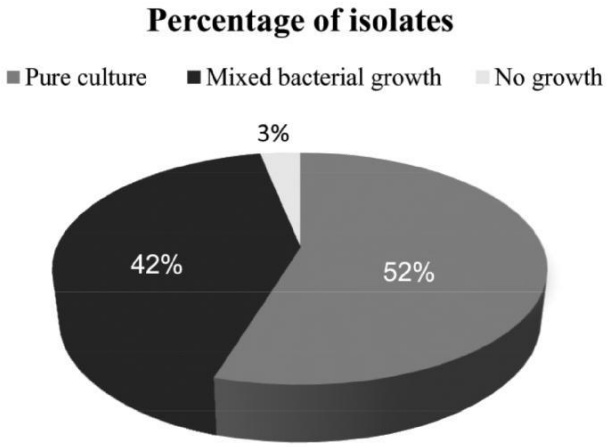

Table 3: Distribution of isolates

Isolates	No. of patients	Percentage
Pure culture	104	54.74
Mixed bacterial growth	80	42.11
No growth	6	3.16

Table 4: Distribution of microorganisms isolated from burns wound

Type of Bacteria	Organism	Number	%
Gram negative bacteria	*Pseudomonas*	72	37.89
	Klebsiella	45	23.68
	Proteus	18	9.47
	Acinetobacter	11	5.79
	Citrobacter	9	4.74
	Escherichia coli	4	2.11
Gram positive bacteria	MRSA	8	4.21
	CONS	4	2.10
	Enterococcus	3	1.57
	Staphylococcus aureus	2	1.05

Table 5. Antimicrobial resistant pattern (%) among bacterial isolates in burn patients.

GRAM NEGATIVE BACTERIA:

Drug	Resistant		Sensitive	
Ceftriaxone	115	71%	46	29%
Aztreonam	100	60%	67	40%
Ciprofloxacin	91	54%	76	46%
Meropenem	87	52%	80	48%
Imipenem	85	51%	82	49%
Amoxicillin/Clavulanate	80	47%	87	53%
Pipercillin/Tazobactum	78	47%	88	52%
Cefotaxime	52	31%	115	69%
Gentamycin	19	11%	148	89%
Colistin	0	0%	167	100%

GRAM POSITIVE BACTERIA :

Drug	Resistant		Sensitive	
Penicillin	14	82%	3	18%
Erythromycin	11	65%	6	35%
Cotrimoxazole	10	59%	7	41%
Cefoxitin	10	59%	7	41%
Clindamycin	9	53%	8	47%
Tetracycline	6	35%	11	65%
Linezolid	1	6%	16	94%
Vancomycin	0	0	17	100%

Discussion :

Burns become infected because of thermal destruction of the skin barrier and concomitant depression of local and systemic host cellular and humoral immune responses (Alexander, 1990)[17]. The burn wound surface is a protein rich environment consisting of avascular necrotic tissue that provides a favorable niche for microbial colonization and proliferation. Despite significant improvement in the survival of burn patients, infectious complication continues to be the major cause of morbidity and mortality. The goal of burn wound management is to reduce the onset and density of bacterial contamination through early microbiological diagnosis, strict isolation technique and proper implementation of infection control policies (Amin and Kalantar, 2004)[18].

In our study, female : male ratio of total burn patients was 2.5 : 1 where females was 136(72%) while in males it was 54(28%) there results were in agreement with the finding of the study by Barrair et al[8] who found that females were commonest than males in burn infection, this may be due to that females were exposed more to burn than males. Other study was also in agreement with this study; Rajput et al.,2008[7] showed that burn infection in females (60%) was more than males (40%) in India. In India higher incidence of burn injuries among females may be related to inadequate precautions during cooking, wearing of loose Indian sarees, inability to cope with the physical and psychological stress of marriage and harassment from parent-in-law (Bilwani and Gupta, 2003).[9]

The mean age of burn patients admitted to hospital was 20-29 years (42%), similar to that of other studies (Akther et al., 2010[10] , Ekrami and Kalantar, 2007[11] and Bagdonas et al., 2004)[12]. High incidence among young adults may be explained by the fact that they are generally active and are exposed to hazardous situations both in home and at work.

In this present study, high culture positivity of 96 % was found in the samples collected from burn patients. This is in agreement with other studies (Ekrami and Kalantar, 2007[11] and Bagdonas et al., 2004[12]). Our finding showed that *P. aeruginosa* (39%) was the most common isolate which coincides with many previous studies within and outside India (Nagoba et al., 1999[13], Rajput et al., 2008[14] and Ekrami and Kalantar, 2007[11]). However, study conducted by Bagdonas et al. had revealed that *S. aureus* (52.1%) was the most predominant isolate (Bagdonas et al., 2004)[12]. Although *S. aureus* remains a common cause of early burn wound infection, *P. aeruginosa* from patient's endogenous gastrointestinal flora or moist environmental source is the most common cause of burn wound infections followed by *K. pneumoniae* (24%) and Proteus species(10%).

Our study showed gram negative bacteria were highly resistant to Ceftriaxone (71%), Aztreonam (59%) & Ciprofloxacin (54%), *Meropenem (52%) and highly sensitive to* Gentamycin (89%) & cefotaxim(69%). Colistin(100%) is highly sensitive to gram negative bacteria particularly to *Pseudomonas*. Multidrug resistant Gram-negative bacilli that possesses several types of beta-lactamases including extended spectrum betalactamases,

ampC beta-lactamases, and metallo betalactamases, have been emerging as serious pathogens in hospitalized patients (Clark et al., 2003)[15].

In our study, 52 percent of *S. aureus* were methicillin resistant (MRSA). This result is in agreement with studies done by Ekrami et al. and Rajput et al. where they had found out 58% and 40% of MRSA isolates respectively. (Rajput et al., 2008[14] and Ekrami and Kalantar, 2007[11]). These MRSA isolates showed 100% susceptibility to both vancomycin and linezolid.

The high percentage of multidrug resistant isolates is probably due to empirical use of broad-spectrum antimicrobials prior to development of infection, extended duration or previous hospitalization and non-adherence to hospital antimicrobial policy. Strict infection control practices i.e., physical isolation in a private room, use of gowns and gloves during patient contact, hand washing before and after each patient visit and appropriate antimicrobial therapy are essential tools to reduce the incidence of infections due to these multidrug resistant organisms (Elliot and Lambert, 1999)[16]. Therefore, routine institutional laboratory surveillance system involving periodic sampling of burn wounds would facilitate the selection and administration of appropriate empirical systemic antimicrobial agents prior to the availability of microbiological culture and susceptibility test results

Conclusion :

To conclude, burn patients were most commonly infected with *P. aeruginosa, Klebsiella* and *S. aureus.* Majority of these isolates were multidrug resistant. In Gram-negative isolates, Gentamycin, piperacillin/ tazobactam & cefotaxim and in Gram-positive, vancomycin or linezolid can be used as empirical antimicrobial therapy prior to the availability of microbiological culture and susceptibility test results. A burn unit-specific nosocomial infection surveillance system may be introduced to reduce the incidence of multidrug resistant infections among burn patients, and for selecting appropriate antimicrobial agents.

REFERENCES :

1. Vindenes H, Bjerknes R. Microbial colonization of large wounds. Burns 1995; 21:575-9.
2. Pruitt Jr BA, McManus AT, Kim SH, Goodwin CW. Burn Wound infections: current status. World J Surg 1998; 22:135-45.
3. Prescott LM, Harley JP, Klein DA. Microbiology. Brown publishers, London. 1990: 214 pp.
4. Garrity GJ, Brenner DJ, Krieg NR, Staley JT. Berages Manual of systematic Bacteriology 2nd edition 2 part A . Springer science Business Media, Inc, New York, USA. 2005.
5. Koneman EW, Allen SD, Janda WM, Schreckenberger PC, Winn WC. Color Atlas & Textbook of Diagnostic Microbiology, 5th edition (Lippincott, Philadelphia). Antimicrobial susceptibility testing. 1997:, Chapter15:785.
6. Rode H, Dovale I, Millar AJW .Burn wound infection, CME.2009 :27(1):26-30.
7. Rajput A, Singh KP, Kumar V, Sexena R, Singh RK. Antibacterial resistance pattern of aerobic bacteria isolates from burn patients in tertiary care hospital. Biomedical Research.2008:19(1):1 -4 .
8. Barrair LM, Vasenwala SM, Malik A, Ansari GH, Chowdhury TE. 199. A clinic- pathological study of infection in burn patients and importance of biopsy. J. Indian Med. Assoc. Nov; 95(11): 573 -575 .
9. Bilwani PK, Gupta R (2003). Epidemiological profile of burn patients in LG Hospital, Ahmadabad. Indian J Burns;11:63-4.
10. Akther JM, Nerker NE, Reddy PS, Khan MI, Chauhan MK, Shahapurkar VV (2010). Epidemiology of Burned Patients Admitted In Burn Unit of A Rural Tertiary Teaching Hospital. Pravara Med Rev;2:11-7.
11. Ekrami A, Kalantar E (2007). Bacterial infections in burn patients at a burn hospital in India. Indian J Med Res;126:541-4.
12. Bagdonas R, Tamelis A, Rimdeika R, Kiudelis M (2004). Analysis of burn patients and the isolated pathogens. Lithuanian Surg;2:190-3
13. Nagoba BS, Deshmukh SR, Wadher BJ, Pathan AB (1999). Bacterioligical analysis of burn sepsis. Indian J Med Sci;53:216-9.
14. Rajput A, Singh KP, Kumar V, Sexena R, Singh RK(2008). Antibacterial resistance pattern of aerobic bacteria isolates from burn patients in tertiary care hospital. Biomed Res;19:1-4.
15. Clark NM, Patterson J, Lynch JP (2003). Antimicrobial resistance among gram-negative organisms in the intensive care unit. Curr Opin Crit;9:413-23.
16. Elliot TS, Lambert PA (1999). Antibacterial resistance in the intensive care unit: mechanisms and management. Br Med Bull;55:259-76.
17. Alexander JW (1990). Mechanism of immunologic suppression in burn injury. J Trauma;30:70-5.
18. Amin M, Kalantar E (2004). Bacteriological monitoring of hospital borne septicemia in burn patients in Ahvaz, Iran. Burn Surgical Wound Care;3:4-8

Original Article

A Study of the Association of Serum Uric Acid levels with ALT and GGT levels in Non-Alcoholic Fatty Liver Disease

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Abstract

Aims and Objectives : 1. Estimation of serum uric acid levels in Non-alcoholic Fatty liver disease (NAFLD)Patients. 2. To study the Co-relation between serum uric acid levels and levels of serum Alanine Amino transferase (ALT) and gamma glutamyl transferase (GGT) in Non-Alcoholic Fatty liver disease (NAFLD) Patients. **Material and Methods :** Total of 300 patients were taken up for the study between 1st July 2015 to30th June 2016 in the department of Medicine ,Assam Medical College and Hospital ,Dibrugarh which is a tertiary care center of upper Assam in North-East India. A detailed history ,clinical examination and necessary investigations were done in all subjects .Patients were selected for the study ,those fulfilling the inclusion and exclusion criteria and necessary informed consent was taken after taking clearance from Ethical committee.

Result and Observation : A total of 300 cases of NAFLD with an age range of 17 to 82 years were analysed in our study with a mean age of 47.3+12.2 and majority of the patients being in the age group of 40-49years. A female predominance was noted among NAFLD patients. About 74.33% of patients of NAFLD cases were found to be type 2 Diabetic patients and the remaining 25.67% cases being non-diabetic patients. A statistically significant association was seen between elevated serum uric acid levels and ALT and GGT. Elevation of GGT levels along with hyperuricaemia was seen in 35 NAFLD patients with mean GGT value of 158.57±19.9U/L showing a significant association between serum uric acid level and GGT levels (p value <0.001) **Conclusion :** Our findings demonstrated significant association between NAFLD (Non-alcoholic Fatty liver disease) and increased serum uric acid levels and Alanine Amino transferase (ALT) and gamma – glutamyl transferase (GGT) levels in NAFLD patients.

Keyword : *NAFLD - non alcoholic fatty liver disease, ALT-Alanine amino transferase,GGT –Gamma glutamyl transferase, NASH-Non alcoholic steato-hepatitis*

Background :

NASH is widely considered to be the hepatic expression of the metabolic syndrome and Cirrhosis due to NASH being an increasingly frequent cause of liver transplantation. There is at present a worldwide epidemic of diabetes and obesity[1] and the numbers are continuing to rise, indicating that NASH will become an increasingly common liver problem in both rich and poor countries, increasing the global burden of liver disease. NAFLD is the cause of asymptomatic elevation of amino transferases in 42–90% of cases once other causes of liver disease are excluded, characterized typically by a hepatocellular pattern of liver-related enzymes with mild elevations (1-2 times the upper limit of normal) in serum alanine amino transferase (ALT) and aspartate amino transferase (AST).The diagnosis of NASH without a liver biopsy remains the most significant clinical challenge in the evaluation of a patient with hepatic steatosis. This poses a great need for new, affordable and rapid methods for early detection of liver fat accumulation in patients at high risk for NAFLD. It is hypothesized that hyperuricemia[2], which strongly reflects and may even cause oxidative stress, insulin resistance, and systemic inflammation, is a risk factor for the development of cirrhosis and in recent years, an association between elevated serum uric acid concentrations and NAFLD has been reported. Some studies have concluded that hyperuricemia is an independent risk factor for NAFLD, and is even related to its histologic severity[3,4,5]. In 1980, Ludwig and colleagues originally coined the term Nonalcoholic steatohepatitis, 'NASH', to describe the morphologic pattern of liver injury in twenty patients

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evaluated at the Mayo Clinic over a 10-year period[6,7,8]. The main lesions described in that study namely, steatosis, liver cell injury, and the unique zone 3 "chicken wire" fibrosis-remain central in establishing the diagnosis. They were the first to use the term 'non-alcoholic steatohepatitis' for this condition, the principal features of which were hepatic steatosis (fatty change), inflammation and exclusion of alcohol as an aetiological factor. Since Non-alcoholic steatohepatitis (NASH) was first identified in 1980, it has been increasingly recognized. Further small case series were published during the next 15 years. Thus, Marchesini and Forlani were able to locate only 161 articles which addressed this topic between 1980 and 1999 but 122 articles were found in 2000-01. The pace of research into the pathogenesis, natural history and treatment of NAFLD/NASH has accelerated in the last few years[9-14]. However, no study from the North-Eastern part of the country has yet been done to determine the association of Serum Uric acid levels with ALT and GGT levels in Non-Alcoholic Fatty Liver Disease.

Methodology :

With a view to understand the association between Serum Uric Acid levels and ALT and GGT levels in NAFLD patients, a Hospital Based Cross Sectional Observational Study was done on a sample size of 300 patients for the time period of 1 year from July 2015 to June 2016 in the Dibrugarh District of Assam, North-East India. Reports of Basic Liver Function tests (ALT and GGT) and Serum Uric Acid obtained from Blood Sampling by Venipuncture, Ultrasonography of Abdomen (USG W/ A) and Computed Tomography (CT) Abdomen (Optional), were included in the analysis of the study.

Statistical Analysis of the study was done by Pearson's co-relation study and Independent sample Student T-TEST

Pearson's co- relation was used to see the co-relation between serum uric acid levels and levels of serum Alanine Amino transferase (ALT) and gamma glutamyl transferase (GGT) in Non-Alcoholic Fatty Liver disease (NAFLD) patients and Independent Student T-TEST were used to compare the mean difference of elevated GGT with and without hyperuricaemia.

CRITERIA FOR SELECTION :

Inclusion Criteria:

- All patients >13 years of age diagnosed as Non-Alcoholic Fatty Liver Disease(NAFLD) cases, who attended the Medicine Outpatient and inpatient Department, Gynaecology Out patient Department and Diabetic Clinic in Assam Medical College and Hospital, Dibrugarh, were included.
- Type 2 diabetics
- Overweight and obese individuals (BMI>=25kg/m2).
- Females with polycystic ovarian Disease (PCOD)

Exclusion Criteria:

- Age <13.
- Patients with history of Alcohol Abuse.
- Liver Disorders (Cirrhosis, Wilson disease, Hepatitis etc.), renal disorders, congestive cardiac failure, pregnant women, Women on Oral Contraceptive pills.
- Patients on drugs such as Amiodarone, Methotrexate. Tamoxifen/ synthethic estrogens, Glucocorticoids, Calcium channel blockers.
- Patient with known history or diagnosed case of Gout or Rheumatoid Arthritis.

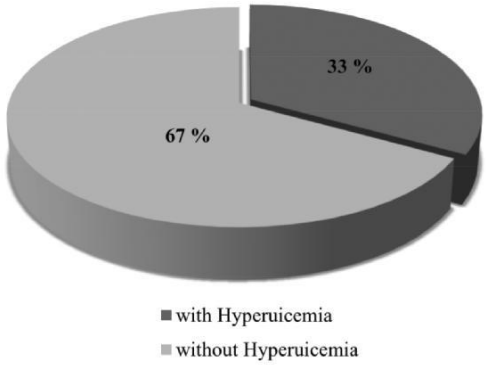
Results and observation :

A total of 300 cases of NAFLD with an age range of 17 to 82 years were analyzed with a mean age of 47.31± 12.26 years and majority of the patients being in the age group of 40-49 years. A female predominance was noted among NAFLD patients; the number of males and female patients being 124 and 176 respectively.74.33% of the NAFLD cases were found to be Type 2 Diabetics, and the remaining 25.67% cases being non-diabetic patients of NAFLD. A statistically significant association was seen between elevated Uric acid levels and ALT and GGT levels in males (p value < 0.05 for both); ALT levels being elevated in 17 out of 38 male patients (44.74%) with hyperuricemia with a mean value of 77.95±24.62 U/L and a median value of 73.5U/L and GGT levels elevated in 15 out of 38 male patients (39.47%) with hyperuricemia with a mean value of 97.95±45.61 U/L and a median value of 81 U/L. There was also a statistically significant association seen between elevated Uric acid levels and ALT and GGT levels in females (p value < 0.05 for both); ALT levels being elevated in 21 out of 61 female patients (34.43%) with hyperuricemia with a mean value of 78.34±31.34 U/ L and a median value of 66 U/L and GGT levels elevated in 20 out of 61 female patients (32.79%) with hyperuricemia with a mean value of 100.28±44.43 U/L and a median value of 80 U/L. A statistically significant association was seen with raised uric acid levels in both male and female diabetic patients (p value < 0.05 for both).Hyperuricemia was observed in 99 cases out of a

total of 300 cases of NAFLD (33%), with a statistically significant association between the two (p value <0.001). Elevation of ALT levels along with hyperuricemia was observed in 38 NAFLD patients with a mean ALT value of 110.53± 16.69 U/L as compared to a mean value of 94.33 ± 11.49 U/L in patients with Normal Serum Uric acid levels (n = 55). Thus, a significant association between Serum Uric acid and ALT levels was observed (p value < 0.001).Elevation of GGT levels along with hyperuricemia was seen in 35 NAFLD patients with a mean GGT value of 158.57± 19.97 U/L as compared to a mean value of 124.96 ± 20.42 U/L in patients with Normal Serum Uric acid levels(n =77). Thus, a significant association between Serum Uric acid and GGT levels was observed (p value <0.001).

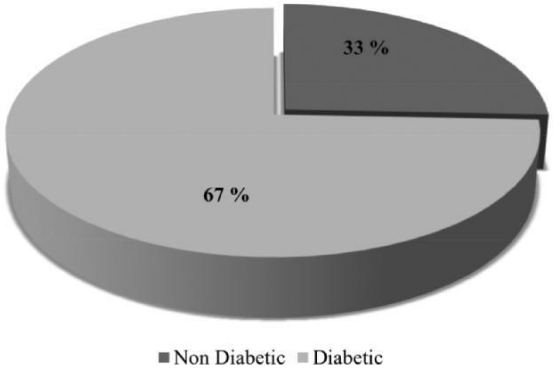
Association Between Non Alcoholic Fatty Liver Disease and Serum Uric Acid Levels

	Total No. of Cases	Hyperuricemia		
		With n (%)	Without n(%)	p value
NAFLD	300	99(33%)	201(67%)	<0.001



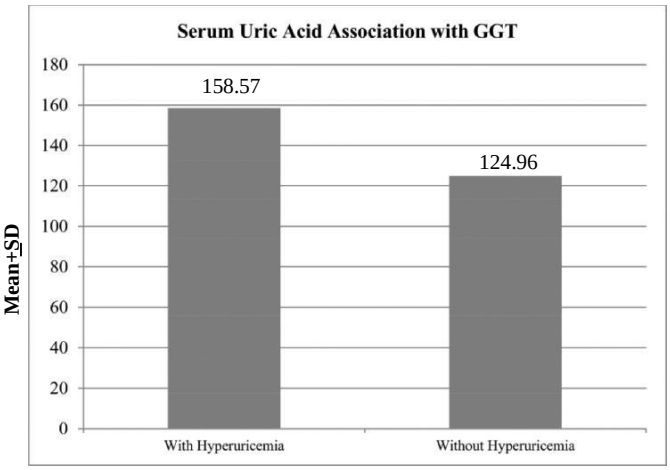
Diabetic / Non-Diabetic Patients among NAFLD Porulation

Diabetic/ Non-Diabetic	Number (n)	Percentage (%)
Diabetic	223	74.33
Non-Diabetic	77	25.67
TOTAL	300	100.00



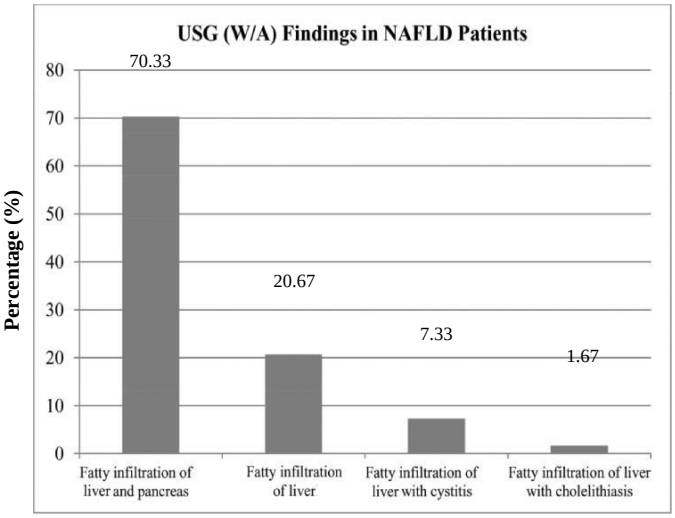
Association of Serum Uric Acid with GGT Levels

	With Hyperuricaemia (n=35) (Mean+SD)	Without Hyperuricaemia (n=77) (Mean+SD)	p value
Elevated GGT (U/L)	158.57+19.97	124.96+20.42	<0.001



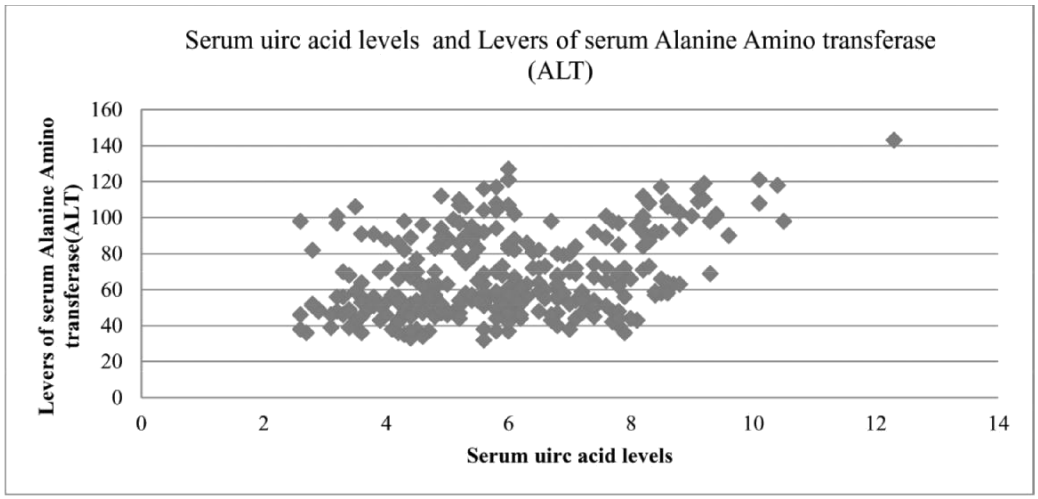
USG Whole Abdomen Findings

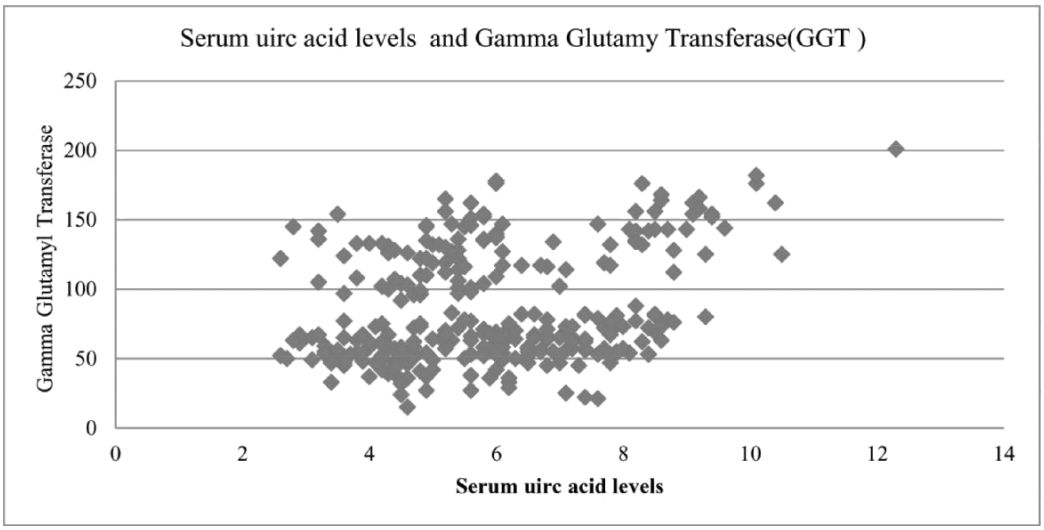
USG Whole Abdomen	No. (n)	Percentage (%)
Fatty infiltration of liver & pancreas	211	70.33
Fatty infiltration of liver	62	20.67
Fatty infiltration of liver with cystitis	22	7.33
Fatty infiltration of liver with cholelithiasis	5	1.67



Co-relation between serum uric acid levels and levels of serum Alanine Amino transferase (ALT) and gamma glutamyl transferase (GGT) in Non-Alcoholic Fatty liver disease (NAFLD) Patients.

		ALT	GGT
Uric Acid	Pearson Correlation	0.385	0.300
	Significance	0.000	0.000





Discussion :

The present study was carried out in three hundred cases of Non-Alcoholic Fatty Liver Disease (NAFLD) to see the prevalence of hyperuricaemia in NAFLD patients as well as to study the association of hyperuricaemia and increase Alanine Aminotransferase (ALT) and Gamma Glutamyl Transferase (GGT) levels in patients diagnosed as NAFLD by imaging studies.

In our study, majority of the participants were in the age group of 40-49 years .The mean age of male NAFLD patients was found to be 45.99±10.04 years while that of female NAFLD patients was 48.24±13.56 years in our study, there was a total of 176 females and 124 male with female : male ratio of 1.42 :1. There was a female predominance in all age groups. These statistics were in accordance to a Cross sectional study by Nomura et al in 1988 and Kojima et al in 2003.

In our study, majority of the patients , i.e., 79% were in the overweight category (BMI 25-29.9) while 21% were in the obese category (BMI 30-34.9). In a recent consensus meeting in Delhi, it was seen that central or abdominal obesity is more commonly associated with insulin resistance and has been observed in 80-90% of Indian patients with NAFLD.[1]

It was observed that out of 300 patients enrolled in the study, 223 were diagnosed cases of type 2 Diabetes Mellitus, which comprised 74.33% of the study group while remainder 77 patients (25.67%) had no history of Diabetes .The means HBA_1C level was 6.69±1.91% while 7.39±1.79% in diabetics and 4.94±0.65% in non – diabetics. In the studies done by Prashanth M et al in 2009, the ultrasonography results of 204 patients with type 2 diabetes mellitus showed fatty infiltration in 62.2% of patients. Steatohepatitis and fibrosis were found in 38.9% and 23.2% respectively, of Indian patients with type 2 diabetes mellitus. Leite et al found a 78% NASH prevalence at the histological examination in nearly 100 patients with type 2 diabetes mellitus and ultrasound evidence of NAFLD. Similar prevalence of nonalcoholic fatty liver disease (NAFLD) and its clinical correlates in a population of patients with type 2 diabetes mellitus was seen by Forlani et al and Mhetre B et al in 2016 where NAFLD was associated with 47.5% of type 2 diabetes mellitus patients.[15,16,17]

The prevalence of increased uric acid levels in the NAFLD population was formed in 99 out of the 300 patients (33%) which included 38 out of 124 male patients (12.66%) and 61 out of 176 female patients (20.33%) which was statistically significance ($p<0.01$). This is in accordance with previous studies done by Sertoglu et al in 2014 where the prevalence of hyperuricaemia was found to be 33.4%. Petta S et al observed that about 20% of

the patients had hyperuricaemia, that was independently associated with younger age and lobular inflammation.

The prevalence rates of NAFLD determined by abdominal ultrasound examination in a study done by Cai et al and hyperuricaemia were 43.9% and 8.4%. respectively with the NAFLD patients having significantly higher serum uric acid levels than those without NAFLD (p value<0.001). The prevalence rate of NAFLD was significantly higher in subjects with hyperuricaemia than those without hyperuricaemia (78.19% versus 40.83% p value<0.001), and the prevalence rate increased with progressively higher serum uric acid levels (p value < 0.001). Prevalence of hyperuricaemia was 53.2% in a 2016 study done by Huang Q et al and in a study conducted by Azharuddin et al 2016, it was seen that Mean SUA were significantly higher in patients with NAFLD (p value <0.001).

The proportion of NAFLD was 29.4% (33.9% in men and 23.5% in women) in a study done by Valiyakath et al in 2015 and in multivariate logistic regression analysis, an independent association between serum uric acid concentrations and the presence of NAFLD was observed. Similar association of hyperuricaemia and NAFLD was shown in the studies done by Lee et al and Afzali et al in 2010[12].

An important significant association was seen with elevated levels of Alanine Amino Transferase (ALT) and Gamma Glutamyl Transferase (GGT) in male patients with elevated serum uric acid levels ALT levels being elevated in 17 out of 38 (44.78%)of male hyperuricaemic patients (<0.001).

On observing the female patients with elevated uric acid levels, the mean serum uric acid levels was 7.73±1.13 µg/dl, on observing the association of hyperuricaemia with increasing age and BMI, a significant association was seen, the mean age and BMI in hyperuricaemic females being 57.72±12.43 yrs and 29.85±1.77 kg/m^2 (p<0.001 for both).

The elevation of Alanine Amino Transferase (ALT) and Gamma Glutamyl Transferase (GGT) in female patients with elevated uric acid levels; ALT levels were elevated in 21 out of 61(34.43%) of female hyperuricaemic patients (p value <0.013) and GGT were elevated in 20 out of 61(32.79%) of female hyperuricaemic patients. There was a significant association between elevated uric acid levels uric ALT and GGT levels. These findings were in accordance with the studies done by Li C et al 2013, Katsiki N et al 2013 and Richette P et al 2013 where a significant association was shown between hyperuricaemia and diabetes risk. The study done by Dehghan et al in 2007 also suggests that serum uric acid is a strong and independent risk factor for diabetes. Similar findings were observed by Nagendra S et al in a 2014 study as well as in the study titled 'The study of prevalence of hyperuricaemia and metabolic syndrome in type 2 diabetes mellitus', done by Mundhe S et al in 2016. The Association between Raised Serum Uric acid levels and ALT and GGT levels was previously shown in a Prospective Observational Study done by Chengfu Xu et al in 2010 where it was observed to be significant.

In the study done by Afzali et al in 2010[12], data was derived from the first National Health and Nutrition Examination Survey (NHANES I) and also from the NHANES II (1988-1994) study and NHANES III(1999-2006) study to determine whether the serum UA level was associated with elevated serum alanine aminotransferase (ALT) or Gamma-glutamyl transferase (GGT), two markers of hepatic necro-inflammation. The study showed that a higher serum Uric Acid level was associated with greater mean serum ALT and GGT levels and a greater probability of elevated serum ALT and GGT which led to the conclusion that the serum Uric Acid level is associated with the development of cirrhosis and the presence of elevated serum liver enzymes after adjustments for important causes and risk factors for chronic liver disease. Our study was in accordance with these studies as well as with the most recent study done by Shuang Chen et al, where a total of 7.4% participants had elevated ALT levels and the prevalence of hyperuricaemia was 14.9% in males and 7.3% in females. There was a significantly positive dose-response association between serum uric acid levels and the prevalence of elevated ALT.

However, this study was not without limitation firstly, the study was single centered cross sectional and observational hospital based study and was done within a short period of one year.

Secondly, although liver biopsy is regarded as the **gold standard** for diagnosis of NAFLD, our diagnosis was based on ultrasound examination, which is an eliminative diagnosis that notable positive differentiate non -alcoholic steatohepatitis (NASH) from fibrosis and has a sensitivity of 67-89% and specificity of 77-89%. However; liver biopsy is a invasive procedure in the standard clinical setting.

Thirdly; the amount of alcoholic intake and exercise was measured by a questionnaire. So that it is likely that this method introduced a measurement bias.

Finally, we did not adjust for lifestyle or dietary factors, such meat intake and fructose intake that may contribute to increase uric acid levels and NALFD.

Conclusion :

Our findings demonstrated an independent association between Non-alcoholic Fatty Liver Disease (NAFLD) and increased Serum Uric Acid (SUA) levels as well as a significant association between Serum Uric Acid levels and Alanine Amino-transferase (ALT) and Gamma Glutamyl-transferase (GGT) levels in NAFLD patients in a small North - Eastern Indian population . For Alanine Amino transferase (ALT) ($r=0.385$, $p<0.05$) and gamma glutamyl transferase (GGT) ($r=0.300$, $p<0.05$, we have found that there is a positive significance and correlation between serum uric acid with Alanine Amino transferase (ALT) and gamma glutamyl transferase (GGT) in Non-Alcoholic Fatty liver disease (NAFLD) patients. Although Hyperuricemia has previously been clearly associated with alcohol consumption, obesity, insulin resistance, systemic inflammation, and metabolic syndrome, the associations that our study has described with elevated liver enzymes (ALT and GGT) persisted after adjustments for these conditions. NAFLD is now recognized worldwide as an important cause of chronic liver disease (CLD) and the disease burden is increasing rapidly[19,20,21]. Further studies are needed to investigate whether this association is causal and has any clinical utility in the prediction of the presence or incidence of Non-alcoholic Fatty Liver disease, as observational studies such as ours cannot definitively distinguish between these two possibilities. However, it may be potentially useful to investigate longitudinally whether hyperuricemia is **a cause or a marker** for disease outcomes in NAFLD. If this is confirmed, further consideration can be given to measures that reduce the serum Uric Acid levels as a means of preventing NAFLD in patients with elevated levels of Uric Acid and Liver enzymes.

References:

1. Wanless IR, Lentza JS. Fatty liver hepatitis (Steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990; 12: 1106-1110.
2. Li C, Hsieh M, Chang S. Metabolic syndrome, diabetes, and hyperuricemia Current Opinion in Rheumotology .2013; 25(2) : 210-216.
3. Richette Perez- Ruiz F. Serum uric acid and metabolic risk. Current Medical research and Opinion . 2013; 29 9sup3): 9-15.
4. Sertoglu E, Ercin C,Celebi G, Gurewl H, Kayadibi H, Gene H *et al.* The relationship of serum uric acid with non-alcoholic fatty liver disease. Clinical Biochemistry. 2014;47(6): 283-388.
5. Dehghan A, van Hoek M, Hofman A. High serum uric acid as a novel factor for type 2 diabetes . Diabetes care 2008; 31: 361-362.
6. Ludwig J,Viggiano TR,McGill DB,Oh BJ:Nonalcoholic Steatohepatits: Mayo clinic experiences with a hitherto unnamed disease. Mayo clin Proc1980;55(7):434-438.
7. Marchesini G,Forlani G. NASH: From liver diseases to metabolic disorders and back to clinical hepatology .Hepatology 2002;35:497-499.
8. Metteoni C, Younossi Z, Gramlich T, Boparai N, Liu Y, Mccullough A. Nonalcoholic fatty liver disease : A spectrum of clinical and pathological severity , gastroentology . 1999; 116(6): 1413-1419.
9. Lohsoonthorn V, Dhanamun B, Williams MA. Prevalance of hyperuricemia and its relationship with metabolic syndrome in Thai adults receving annual health exams. Archives of Medical Research. 2006; 37: 883-889.
10. Sui X, Church TS, Meriwether RA, Lobeto F, Blair SN. Uric acid and the development of metabolic syndrome in woman and men. Metabolism 2008; 57: 845-852.
11. Lee J , Cho Y, Ryan M, Kim H, Lee S, Chang E et al. Serum Uric Acid as a Predictor for the Development of Non-alcoholic Fatty Liver Disease in Apparently Healthy Subjects: A 5-Year Retrospective Cohort Study. Gut and Liver. 2010;4(3):378-383.
12. Afzali A, Weiss N, Boyko E, Ioannou G. Association between serum uric acid level and chronic liver disease in the United States. Hepatology.2010;52(2):578-589.
13. Xu C, Yu C, Xu L, Miao M, Li Y. High Serum Uric Acid Increases the Risk for Nonalcoholic Fatty Liver Disease: A Prospective Observational Study. PLoS ONE. 2010;5(7):e11578
14. Valiyakath DM D.Association Between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease in a Tertiary Care Center in Northern Kerala, India. ISSN 2015;4(12).
15. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T et al. Prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Journal of Association of Physicians of India. 2009;57;205-210.
16. Mundhe S, Mhasde D. The study of prevalence of hyperuricemia and metabolic syndrome in type 2 diabetes mellitus. International Journal of Advanced Medicine. 2016;241-249.
17. Sanyal D, Mukherjee P, Raychaudhuri M, Ghosh S, Mukherjee S, Chowdhury S. Profile of liver enzymes in non-alcoholic fatty liver disease in patients with impaired glucose tolerance and newly detected untreated type 2 diabetes. Indian Journal of Endocrinology and Metabolism.2015;19(5):597.
18. Chen S, Guo X, Yu S, Sun G, Yang H, Li Z et al. Association between Serum Uric Acid and Elevated Alanine Aminotransferase in the General Population. International Journal of Environmental Research and Public Health. 2016;13(9):841.
19. Bacon BR, Farahvash MJ, Janney CG, NeuschwanderTetri BA. Non-alcoholic steatohepatitis: an expanded clinical entity. Gasemtrology 1994: 107: 1103-1109.
20. Singh S, Panigrahi M. Guidelines for Assessment and Management of Nonalcoholic Fatty Liver Disease in Indians Gastroenterology. 2013.
21. Petta S, Camma C, Cabibi D, Di Marco V, Craxi A. Hyperuricemia is associated with histological liver damage in patients with non-alcoholic fatty liver disease. Alimentary Pharmacology & Therapeutics. 2011;34(7):757-766

Review Article

Macrophage Activation Syndrome : An update

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1. Introduction :

Macrophage activation syndrome (MAS) is a severe and life-threatening complication of several systemic inflammatory disorders. It primarily occurs as a complication of systemic juvenile idiopathic arthritis (sJIA), and its adult equivalent, adult-onset Still's disease (AoSD)[1]. However, MAS has also been found to occur in Kawasaki disease, childhood systemic lupus erythematosus (SLE) and autoinflammatory syndromes and various vasculitic syndromes[1]. Hadchouel *et al*. in 1985, first described this phenomenon as a syndrome characterized by neurologic, hepatic, hemorrhagic and metabolic manifestation brought about by unchecked production and activation of macrophages[2]. In 1993, the same investigators proposed the term MAS for this novel albeit life-threatening condition[3]. SJIA and MAS are now thought to be two extremes of the same disease entity, where sJIA represents hidden or inactive MAS[4].

MAS can occur at any time during the course of the disease in sJIA- at onset, during active disease, during change of medications and during remission. The presentation of MAS is acute and often dramatic. A patient with chronic or quiescent disease becomes acutely ill presenting with high grade, unremitting fever, hepatosplenomegaly, and lymphadenopathy. There is profound depression of one or more blood cell lines, low erythrocyte sedimentation rate (ESR), elevated C-reactive protein, liver enzymes, a high concentration of triglycerides, lactate dehydrogenase, low serum sodium levels, abnormal coagulation profile, hypofibrinogenemia, and increase in fibrin degradation products[5]. The pathognomonic feature of this syndrome is seen on bone marrow examination which reveals numerous well-differentiated macrophages actively phagocytosing hematopoietic cells. Such cells may be found in various organs and may be responsible for many of the systemic features in this condition[6].

The exact cause of MAS is not properly understood. It shares many clinical characteristics with primary hemophagocytic lymphohistiocytosis (HLH) and as such is now-a-days considered an acquired or secondary HLH disorder[7]. HLH and MAS share similar functional defects in the granule dependent cytotoxic lymphocyte activity. There is persistent lymphocyte activation associated with the production of large amounts of IFN-ã and granulocyte – macrophage colony stimulating factor (GM-CSF). This leads to uninhibited macrophage activation followed by a cytokine storm mainly due to TNFá, IL-1, IL-6 and IL-18 which produce various clinical manifestations of MAS and tissue damage[8,9].

At present there is no validated diagnostic criteria for MAS. This poses considerable difficulties in early identification of cases. MAS in the setting of sJIA can be confused with disease exacerbations, infections or side effects of medications. During the early phase when the joint manifestations of sJIA have not presented, it becomes difficult to differentiate between primary HLH and MAS. If unrecognized, MAS can lead to progressive multi-organ failures and fatal outcome. The mortality rate is reported to be 20-30%[10]. Thus validated diagnostic criteria is necessary for the timely diagnosis of MAS and prompt initiation of therapy.

2. Epidemiology :

The exact incidence of MAS in childhood systemic inflammatory diseases is not known. Now-a-days, the syndrome has been increasingly recognized due to increased awareness among the physicians. Approximately 7-17% of patients with sJIA are complicated with MAS[1]. However subclinical MAS can occur in 30-40% of patients with sJIA[10]. MAS can be seen in 1% of patients with SLE[1].

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The highest incidence of MAS occurs in children, but patients of any age can be affected. There is no definite gender or racial predilection in MAS[1,10].

In a recent and the only multinational and multicentre study[10] in 362 patients with sJIA associated MAS from 33 countries, observed that females (57.5%) outnumbered males, the median age at onset of systemic JIA was 5.3 years and the median duration of systemic JIA at MAS onset was 3.5 months. In 22.2% of the patients, MAS occurred at the onset of sJIA. These patients were younger, had a lower frequency of central nervous system (CNS) involvement, admission in intensive care unit and death and had a higher erythrocyte sedimentation rate (ESR).

MAS has been reported in a minority of patients with adult-onset Still's disease[11]. It generally develops early during the disease course and mostly occurs during active disease. However, occasionally it can be the presenting manifestation of the disease and may also occur during phase of remission.

3. Pathophysiology of MAS :

MAS bears close similarities with primary or familial HLH (pHLH), both in clinical and laboratory parameters. pHLH consists of cases with inherited monogenic disorders[12] while sHLH complicates various medical conditions like infections, malignancies, and rheumatic diseases. At present, MAS is classified among acquired or secondary forms of hemophagocytic lymphocytosis (sHLH) in the classification of histiocytic disorders[13]. The term MAS is used typically in the setting of rheumatological disorders.

3.1 Triggers for development of MAS

Several conditions can act as trigger factors for the development of MAS. In the study conducted by Minoia *et al*, active sJIA or flare had triggered the development of MAS in 51.7% of patients[10]. Infection was a trigger factor in 34% of patients and Epstein-Barr virus was the most common organism[10]. Additional typical triggers include flare-up of the underlying disease, change in therapy or treatment side effects, e.g., aspirin or other non-steroidal anti-inflammatory drug (NSAID) toxicity or sulfasalazine therapy, treatment of sJIA with TNFá blocker – etanercept or IL-6 receptor blocker-tocilizumab[1,14]. A possible relationship between MAS and methotrexate (MTX) toxicity has also been suggested[15]. MAS may, however, occur without any identifiable precipitating factor.

3.2 Genetic predisposition

Primary HLH is caused by a mutation in genes that code for proteins that are involved in perforin-mediated cytolytic function. These proteins may be involved directly in cytotoxicity, in vesicle transport or fusion with the plasma membrane. Mutations in these genes predispose patients with pHLH to develop hemophagocytosis. The distinction between pHLH and sHLH is becoming blurred due to the discovery of new genes in both conditions[16]. Though most of the patients with pHLH manifest early (as early as 2 months) some of these genes are associated with milder disease and can manifest later in life. Pathogenic mutations in PRF1, MUNC 13-4, Syntaxin 11 or STX11 and Syntaxin-binding protein 2 or STXBP2 (also known as MUNC18-2) and RAB27a are integral to the pathogenesis of HLH[16,17]. PRF1 encodes perforin which is responsible for 15-40% of cases with pHLH. MUNC 13-4 encodes a protein which is responsible for docking and fusion of cytotoxic granules to the cytoplasmic membrane. Patients with a mutation in this gene may have sufficient amount of perforin but have poor ability to deliver cytotoxic granules to immunological synapse with target cells. MUNC 13-4 mutation is responsible for 10-30% of patients with pHLH. STX11 and STXBP2 are recently discovered genes that code for proteins involved in vesicle transport and fusion[16]. Kaufman *et al*. performed whole genome sequencing in 14 cases of MAS in the context of sJIA and found that 5 out of 14 patients (36%) were heterozygous for at least one mutation of the known genes related to pHLH[18]. Other studies performed thereafter also found hypomorphic variants or pathogenetic heterozygous mutations in MUNC 13-4 and PRF 1 in patients with sJIA associated with MAS[1]. There appears to be a significant role of genetics on the recurrence of the disease as well. The clinical and laboratory features of MAS in patients carrying the above mutations do not differ much from those that do not carry such mutations. However, recurrences appear to be more frequent in patients who carry the mutations[1,19].

Recent studies have suggested possible role of genes in macrophage hyper responses. A recent study from Japan suggested that polymorphism in interferon regulatory factor 5 (IRF5) is associated with the risk of MAS in patients with sJIA[20]. Experiments with animal models (mice) showed that repeated stimulation of toll-like receptor 9 (TLR 9) produces some features of MAS[16]. In a recent observation, a gain of function mutations of NLRC4, an inflammasome sensor, thought to be a regulator of IL-18

production, has been found to be associated with recurrent or dramatic HLH[21].

3.3 Pathogenic mechanisms of development of MAS

Cytotoxic T cells (CTLs) i.e., CD8+ T -cells, contain granules consisting of pore-forming protein, perforin, and several serine proteases called granzymes. Activation of CTL is associated with mobilization of its granules to the surface via the activity of the microtubule organizing center. There is fusion of the vesicles with the outer membrane. This is followed by the release of perforin monomers and granzyme proteases in the space at the junction between the killer and the target cell. Perforin mediates the formation of pores at the cell membrane of the target cells. Inside the cytoplasm of the target cell, granzymes induce apoptosis[7, 22]. In MAS there is a defect in the cytotoxic mechanism of natural killer (NK) cell and CTLs. Defects in cellular assembly, cytoskeletal organization, and pore formation is thought to be the mechanism responsible for the defect in cellular cytotoxicity in these patients. However, exact mechanisms of this cytotoxic dysfunction and its link to the expansion of macrophages are not clear[3,17]. One possible mechanism as described in the literature is that defective cytotoxicity of NK cells and CTLs impair the clearance of infected cells and may prolong lymphocyte–antigen-presenting cell interactions leading to increased proliferation and activation of T cells with exaggerated production of proinflammatory cytokines like IFN-ã and GM-CSF. Prolonged stimulation of monocytes by these cytokines lead to excess activation and differentiation into hemophagocytic macrophages (Fig. 1). These activated

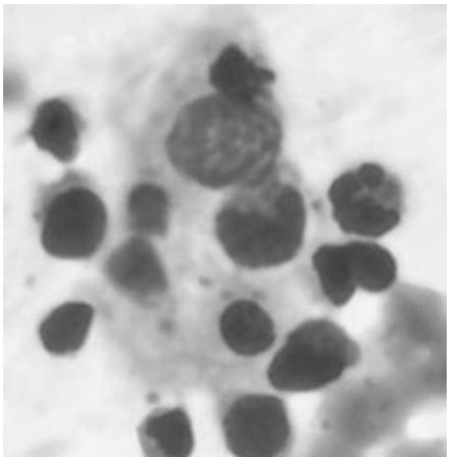

Fig. 1: A hemophagositic macrophage in macrophage activation syndrome.

macrophages, in turn, produce proinflammatory cytokines like IL-1, IL-6, IL-18, and TNF-á.This results in a profound cytokine storm and blood cell hemophagocytosis by CD163+ macrophages bringing about the clinical and laboratory features of HLH/MAS[15,22]. Tissue factor (TF) liberated by these macrophages and TNF-á act on vascular endothelial cells to produce coagulopathy[17].

3.4 Mechanism of hyperferritinemia in MAS

Ferritin is an acute phase protein elevated in any inflammatory conditions. In MAS-related to sJIA, it reaches extremely high levels. The activated macrophages in MAS expresses a scavenger receptor CD163 (sCD163) on their surface. The only known function of this receptor is to bind hemoglobin-haptoglobin (Hb-Hp) complexes. Excess binding of CD163 to Hb-Hp complexes result in increased endocytosis of hemoglobin (Hb) to the cytoplasm of these activated macrophages where heme is degraded to liberate free iron (Fe^{2+}). Excess Fe^{2+} produces oxidative stress inside the cell. To prevent cell damage exerted by oxidative stress Fe^{2+} is sequestered by ferritin. Increased uptake of Hb-Hp complexes by CD163 lead to excess production of ferritin which results in hyperferritinemia[1].

4. NOVEL BIOMARKERS OF MAS

Some new biomarkers with promising diagnostic potential have been recently studied. Among these soluble IL-2 receptor á chain (sIL-Rá, or sCD25) and soluble CD163 (sCD163) has been found to be significantly higher in the acute phase of MAS compared to untreated new-onset sJIA patients and were found to correlate with disease activity[23]. sIL2Rá and sCD163 are expressed on the surfaces of activated T-cells and macrophages respectively. Some of these receptors shed into the circulation leading to increased levels of these proteins during the acute phase of MAS[1,13]. Assessment of their levels can also identify patients with subclinical MAS.

Follistatin–related protein 1 (FSTL-1) levels is another marker which is elevated in active sJIA but to a greater level during MAS and has been found to normalize after treatment[24]. IL-18 is another marker which is found to be significantly elevated in the serum of patients with MAS than in patients with infection-related HLH and KD. It was suggested that IL-18 may be a specific marker for MAS in sJIA[13]. The ratio of ferritin to ESR was recently found to be a good identifier of MAS in the setting of systemic JIA, with a ratio of >80 providing optimal sensitivity and specificity[24].

Serum and urine â2 microglobulin is another marker which is markedly elevated in patients during episodes of MAS. It is the only possible biomarker that was studied in

urine[13]. Similarly the levels of serum neopterin and sTNF–RII, believed to reflect immune activation have also been studied in MAS in relation to sJIA, infection and KD[25].

5. CLINICAL FEATURES OF MAS

The onset of MAS is dramatic. Changing of usual quotidian fever pattern of sJIA to continuous fever heralds the onset of MAS .There can be a relative improvement of joint symptoms like swelling and pain at the onset of MAS. Mental changes, hemorrhagic manifestations, generalized lymphadenopathy, and hepatomegaly are other common clinical features of MAS. The clinical picture closely resembles a case of bacterial sepsis[1,10].

Minoia *et al*. in a cohort of 362 patients with sJIA associated MAS reported fever as the most common manifestation occurring in 96% patients[10]. The common clinical and laboratory findings at the onset of MAS in the cohort are given in Table 1.

Table 1: Clinical manifestations of MAS at its onset. Adapted from observations of the study by Minoia et al [10].

Parameter	% of patients
Fever	96.1
Hepatomegaly	70
Splenomegaly	57.9
Lymphadenopathy	51.4
Active arthritis	65
CNS involvement (Lethargy, seizures, irritability, confusion, headache, mood changes, coma)	35
Cardiac involvement (Pericardial involvement, arrhythmia, heart failure, cardiomegaly)	25.5
Lung involvement (Pleural effusion, respiratory failure, pneumonia, interstitial infiltrates, pleurisy, pulmonaryhemorrhage, acute respiratory distress syndrome)	21.9
Hemorrhagic manifestations (Petechiae, ecchymosis, or purpura, mucosal bleeding, gastrointestinal bleeding, disseminated intravascular coagulation)	20.4
Renal involvement (Renal failure, proteinuria, hematuria)	15.3

6. LABORATORY ABNORMALITIES IN MAS

High index of clinical suspicion and careful observation at changing trend of laboratory parameters can only help in early recognition of MAS. There is precipitous fall in e”2 blood cell lines. Fall in platelet count is the most common early finding in MAS. ESR shows a sharp drop and CRP is markedly elevated[1,10,16]. Fall in ESR reflects fall in fibrinogen levels. Other abnormalities are elevated transaminases, triglyceride level, lactate dehydrogenase (LDH) and D-dimers. Marked elevation of serum ferritin (often more than 10,000 µg/L) is a characteristic laboratory feature in MAS[1]. Bone marrow or other tissues like the lymph node, liver and spleen may demonstrate characteristic hemophagocytosis seen in this syndrome (Fig.1). However florid MAS can occur in the absence of demonstrable tissue hemophagocytosis. This is a late finding in the course of MAS and found only in approximately 60% of cases[10].

7. PROBLEMS IN EARLY DETECTION OF MAS

Till early part of the last decade MAS was thought in the context of rheumatology. Due to the similarities in most of the clinical and laboratory features with HLH, MAS is now recognized as sHLH. There are lots of difficulties in arriving a diagnosis of MAS as highlighted below[1,10,16,26]:

1. There is no pathognomonic clinical or laboratory feature of MAS.
2. Many features of MAS overlap with flare of sJIA or with systemic infection
3. All features may not be present in an individual patient. There is a wide inter-individual disparity in the severity and frequency of classical and laboratory features.
4. The classical histopathologic features of hemophagocytosis may not be present at the initial stage of MAS.
5. The distinction between MAS and pHLH becomes more difficult when MAS is the initial clinical presentation of sJIA and arthritis is not yet present.

8. DIAGNOSIS OF MAS

Till 2015, there were no validated diagnostic or classification criteria of MAS. Due to similarities of clinical and laboratory features to HLH, many opted to use the HLH-2004 diagnostic guidelines[1] for the diagnosis of MAS in sJIA. However, there are many pitfalls in using this criterion for the diagnosis of sJIA associated MAS which are highlighted below[1,16]:

1. Need for molecular diagnosis: Molecular diagnosis for a proven mutation (PRF1/MUNC 13-4) is one of the criteria in HLH-2004 guidelines. Such facilities may not be available in resource-limited settings.

2. Cannot differentiate MAS from sJIA flare: Some of the markers of HLH like lymphadenopathy, splenomegaly, and hyper ferritinemia are also common in sJIA.

3. Most of the laboratory features of HLH-2004 guidelines are seen at the late stages of sJIA associated MAS: Marked thrombocytosis, neutrophilic leucocytosis, anemia and increased fibrinogen levels are common in sJIA flare. At the onset of MAS, there is decreasing trend of

these levels and reduction of these values to the cut –off values present in HLH-2004 occurs at the late stages of MAS when its management becomes challenging.

4. SLE associated MAS: In SLE there is autoimmune cytopenia. Therefore diagnosis of MAS in this condition is very difficult using HLH-2004 guidelines. In 2005, Ravelli *et al* had proposed preliminary diagnostic guidelines based on clinical and laboratory parameters to differentiate between MAS and flare of active sJIA[27]. In a multinational initiative led by the Pediatric Rheumatology International Trials Organization (PRINTO) the application of Ravelli's criteria was compared to HLH-2004 diagnostic guidelines to differentiate MAS in sJIA from a flare of sJIA and sepsis[28]. It was found that the sensitivity and specificity of the Ravelli's criteria in differentiating MAS from sJIA flare was 86% and the sensitivity and specificity of the same in distinguishing MAS from infection was 86% and 95% respectively. But the lack of validation was the major limitation of the preliminary diagnostic guidelines.

To overcome the limitations observed in HLH-2004 and preliminary diagnostic guidelines a new set of classification criteria was developed in 2016 through a multinational collaborative effort of European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and PRINTO[29]. The new classification criteria is depicted in Table 2.

The preliminary validation of 2016 classification criteria showed that, this set of criteria has a sensitivity of 73%, specificity of 99% and a positive predictive value of 97.4% in discriminating MAS in sJIA from other comparable conditions like sJIA and infection[29]. However, classification criteria are usually intended for case definition in clinical trials and research studies and may not capture all MAS particularly subclinical MAS or MAS with incomplete clinical expression.

Table 2: 2016 Classification criteria of MAS in sJIA [29].

A febrile patient with known or suspected sJIA with serum ferritin>684ng/ml AND any 2 of the following	
Parameter	**Value**
Platelet count	d"181 $\times 10^9$ /L
Aspartate aminotransferase	>48 U/L
Triglycerides	>156 mg/dl
Fibrinogen	d"360mg/dl

9. DIAGNOSTIC TOOL TO DIFFERENTIATE pHLH FROM MAS-RELATED TO sJIA

Minoia *et al* recently developed and validated a diagnostic score known as MAS/pHLH score (MH score) to differentiate pHLH from sJIA related MAS[26]. Timely diagnosis of pHLH and its differentiation from MAS is essential because the former is more life-threatening than the latter and the treatment protocol used for pHLH is different than MAS-related to sJIA. The MH score is showed in Table 3.

Table 3: The MH score (26)

Parameter	Points for scoring
Age at onset, year	0(>1.6); 37(d"1.6)
Neutrophil count, $\times 10^9$ /L	0(>1.4);37(d"1.4)
Fibrinogen, mg/dL	0(>131);15(d"131)
Splenomegaly	0(no);12(yes)
Platelet count, $\times 10^9$ /L	0(>78);11(d"78)
Hemoglobin, g/dL	0(>8.3); 11(d"8.3)

The MH score contains 6 variables as shown in Table 3 with scores ranged from 0 to 123. The median value for pHLH is 97 (interquartile range 75-123) and the median value for MAS is 12 (interquartile range 11-34). The probability of a diagnosis of pHLH ranged <1% for a score of <11 to 99% for a score of e"123. A cut off value of e"60 revealed the best performance in discriminating pHLH from MAS (sensitivity 91% and specificity 93%)[26]. It is evident from parameters used in MH score that alterations in laboratory parameters contribute more towards differentiating MAS from pHLH than do the clinical features as 4 out of the 6 variables of the MH score are laboratory tests. Also, the strongest discriminating power between the two illnesses rests with the age at onset and the neutrophil count, together accounting for 60.2% of the total score.

10. MAS IN THE SETTING OF SLE

Data on MAS in both childhood and adult SLE patients are very limited. It is even rare for MAS to be an initial presentation of SLE. Over the years a few case reports of patients presenting with MAS as an initial feature of SLE has been reported[30-33]. Gavand PE *et al*[34] described the clinical characteristics, laboratory findings, treatments, and outcomes in a retrospective study of a large series of SLE-associated MAS. Fever was a common in all the patients. Every new episode was also associated with fever. Laboratory parameters like serum levels of aspartate transaminase (AST), LDH, CRP, ferritin, and procalcitonin were increased. The study suggested that high fever and high levels of AST, LDH, CRP, ferritin and procalcitonin should be considered as red flags for early diagnosis of MAS in SLE.

The incidence of MAS in patients with JIA is more common than in patients with SLE[35,36]. But this may, in turn, be due to the fact that fewer cases are recognized, more so when MAS presents as a debut feature of SLE. Bennett *et al*[36] compared MAS in the two disease settings in terms of demographics, therapeutic interventions and outcome. The course of MAS in SLE as compared to that in JIA patients was found to be more severe and protracted as evidenced by a higher rate of ICU admissions, longer duration of hospital stay and more need for mechanical ventilation and in vasopressor support. The treatment regimen for MAS between SLE and JIA also varied. More children with underlying JIA were treated with IL-1 antagonist whereas children with SLE received cyclophosphamide and mycophenolate mofetil.

11. MAS IN KAWASAKI DISEASE

KD is included on the list of important causes of MAS in childhood[37]. Some isolated case reports[38,39] have suggested that MAS should be considered in children with KD refractory to treatment with IVIG when hepatosplenomegaly with abnormal laboratory findings such as cytopenia, liver dysfunction, hyperferritinemia, elevated serum LDH, hypofibrinogenemia and hypertriglyceridemia are present.

MAS in children with KD and SLE has led to similar challenges in early recognition and prompt treatment. As such the new diagnostic criteria for MAS in sJIA appears to be applicable for the diagnosis of MAS in refractory KD and SLE. But this requires validation and further studies.

12. TREATMENT OF MAS

Currently, there are no validated evidence-based treatment guidelines on MAS in sJIA. Treatment depends on the experience of the treating physician. Prompt institution of aggressive immunosuppressive therapy is essential for reversal of severity of the syndrome.

The most common therapeutic agent used in the treatment of MAS is intravenous pulse injections of methylprednisolone (30 mg/kg/d for 3 consecutive days) followed by oral prednisolone (2mg/kg/day) till hematological abnormalities are normalized and coagulopathy resolved[1]. Subsequently steroid dose is tapered slowly.

Cyclosporine, also used in treating HLH, was the second most commonly prescribed therapeutic intervention. It cases refractory to high-dose intravenous corticosteroids, cyclosporine was found to be dramatically efficacious was[40,41]. It is thought to preferentially target lymphocytes by inhibiting the NFAT family of transcription factors responsible for the activation of a wide array of cytokine genes[42]. One of the likely benefits of cyclosporine is dampening of the cytokine storm that occurs during MAS[43]. It is used at dose of 2-7 mg/kg/day[10,16]. However, there is no data regarding how long the treatment with cyclosporine is to be continued after clinical improvement. Intravenous immunoglobulin (IVIg) is another therapeutic option by virtue of its immunomodulatory properties[1,16], it's potential to aid in preventing septic complications. The success of treatment with IVIg requires initiation of treatment early in the course of MAS[44].

Biological agents like anakinra (IL-1R blocker) and canakinumab (IL-1â antibody), IL-6 receptor blocker tocilizumab are being increasingly used in the treatment of MAS in sJIA particularly in cases refractory to first-line treatment. There have been reports of MAS occurring in patients with sJIA being treated with canakinumab and tocilizumab[45-47]. This appears to be brought about by an imbalance between up- and down-regulation of the various cytokines or due to increased rate of infections associated with biologic therapies[48]. However, it can be overcome by increasing the dose of the biologic medications[49]. But IL-1 blockers are not available in our country and the cost of therapy is a major constraint for the use of tocilizumab in the treatment of MAS.

Since TNF-á is raised in patients with MAS and the implication that this cytokine may have a major role in the pathogenesis of MAS, anti-TNF-á therapy may also be of benefit in treating patients with MAS[50,51].

Use of apheresis therapy, in the management of steroid and cyclosporine resistant MAS, has been reported by Kinjo *et al*[52]. Use of plasma exchange, leukocytapheresis and plasma diafiltration for the removal of proinflammatory cytokines provides an interesting treatment option to explore.

13. CONCLUSION

MAS is a life-threatening condition. High degree of suspicion is necessary for early diagnosis and prompt administration of treatment. Changing trend in the laboratory parameters is most important than decrease or increase from absolute cut-off values as mentioned in various criteria for early diagnosis of this syndrome. The

2016 classification criteria for MAS-related sJIA have been validated for MAS and intended to use for clinical trials and research purposes. The recently developed MH score helps to differentiate pHLH from sJIA related MAS which has therapeutic implications. Early expert consultation is recommended as soon as MAS is suspected.

References:

1. Groom AA. Macrophage activation syndrome. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR (eds). Textbook of Pediatric Rheumatology.7thed, Philadelphia, USA: Elsevier Saunders; 2015 pp 642-649.
2. Hadchouel M, Prieur A, Griscelli C. Acute hemorrhagic, hepatic and neurologic manifestations in juvenile rheumatoid arthritis : possible relationship to drugs or infection. J Pediatr. 1985;106: 561-566
3. Stephan J, Zellar J, Hubert P e*t al*.: Macrophage activation syndrome and rheumatic disease in childhood: a report of four new cases .Clin Exp Rheumatol 1993; 11: 451-456.
4. Ramanan A, Groom A. Does systemic–onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis? Rheumatology.2005; 44(11): 1350-1353.
5. Grom A, Paso M. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis. J Pediatr 1996; 129: 750-4
6. Reiner A, Spivak J. Hemophagocytic Histiocytosis.: a report of 23 new patients and a review of literature. Medicine 1988;67(6): 369-388.
7. Janka G. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr. 2006;166(2): 95-109
8. Stepp SE, Dufourcq- Lagelouse R, Le Deist F, *et al*. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science 1999, 286(5446): 1957-1959..
9. Baldovinac V, TvinnereimA, Harly J. Regulation of Antigen-Specific CD8(+) T cell Homeostasis by Perforin and Interferon-gamma. Science 2000, 290(5495): 1354-1358
10. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C *et al*. Clinical features, treatment and outcome of macrophage activation syndrome complicating juvenile idiopathic arthritis. Arthritis Rheumatol. 2014;66 (11): 3160-3169.
11. Egues Dubuc C, Uriarte Ecenarro M, Errazquin Aguirre N, Belzunegui Otano J. Macrophage Activation Syndrome as a Severe Manifestation of Adult's Still's Disease. Hemophagocytic Cells in Ascites. Rheumatol Clin. 2014;10(6) :420-421.
12. Emile J, Alba O, Fraitag S, Horne A, Haroche J, Donadieu J *et al*. Revised classification of histiocytoses and neoplasms of macrophage-dendritic cell lineages. Blood 2016; 127(22): 2672-2681.
13. Boom V, Anton J, Lehdenne P, Quartier P, Ravelli A,Wulffraat N *et al*. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol. 2015;13(1):55; DOI 10.1186/s12969-015-0055-3.
14. Bracaglia C, Sieni E, Da Ros M, De Fusco C, Micalizzi C, Cetca V *et al.* Mutations of familial hemophagocyticlymphohistiocytosis (FHL) related genes and abnormalities of cytotoxicity function tests in patients with macrophage activation syndrome (MAS) occurring in systemic juvenile idiopathic arthritis (sJIA). Pediatr Rheumatol. 2014;12 (Suppl 1): P53. DOI:10.1186/1546-0096-12-s1-p53.
15. Ravelli A, Caria M, Buratti S *et al*. Methotrexate as a possible trigger of macrophage activation syndrome in systemic juvenile idiopathic arthritis. J Rheumatol 2001, 28(4): 865-867.
16. Ravelli A, Grom A, Behrens E, Cron R. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes and Immunity. 2012;13(4): 289-298.
17. Bracaglia C, Prencipe G, De Benedetti F. Macrophage Activation Syndrome: different mechanisms leading to a one clinical syndrome. Pediatr Rheumatol 2017; 15(1):5 DOI 10.1186/ s12969-016-0130-4.
18. Kaufman K, Linghu B, Szustakowski J, Husami A, Yang F, Zhang K, *et al*. Whole-Exome Sequencing Reveals Overlap Between Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis and Familial Hemophagocytic Lymphohistiocytosis. Arthritis Rhematol. 2014; 66(12): 3486-95. doi: 10.1002/art.38793.
19. Yanagimachi M, Naruto T, Miyamae T, Hara T, Kikuchi M, Hara R *et al.* Association of IRF5 polymorphisms with Susceptibility to Macrophage Activation Syndrome in Patients with Juvenile Idiopathic Arthritis. J Rheumatol 2011; 38(4): 769-774. doi: 10.3899/jrheum.100655
20. Canna S, de Jesus A, Gouni S, Brooks S, Marrero B, Liu Y *et al*. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet. 2014; 46 (10): 1140-1146. DOI: 10.1038/ ng.3089.
21. Owen JA, Punt J, Stanford SA. Effector Responses: Cell and Antibody Mediated Immunity. Kuby Immunology. 7th ed. New York: W. H . Freeman and Company, 2013. Pp 432-435.
22. Janka G. Familial and Acquired Hemophagocytic Lymphohisticytosis. Annu Rev Med. 2012; 63(1): 233-46.DOI: 10.1146/annurev-med-041610-134208.
23. Bleesing J, Prada A, Siegel DM, Villaneuva J, Olson J, Ilowite NT *et al*. The diagnostic significance of soluble CD163 and soluble IL-2 Receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2007; 56(3): 965-71. DOI: 10.1002/ art.22416.
24. Gorelik M, Fall N, Altaye M, Barnes M, Thompson S, Grom A *et al*. Follistatin-like protein 1 and Ferritin /Erythrocyte Sedimentation Rate Ratio Are Potential Biomarkers for Dysregulated Gene Expression and Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis. J Rheumatol. 2013; 40(7): 1191-1199. DOI: 10.3899/ jrheum. 121131
25. Shimizu M, Yokoyama T, Yamada K, Kaneda H, Wada H, Wada T *et al*. Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis- associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis. Rheumatology.2010; 49(9): 1645-53. DOI: 10.1093/rheumatology/keq133.
26. Minoia F, Bovis F, Davi S, Insalaco A, Lehmberg K, Shenoi S *et al*. Development and initial validation of the macrophage Activation syndrome/Primary Hemophagocytic Lymphohistiocytosis Score, a Diagnostic Tool that differentiates Primary Hemophagocytic Lymphohistiocytosis from Macrophage activation syndrome. J Pediatr.2017, Oct;189:72-78.e3. DOI: 10.1016/j.jpeds.2017.06.005.
27. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, *et al.* Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; 146(5): 598–604. DOI: 10.1016/j.jpeds.2004.12.016.
28. Davi S, Minoia F, Pistorio A, Horne A, Consolaro A, Rosina S *et al*. Performance of Current Guidelines for Diagnosis of Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis.Arthritis Rheumatol. 2014; 66(10): 2871-2880. DOI: 10.1002/art.38769.
29. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A *et al*. 2016 classification criteria for macrophage activation syndrome

complicating systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2016; 68:566-576.
30. McCann L, Hasson N, Pilkington CA. Macrophage activation syndrome as an early presentation of lupus. J Rheumatol 2006; 33: 438"40.
31. Benarroch L, Sterba G, Bosque M. Macrophage Activation Syndrome (MAS) as a Debut of Systemic Lupus Erythematosus. J Allergy ClinImmunol 2006;117(2): S210. DOI: 10.1016/ j.jaci.2005.12.830
32. Stephan J, Kone-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur A. Reactive haemophagocytic syndrome in children with inflammatory disorders: a retrospective study of 24 patients. Rheumatology 2001; 40: 1285"92.
33. Yeap S, Sheen J, Kuo H, Hwang K, Yang K, Yu H. Macrophage Activation Syndrome as Initial Presentation of Systemic Lupus Erythematosus. Pediatr Neonatol 2008; 49(2): 39"42. DOI: 10.1016/s1875-9572(08) 60010-8.
34. Gavand P, Serio I, Arnaud L, Costedoat-Chalumeau N, Carvelli J, Dossier A *et al* . Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. Autoimmun Rev. 2017; 16(7): 743-749. DOI:10.1016/ j.autrev.2017.05.010
35. Bennett T, Fluchel M, Hersh A, Hayward K, Hersh A, Brogan T *et al*. Macrophage Activation Syndrome in Children with Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis. Arthritis Rheum. 2012 ; 64(12): 4135–4142.doi: 10.1002/ art.34661
36. Stéphan J, Koné-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur A. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford) 2001;40(11):1285–1292.
37. Latino G, Manlhiot C, Yeung R *et al*. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol 2010;32:527–31.
38. Muise A,Tallett S, Silverman E.(2003). Are Children With Kawasaki Disease and Prolonged Fever at Risk for Macrophage Activation Syndrome? PEDIATRICS,112(6), pp.e495-e497. DOI: 10. 1542/peds.112.6.e495
39. Mukherjee D, Pal P, Kundu R *et al*. Macrophage Activation Syndrome in Kawasaki Disease. Indian Pediatr 2014;51: 148-149
40. Mouy R, Stephan J, Pillet P, Haddad E, Hubert P, Prieur A. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. J Pediatr 1996; 129:750–754.
41. Ravelli A, De Benedetti F, Viola S, Martini A. Macrophage activation syndrome in systemic juvenile rheumatoid arthriti successfully treated with cyclosporine. J Pediatr 1996;128:275–8.
42. Rao A, Luo C, Hogan P. Transcription factors of the NFAT family: regulation and function. Annu Rev Immunol 1997; 15: 707 — 747.
43. Behrens E. Macrophage activation syndrome in rheumatic disease: what is the role of the antigen presenting cell? Autoimmun Rev 2008; 7: 305 — 308.
44. Emmenegger U, Frey U, ReimersA, Fux C, Semela D, Cottagnoud P *et al.* Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. Am J Hematol 2001; 68: 4—10
45. Nigrovic P, Mannion M, Prince F, Zeft A, Rabinovich C, vanRossum M *et al*. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011; 63:545–55.
46. Ruperto N, Brunner H, Quartier P, ConstantinT,Wulffraat N, Horneff G *et al*. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012; 367:2396–406.
47. De Benedetti F, Brunner H, Ruperto N, Kenwright A, Wright S, Calvo I, *et al*. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012; 367:2385–95.
48. Buoncompagni A, Loy A, Sala I, Ravelli A. The paradox of macrophage activation syndrome triggered by biologic medications. Pediatr Rhematol Online J 2005;3:70–3.
49. Nigrovic P, Mannion M, Prince F, Zeft A, Rabinovich C, van Rossum M, *et al*. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011; 63:545–55.
50. De Benedetti F, Pignatti P, Massa M, *et al.* Soluble tumor necrosis factor receptor levels reflect coagulation abnormalities in systemic juvenile chronic arthritis. Br J Rheumatol 1997; 36:581-8.
51. Pralahad S, Bove K, Dickens D, Lovell D, Grom A. Etanercept in the treatment of macrophage activation syndrome . J Rheumatol 2001 Oct; 28(10): 2370
52. Kinjo N, Hamada K, Hirayama C, Shimizu M.(2017). Role of plasma exchange, leukocytapheresis and plasma diafiltration in management of refractory macrophage activation syndrome. J Clin Apher. DOI: 10.1002/jca.21570.

Case Report

Uraemic Pericardial Tamponade

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Abstract

Uremic pericardial tamponade is considered to be a rare complication of renal failure. Every patient with uremic pericarditis can potentially develop a cardiac tamponade either due to pericardial effusion, chronic volume overload or hemorrhage into the pericardial sac. It is a life threatening condition that needs to be diagnosed and treated promptly. Patients usually present with dyspnea associated with hypotension, elevated jugular venous pressure and muffled heart sounds. Urgent pericardial tapping is the only life-saving procedure. Echocardiographic or fluoroscopic guided pericardiocentesis is the procedure of choice. A blind sub xiphoid approach should be attempted in the absence of echocardiographic or fluoroscopic guidance. Definitive treatments involve intensive hemodialysis regiments with proper input and output monitoring.

Key words : *Uremia, cardiac tamponade, pericardial effusion*

Introduction :

Cardiac tamponade is characterized by an abnormal accumulation of fluid in the pericardial space, resulting in obstruction to the inflow of blood into the ventricles and subsequent hemodynamic compromise. It was first described by Dr Claude Beck in 1935 as the clinical diagnostic triad of hypotension, elevated jugular venous pressure and muffled heart sounds. The normal pericardium is a double-layered sac, consisting of visceral and parietal pericardium which is separated by a small quantity of fluid (15–50 mL). The pericardial fluid is essentially an ultrafiltrate of plasma and serves to lubricate the two layers of the pericardium. Abnormal and excessive accumulation of fluid in the pericardial space may be seen in many pathological conditions including malignancies, infectious diseases, tuberculosis, autoimmune diseases, trauma and renal failure. As fluid accumulates in the pericardial space, the intra pericardial pressure increases. The normal pericardium is able to stretch to some extend to accommodate this extra fluid and limit the rise in intra pericardial pressure. However, when this limit is surpassed, the intra pericardial pressure begins to rise resulting in increasing stiffness of the ventricles. With increasing pressure in the pericardial space, the ventricular filling pressure also increases. As more fluid accumulates, the intra pericardial pressure rises above the ventricular filling pressure resulting in marked reduction in the diastolic filling and subsequent reduction in cardiac output. Further accumulation of fluid leads to equalization of pericardial and left ventricular filling pressure resulting in further deterioration of cardiac output. The rate of accumulation of fluid and compliance of the pericardium are important factors that determine the development of tamponade. As little as 150ml of fluid can cause obstruction to diastolic filling with significant increase in intra pericardial pressure if it accumulates rapidly. Whereas a compliant pericardium can accommodate more than 1000ml of fluid without significantly impairing diastolic filling if the fluid accumulates slowly over a longer period of time.

Case report :

A 30 year old female presented at the emergency department with gradually progressive dyspnea and swelling of the whole body over a period of two months. There was a history of cough and decreasing urine output over the same period of time. There was no history of fever, loss of weight, loss of appetite, joint pains or skin

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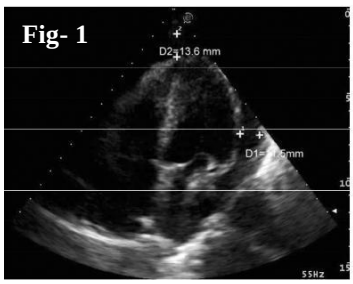
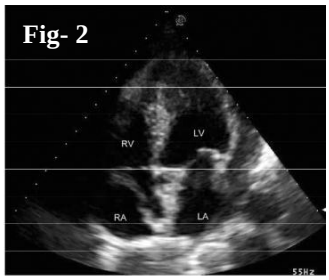
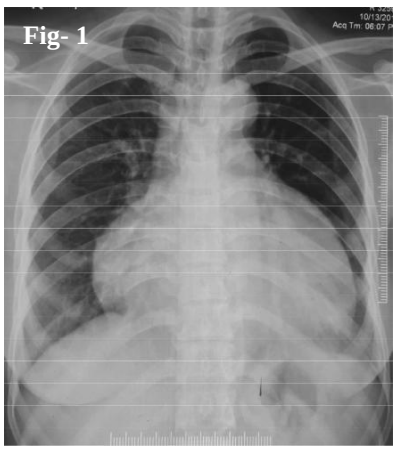
rashes. Five years earlier she was diagnosed with hypertension but was on irregular medication. There was no history of diabetes mellitus or any other major illness in the past. The patient is a non-alcoholic and a non-smoker.

On presentation at the emergency department, patient was severely dyspneic. She had mild pallor, facial puffiness and bilateral pitting pedal edema with a blood pressure of 86/60 mm of Hg. A paradoxical pulse was present. She was afebrile and her jugular venous pressure was raised. There were fine crepitations on bilateral basal lung fields. Her heart sounds were soft and appear muffled. The abdomen was soft and liver was palpable. The remainder of the physical examinations was normal. Bedside echocardiography revealed a pericardial effusion with right atrial collapse (Figure 1 and 2).





Her blood investigations revealed deranged renal function with a serum urea of 257 mg/dl and serum creatinine of 18 mg/dl. She had severe anemia with a hemoglobin level of 6.6 gm/dl. Her blood glucose levels, serum electrolytes and liver functions were all normal. Her anti nuclear antibody (ANA) and rheumatoid factor were both negative. Viral markers for human immunodeficiency virus, hepatitis B and hepatitis C were all non-reactive. Her thyroid function test was normal. Blood cultures (three samples taken within 12 hours of hospitalization), as well as her urine cultures were all sterile. Chest X-ray showed cardiomegaly (Figure 3). Ultrasonography of the abdomen showed mild hepatomegaly with pericardial effusion with features suggestive of chronic kidney disease. Examination of her urine revealed mild proteinuria. Her serum ferritin and serum parathyroid hormone levels were elevated (444.7ng/ml and 636.27pg/ml respectively). Her electrocardiograph showed sinus tachycardia with normal-sized QRS complexes. There were no changes suggestive of ischemia or pericarditis.



A diagnosis of chronic kidney disease with cardiac tamponade was made and an emergent pericardiocentesis was performed. About 400ml of bloody pericardial fluid was drained with immediate cardiovascular improvement. Her blood pressure recovered and her dyspnea subsided. Post-procedural echocardiogram confirmed resolution of the pericardial effusion. The patient's post-procedural recovery was uneventful. Pericardial fluid analysis showed a total cell count of 200cells/cmm with a polymorphic predominance (Polymorphic cells - 85%, Lymphocytes - 15%). There were no malignant cells seen. Biochemical analysis showed a transudative pericardial fluid with low total protein (1 gm/dl) and low albumin levels (0.4 gm/dl). The levels of glucose, amylase and lipase in the pericardial fluid were 137mg/dl, 68 U/L and 25 U/L respectively. Pericardial fluid adenosine deaminase level (ADA) was low (23 U/L). Pericardial fluid was negative for acid-fast bacilli. A computed tomography (CT) scan of the thorax, abdomen and pelvis showed no evidence of any neoplastic disease or tuberculosis.

The patient was taken up for hemodialysis and her condition stabilized. Anemia was corrected by giving blood transfusion (PRBC). Patient was discharged in a stable condition and was put on maintenance hemodialysis.

Discussion :

Cardiac tamponade is a rare complication of uremic pericarditis. It was first reported in patients with end stage renal disease (ESRD) in 1956 by Goodner and Brown[1]. Since then the incidence of uremic pericarditis has decline significantly with the advent of earlier dialysis initiation, more frequent dialysis prescription, more effective dialyzers and effective renal transplant procedures. Earlier studies based on autopsy findings showed an incidence of 41% to 50%[2,3]. More recently, with effective dialysis, the incidence of pericarditis in ESRD has declined to approximately 5%[4].

Three pathological forms of pericarditis have been described in uremic patients:

1. Uremic pericarditis— it presents before renal replacement therapy or within 8 weeks of its initiation.

2. Dialysis pericarditis—it occurs after a patient is being stabilized on dialysis (usually e”8 weeks after its initiation)[5].

3. Constrictive pericarditis – it is very rare. Clinically, a patient with uremic pericarditis can present as acute pericarditis, chronic pericardial effusion or constrictive pericarditis. Among patients who present with chronic pericardial effusion, the fluid is usually of limited amount and causes no significant hemodynamic disturbance. Significant collection of fluid leading to tamponade is rare. Pericardial effusion in uremic pericarditis is characterized by a sterile serofibrinous, exudative effusion with high levels of protein and mononuclear cells. Hemorrhagic fluid can also be seen. The onset is usually insidious and many patients remain asymptomatic. Patient may present with pleuritic chest pain and fever. A pericardial friction rub incidentally heard over the chest on routine examination may be the initial presentation of uremic pericarditis. The typical electrocardiographic changes as described in other causes of pericarditis are rare in uremic pericarditis, probably due to the lack of associated myocardial inflammation[6]. When cardiac tamponade develops patient will present with dyspnea associated with hypotension, elevated jugular venous pressure and muffled heart sounds. Extremities may be cold and clammy due to hypoperfusion. Tachycardia with a pulsus paradoxus (deûned as an inspiratory decrease in systolic arterial pressure of >10 mmHg during normal breathing) may be present. A paradoxical increase in venous distention and jugular pressure during inspiration may also be seen (Kussmaul Sign). Sometimes dullness with bronchial breath sounds are heard over an area below the angle of the left scapula due to consolidation or atelectasis caused by compression of the left lower lobe of the lung (Ewart sign)[7].

The cause of uremic pericarditis remains obscure. The most probable cause is the retention of some yet unknown toxic metabolites[4]. This may be explained by the fact that the incidence of pericarditis has significantly decreased with the use of modern dialysis techniques probably due to the removal of these toxic metabolites. With significant advancement in renal replacement therapy, pericardial tamponade complicating a case of uremic pericarditis is extremely rare. However, every patient with ESRD with pericarditis is at risk of developing a tamponade. One possible mechanism includes a progressively increasing chronic pericardial effusion resulting from inadequate dialysis or continuous volume overload. Tamponade can also occur due to hemorrhage into the pericardial cavity as a manifestation of uremic bleeding diathesis. The use of anticoagulation during hemodialysis in ESRD patients with pericarditis can also lead to hemorrhage into the pericardial space. Bleeding can also occur from the granulation tissue that organizes the fibrinous exudates[8].

Our patient presented with gradually progressive dyspnea and swelling of the whole body over a period of two months associated with decreasing urine output. Although she had these symptoms for about two months, yet she never consulted a doctor probably due to the vagueness and insidious nature of her symptoms. Considering the sub clinical nature of most uremic pericardial effusions, there is a distinct possibility that her uremic pericardial effusion must have predated her symptoms by many months. With decreasing urine output and chronic unrestricted fluid intake, she started developing volume overload resulting in progressive dyspnea and swelling of the whole body. This is supported by the fact that her pericardial fluid was transudative in nature with low protein and low albumin levels. This is very unlike the type of fluid found in uremic pericarditis which is usually exudative and serofibrinous in nature. It is likely that she had initially developed a sub clinical uremic pericarditis which was unmasked by chronic volume overload resulting from her decreasing urine output and unrestricted fluid intake. The chronic volume overload ultimately pushed her into a cardiac tamponade. She finally presented in the emergency department with features of frank cardiac tamponade.

Cardiac tamponade is a clinical diagnosis. Echocardiography is the single most useful investigation to confirm the collection of fluid in the pericardial space. It is a fast and reliable tool that can provide valuable information about the size, location and degree of hemodynamic impact. It can also be used to guide pericardiocentesis. Findings on echocardiography include early diastolic collapse of the right ventricle, late diastolic collapse of the right atrium, swinging heart and exaggerated respiratory variability (>25%) in mitral inûow velocity. Chest radiograph may show cardiomegaly with a water-bottle shaped heart[9]. As stated earlier, the typical electrocardiographic changes as described in other causes of pericarditis are rare in uremic pericarditis. The electrographic tracing of our patient did

not show any low voltage QRS complexes or an electrical alternans.

Once diagnosed a cardiac tamponade needs to be evacuated immediately to relieve the pressure and improve filling into the ventricles. Pericardiocentesis is life saving procedure in cardiac tamponade. Pericardiocentesis can be done as a blind procedure via the subxiphoid approach with electrocardiographic monitoring. However, when available, echocardiographic or ûuoroscopic guided pericardiocentesis is preferred. Aortic dissection is a major contraindication. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy and thrombocytopenia <50000/mm^3. Complications of pericardiocentesis include injury to the myocardium and the coronary vessels, air embolism, pneumothorax, arrhythmias (usually vasovagal bradycardia) or puncture of the peritoneal cavity or abdominal viscera.

Pericardiocentesis will relieve the pericardial pressure and reverse the hemodynamic compromise. However, the definitive treatment of patients with uremic pleural effusion involves a more intensive hemodialysis program with strict input and output monitoring. The use of anticoagulation during dialysis should be carefully considered or avoided in patients with uremic pleural effusion as it can precipitate hemorrhage into the pericardial sac which can lead to a tamponade[4,10] Our patient recovered well after pericardiocentesis and is now on regular maintenance hemodialysis.

Conclusion :

Although pericardial tamponade is a rare complication of uremic pericarditis, it is a syndrome that is rapidly and universally fatal if undiagnosed and not treated promptly. Because of its subclinical nature, a clinician should pay more attention to the pericardial sac in patients with ESRD and keenly look for signs and symptoms of pericarditis. If undetected, every patient with uremic pericarditis can potentially develop a tamponade. Rapid and prompt diagnosis of this medical emergency is the key to reducing mortality. Pericardiocentesis is the life saving procedure that should be attempted even in the absence of fluoroscopic or echocardiographic guidance.

References :

1. Brown H, Goodner CJ. Report of two cases of cardiac tamponade in uremic pericarditis. J Am Med Assoc. 1956; 162(16):1459-61.
2. Langendorf R, Pirani CL. The heart in uremia. An electrocardiographic and pathologic study. Am Heart J 1947; 33:282-307.
3. Wacker N, Merrill JP. Uremic pericarditis in acute and chronic renal failure. JAMA 1954; 156:764-5.
4. Alpert MA, Ravenscraft MD. Pericardial involvement in end-stage renal disease. Am J Med Sci 2003;325:228–236
5. Renfrew R, Buselmeier TJ, Kjellstrand CM. Pericarditis and renal failure. Annu Rev Med 1980; 31:345–360.
6. Gunukula SR, Spodick DH. Pericardial disease in renal patients. Semin Nephrol 2001; 21:52–7.
7. Ewart W. Practical Aids in the Diagnosis of Pericardial Effusion, in Connection with the Question as to Surgical Treatment. Br Med J. 1896,21;1(1838):717-21
8. Baldwin JJ, Edwards JE. Uremic pericarditis as a cause of cardiac tamponade. Circulation. 1976;53(5):896-901
9. Eisenberg MJ, Dunn MM, Kanth N, Gamsu G, Schiller NB. Diagnostic value of chest radiography for pericardial effusion. J Am Coll Cardiol 1993; 22:588–93.
10. Wood JE, Mahnensmith RL. Pericarditis associated with renal failure. Evolution and management. Semin Dial 2001;14:61–66

Case Report

Isolated Pericardial Effusion in Melioidosis

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Abstract

Melioidosis, a tropical infection, rarely presents with pericardial effusion. We present a case of a 65 year old man presenting with fever and breathing difficulty who, on evaluation, was found to have massive pericardial effusion. *Burkhloderia pseudomallei was isolated from the pericardial fluid after aerobic culture and the patient was treated with antibiotics based on sensitivity report.*

Keywords: *Melioidosis, Pericardial effusion, Septicemia, Burkhloderia*

Introduction :

Burkhloderia pseudomallei has recently gained importance as an emerging pathogen in India and worldwide. It causes various clinical manifestations like pneumonia, septicemia, arthritis, abscess etc. Cases have been reported from Southeast Asia, mainly from Thailand, Malaysia, Vietnam etc.[1] In India, a few cases have been reported mainly from the southern part of the country.[2,3] Sporadic cases have also been reported from eastern and north-eastern parts of India.[4] Cardiac involvement in Melioidosis is rare and is often associated with septicemia. In endemic regions, pericardial effusion is found in 1-3% of melioidosis cases.[5] We present a case of septicemic melioidosis with pericardial effusion without temponade.

Case Report :

A 65 year old male farmer, non-diabetic non-hypertensive, presented to the Emergency Room(ER) of Gauhati Medical College, Guwahati with history of low-grade fever for 2 weeks and breathing difficulty for 4 days. The patient was initially treated with Amoxycillin-Clavulanic Acid at a primary health center for 5 days with no clinical improvement. There was no history of breathing difficulty in the past. The patient had no known cardiovascular or respiratory illness.

On admission, the patient was febrile(38.2 C), had tachycardia(110 beats/min), blood pressure of 110/70 mm of Hg and was tachypnoeic (respiratory rate 42/min). The neck veins were distended. However, neither peripheral oedema nor hepatomegaly nor Kussmaul's sign were present. His breath sounds were normal. But, heart sounds were muffled with no added sounds.

Laboratory tests revealed Hb 11.2gm/dl, leucocytosis (Total count 26,000/cumm) with neutrophilia (85% Neutrophils). His kidney function tests and liver function tests were within normal limit. ESR was high (75 AEFH), so was CRP (48 mg/l). Plasma fasting sugar was 96mg/dl and HIV negative.

Electrocardiogram showed sinus tachycardia with low QRS voltage. The chest radiograph showed normal lung fields with enlarged cardiac silhouette. HRCT thorax showed no abnormality in the lung parenchyma.

Echocardiogram confirmed haemodynamically significant pericardial effusion with an left ventricular ejection fraction of 45%. Immediate pericardiocentesis was done and around 500ml of clear yellowish fluid was aspirated. Following which, the patient's breathing difficulty improved. The cardiac function improved with ejection fraction raised to 60% with normalization of QRS voltage.

The pericardial fluid came out to be exudative in nature (protein 5.3gm/dl , sugar 86mg/dl , LDH 164) with a total cell count of 750/cumm (neutrophil 60%, lymphocyte 20%, degenerated cells 20%) and elevated

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levels of ADA (84 u/l). Pericardial fluid samples for culture and sensitivity, malignant cytology and CB-NAAT were sent. The patient was started on intravenous Meropenem 1 gram 8 hourly empirically after blood and urine samples were sent for culture and sensitivity.

After 48 hours of admission the patient was afebrile and his total count also declined significantly to 10000/ cumm. On day 3, malignant cytology and CB-NAAT reports came negative. After 48 hours of aerobic culture of the fluid, Burkhloderia pseudomallei was isolated. The isolate was sensitive to Meropenem (MIC 1), Levofloxacin (MIC 2), Ceftazidime(MIC 4) and Cotrimoxazole. The urine and blood culture showed no growth after 72 hours of incubation.

He continued to receive intravenous Meropenem for next 2 weeks and was discharged with Cotrimoxazole orally as maintenance therapy. The patient is currently on follow up with ongoing maintenance therapy. On follow up Echocardiogram at 2 weeks after discharge, there was minimal pericardial effusion and the patient was clinically doing well.

Discussion :

Burkhloderia pseudomallei is an environmental pathogen and is found in soil and water. The most common modes of infection are direct inoculation to damaged skin from muddy soil and water and inhalation.[6] Our patient, being a farmer, could have acquired the infection through any of the two routes.

Melioidosis presenting as pericardial effusion is a rare incidence even in endemic regions. In a 10 year retrospective study from Thailand, only 12 cases of melioidosis complicated by culture-confirmed pericardial effusion was found.[7] Out of these, one-third had underlying risk factors and two-third showed underlying pneumonia with septicemia with secondary seeding in pericardium. In the Darwin prospective study from Australia only 4 out of 540 cases had pericarditis.[8]

Isolated pericardial effusion without pneumonia in Melioidosis is even rarer. However, the absence of bacteremia and radiologically significant pneumonia could be due to empirical therapy with oral Amoxycillin-Clavulanic Acid, although the same was inadequate as an intensive therapy for systemic melioidosis.

Melioidosis can occur in all age groups. But, severe clinical manifestations are mostly seen in patients with immunocompromised status, as in Diabetes mellitus, HIV, chronic steroid usage, alcoholism or chronic kidney disease. Our patient neither had the risk factors nor had any underlying disease.

In developing and underdeveloped countries, the most common cause of pericardial effusion is Tuberculosis. As Tuberculosis and Melioidosis have similar clinical manifestations and difficult to differentiate clinically, pericardial fluid culture or pericardial biopsy is essential to reach the final diagnosis.

Conclusion :

Melioidosis is a great mimicker and clinicians in endemic countries should be aware of its diverse clinical manifestations. It should be considered among differential diagnosis of exudative pericardial effusion even in the absence of risk factors. This case focuses the need to record the presence of Melioidosis cases with rare manifestations in India. Moreover, this case highlights the need for improved microbiology feedback in a situation of high clinical suspicion. We were able to treat the patient successfully by applying correct antibiotic based on timely laboratory response.

References :

1. Raja NS, Ahmed MZ, Singh NN. Melioidosis: An emerging infectious disease. J Postgrad Med 2005;51:140-5
2. Anuradha K, Meena AK, Lakshmi V. Isolation of Burkhloderia pseudomallei from a case of septicemia: A case report. Indian J Med Microbial 2003;21:129-32
3. Jesudason MV, Anbarasu A, John TJ: Septicaemic melioidosis in a tertiary care hospital in south India. Indian J Med Res 2003;117:119-21
4. Vishwaroop BS, Balaji V, Mathai E, Kekre NS: Melioidosis presenting as genitourinary infection in two men with diabetes. J Postgrad Med 2007;53:108-10
5. Cheng AC, Currie BJ: Melioidosis: epidemiology, pathophysiology and management. Clin Microbiol Rev 2005; 18:383-416
6. Ramphal R : Harrison's principles of internal medicine 20th edition, vol 1, chapter 159:1172-1173
7. Chetchotisakd PS, Anunnatsiri S, Kiatchoosakum S, Kularbkaew C: Melioidosis pericarditis mimicking tuberculous pericarditis. Clin Infect Dis 2010;51:46-49
8. Currie BJ, Ward L, Cheng AC: The epidemiology and clinical spectrum of melioidosis: 540 case from the 20 year Darwin prospective study. PLoS Trop Dis 2010;4: 900-10

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