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ASSAM JOURNAL OF INTERNAL MEDICINE

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Anti CCP antibodies and diagnosis of RA

Ramnath Misra^{*}

Antibodies to cyclic citrullinated antibodies have proved to be an useful diagnostic and prognostic markers in Rheumatoid arthritis. Its presence even before the signs and symptoms of the disease suggests it has a pathogenic role. The strong association with the presence of shared epitopes and association of anti CCP antibodies with smoking provide further support of its role in the pathogenesis. The clinical relevance of antibodies to CCP has been examined in a cohort of patients from Western India¹ and provide confirmation that in Rheumatoid arthritis, the sensitivity and specificity of antibodies to CCP is 47-76% and 90-96% in Rheumatoid arthritis has already been well documented in all ethnic groups including Indians²⁻⁵. The issue of specificity has not been addressed in the manuscript as they had not included healthy controls or non RA disease controls. What would have been really interesting to know how many patients with early RA (less than 1 year duration) were in this cohort to substantiate the fact that antibodies to CCP is more sensitive than RF at this phase of the disease. Also, the study did not address the relation of functional disability with the presence of antibodies to CCP as was shown by the study from Japan⁶.

The association of disease extent or activity parameters with presence of antibodies to CCP did reveal some unexplained association. For example, the significant association of tenderness with positivity and hand joint involvement or polyarticular joint disease with negativity to antibodies are chance observation rather

than of mechanistic significance. Similarly, the attempt to find an association with acute phase response with the presence of RF and antibodies to CCP was largely unwarranted. Clearly there is no such association between disease activity and the presence of autoantibodies. The former is more convincingly related with treatment. There is no mention of any drugs the subjects were receiving for interpretation of the results. Therefore, the study while providing confirmation that antibodies to CCP is more sensitive than Rheumatoid Factor in the diagnosis of RA falls short of addressing the issue of specificity, relation to functional disability or severity of damage. Of these the specificity is most important in the Indian context as antibodies to CCP has been reported in tuberculosis and due to high burden of the disease in our country, it is important to confirm the observation.

Even if antibodies to CCP proves to be more specific than Rheumatoid Factor, the gain in sensitivity as shown in this study is only 11%, from 72% to 83%. Therefore, at least in 2/3rd of cases with suspected diagnosis of RA, antibodies to CCP does not provide any additional serological support. And in only one tenth of cases it is helpful to the diagnosis provided these are early disease of less than one year disease, without typical clinical or radiological features of Rheumatoid arthritis. So, one may wait for Rheumatoid factor results are available before ordering for antibodies to CCP, if clinically the diagnosis is obvious in resource crunch setting. The cost of testing for antibodies to CCP is at least twice if not more than Rheumatoid factor in most commercial laboratories.

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Original Article

A study on anti-cyclic citrullinated peptide (anti-CCP) antibodies in Rheumatoid Arthritis patients from Mumbai, Western India

V. Pradhan*, J P Devaraj*, A. Rajadhyaksha**, A. Yeola***,
M. Patwardhan****, N. Dhavale*****, K. Ghosh*****

Abstract

Background: Antibodies to citrullinated peptide (anti-CCP) i.e., antibodies to peptides post-translationally modified by the conversion of arginine to citrulline, are specific serological makers for Rheumatoid Arthritis (RA). These antibodies are highly specific for RA, but are not detectable in all RA patients.

Aim: To know the diagnostic potential of anti-CCP antibodies in clinically proved RA and its association with Rheumatoid Factor (RF), clinical manifestations and associated immune parameters.

Settings and Design: One hundred clinically proven RA patients from Mumbai were included. Ages ranged between 17 and 70 years, where 76 were females and remaining 24 were males.

Material & methods: Anti-CCP antibodies were detected by ELISA (Immco Diagnostics, USA). C reactive protein (CRP) and RF levels were also detected. Autoantibodies like anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) were detected by indirect immunofluorescence (IIF) technique.

Statistical analysis: Continuous variables were expressed as mean \pm SD. Pairs of groups were compared using student 't' test for normally distributed continuous distribution. The 'X²' test was used for the categorical variables as needed. Statistical significance was set at $p < 0.05$.

Results: An incidence of anti-CCP antibodies was 62.7%, indicating that anti-CCP negativity does not rule out RA. RF positivity was 70.7% patients, of which 47.2% were anti-CCP positives. Among RF negative patients, 63.6% were anti-CCP positives. Our study showed that anti-CCP test is more specific (95%) than the commonly used RF test (< 90%) and has a comparable sensitivity (>70%). There was no statistically significant difference when age at onset of RA with anti-CCP positivity as anti-CCP positivity was noted among RA patients irrespective of age.

Conclusion: Detection of anti-CCP antibodies and associated immune parameters help to evaluate disease severity in RA.

Keywords: Rheumatoid Arthritis (RA), Anti-citrullinated peptide (anti-CCP), Rheumatoid factor (RF), autoantibodies.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of synovial joints ultimately leading to joint destruction. Early diagnosis, coupled with aggressive use of disease-modifying anti rheumatic drugs (DMARDs), has been shown to have a

favorable effect on the course of disease. RA is the commonest inflammatory joint disease affecting nearly 0.75 per cent of adult Indian population.¹ Measurement of Rheumatoid Factor (RF) is important in the diagnosis, prognosis and management as high titers of RF are associated in RA patients who develop extra-articular complications. RF is considered as a continuous parameter that reflects a higher probability of acquiring RA. RF can be detected not only in RA patients, but also in patients with other rheumatic or inflammatory diseases. Hence, the presence of RF is not specific for RA but is a general consequence of immune complex formation.²

Citrullination and the anti-citrullinated peptide antibodies (ACPA) play a critical role in initiating inflammatory responses in RA. The most commonly accepted molecular mechanism for citrullinated peptides/proteins in RA is that the modified antigen resulting from

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cell damage or uncontrolled apoptosis could evoke an immune response leading to autoantibodies against these peptides or the whole protein. Citrullination of arginine is catalyzed by the enzyme peptidyl arginine-deaminase (PAD) in the presence of calcium, changing the positively charged arginine to a polar but neutral citrulline. These citrullinated peptides/proteins and the relevant antibodies (ACPA) are important, not only in initiation of RA, but also in the diagnosis of the disease.³ The value of combined testing of RF and anti-CCP antibodies has been helpful in early or undifferentiated arthritis to predict RA. C reactive protein (CRP) levels directly correlate with the disease activity of many inflammatory diseases such as RA indicating that increased CRP levels can contribute to disease progression.⁴ According to the revised American College of Rheumatology (ACR) classification criteria, at least one serological test (RF or ACPA) and either of the acute phase response measures (ESR or CRP) is essential.⁵ This study was designed to know the prevalence of anti-CCP antibodies and their association with other immune parameters like CRP and ESR in RA patients from Mumbai, Western India.

Materials and Methods

This study was conducted in 100 clinically evaluated RA patients referred to our center in Mumbai, India over the period of 2 years (2009-2011). RA patients were classified according to the revised ACR criteria.⁶ This study was carried out after obtaining the requisite Ethics Committee approval and a written consent from the patients. Patients with Juvenile Rheumatoid Arthritis (JRA), patients with pain in sacro-iliac joint, pregnant women, patients with diabetes and patients with significant hyperlipidemia were excluded. After blood collection, sera were stored in aliquots at -80°C until tested. Rheumatoid factor (RF) was detected by IgM RF ELISA, Euroimmune, Lubek, Germany and values were interpreted in RU/ml. Anti-CCP antibodies were detected by ELISA using commercially available kits (Immco Diagnostics, USA). CRP levels were detected using a Nephelometer (BN ProSpec, Dade Behring, Germany). The laboratory was blinded to the disease status of patients and their visceral involvement and a double blinded study was conducted on the autoantibody positive samples.

Results

Among one hundred RA patients studied, 90 were females (90%) and 10 were males (10%). The ages ranged between 21 to 65 years. Among these, 23 patients had an early disease onset (age < 30 years), with mean age 26.3+3.8 years and 77 patients showed the late onset of disease (≥ 30 years of age) with mean age 46.5+12.4 years. Clinical manifestations revealed that 70% had multiple joint swelling, 62% patients had hand joint involvement, 64% patients had more than 3 joints involvement, 57% had symmetrical joint involvement, 59% patients had morning stiffness, 31% had tender joints whereas 14% had erosive joints. RF positivity was seen among 72% RA patients studied where titer values ranged between 61 RU/ml and 325 RU/ml. The overall incidence of anti-CCP antibodies was 83%. Anti-CCP antibody positivity among RF positive patients was 66/72 patients (91.7%) and RF levels in them had a mean+SD value of 197.1+76.5 RU/ml (Figure 1). Remaining 6/72 patients (8.3%) were anti-CCP negatives indicating that anti-CCP negativity does not rule out RA. It was observed that 17/28 RF negative patients had anti-CCP antibodies (60.7%) suggesting that anti-CCP antibodies are more specific. Anti-CCP antibodies were predominantly found in patients having tender joints (p<0.05). The details of clinical manifestations among anti-CCP positive and anti-CCP negative groups are as shown in table 1.

Table 1: Clinical presentation among anti-CCP positives and anti-CCP negative patients. (n= 100)

Clinical Manifestations	Anti-CCP Positives(n=83)	Anti-CCP Negatives(n=17)
Morning Stiffness	37 (44.6%)	9 (52.9%)
Symmetry	36 (43.4%)	8 (47.1%)
Hand Joint Involvement	35 (42.2%)	12 (70.6%)*
Polyarticular joint Involvement	19 (22.9%)	12 (70.6%)**
Tender joints	36 (43.4%)*	2 (11.8%)
Swelling	42(50.6%)	13 (76.5%)*
Erosive joints	12 (14.4%)	5(33.6%)

* p value < 0.05 is statistically significant

Among RF positive patients, raised CRP levels were found in 53/72 patients (73.6%) and raised ESR were noted in 37/72 patients (51.3%). When RF and anti-CCP positivity were considered together, 44/66 patients (66.7%) had elevated CRP levels and 11/66 patients (16.7%) had elevated ESR. The details of the ranges of

CRP and ESR levels within different groups are as depicted in table 2. Among RF positive patients, 73.6% patients

had raised CRP levels (46.9+34.8 mg/l). The levels of CRP were found to be higher (49.8+35.8 mg/l) in patients having both RF and anti-CCP positivity. It was observed that 51.3% RF positive patients had raised ESR levels (46.6+16.4mm/hr). RF negatives but anti-CCP antibody positive patients showed higher ESR levels (51.2+42 mm/hr). (Table 2)

Table 2: Comparison of RF levels with respect to raised CRP and ESR

Parameter	Raised CRP		Raised ESR	
	N (%)	Range Mead±SD	N (%)	Range Mead±SD
RF positives (n=72)	53 (73.6%)	5.5-230 (46.9±34.8)	37 (51.3%)	55-105 (46.6±16.4)
RF positives, anti-CCP positives (n=66)	44 (66.7%)	5.5-230 (49.8±35.8)	11 (16.7%)	25-80 (42±14.8)
RF negatives, anti-CCP positives (n=17)	6 (35.3%)	7.85 (46.9±34.8)	8 (47%)	30-100 (51.2±42)

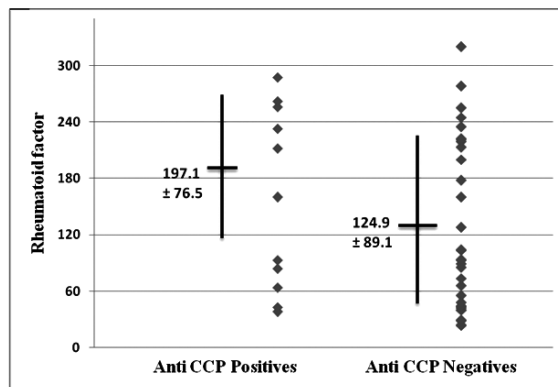
Discussion

RFs are antibodies directed to the Fc region of immunoglobulins of the IgG class and are found in 80-90% of patients with RA. Higher titers of RF are associated with severe forms of RA such as radiological progressions, rapid erosions and extra articular manifestations.⁶ However, these autoantibodies are not specific for RA.⁷ Furthermore, RF but not ACPA is sometimes present in healthy older persons, suggesting that RF can be a consequence of nonspecific immune activation. Therefore, a group of more disease specific autoantibodies like anti-CCP, which are detected in 80% of RA patients on an average and hence have been found to be useful in the

diagnosis and prognosis of RA. The fact that these antibodies may appear before the onset of the disease, suggests a potential role in primary prevention. The process of citrullination with its pathophysiologic role in RA is vividly described.^{12, 15} It was also reported that anti-CCP antibodies are useful predictive and discriminative marker for progression of disability in the longer outcome of RA patients compared to RF.

ACPAs are disease-specific, their presence is fairly stable in time and does not increase with age, and ACPA levels are not correlated with the acute-phase response. Anti-CCP antibodies can therefore be considered as better marker of early RA as compared to RF and these antibodies are reported to predict the development of erosive RA.^{8,13} Anti-CCP antibodies are also capable of predicting eventual development into RA, when found in undifferentiated RA and also have prognostic potential as these autoantibodies can distinguish between erosive and non-erosive disease.⁹ These antibodies thus represent an important addition to the diagnostic armamentarium in RA. Gupta et al, 2009 had reported that anti-CCP antibodies are highly specific and moderately sensitive for RA in Indian

Figure 1: Comparison of RF levels among anti-CCP positive and anti-CCP negative patients



CCP positivity in 84.2% patients and they had longer disease duration and a higher disease activity score as compared to anti-CCP negative patients.¹³ Further, Heidari B et al, 2009 reported an incidence of 85.6% for anti-CCP antibody among RA patients, where the test discriminated RA from non-RA patients with high accuracy and predicted progression of UIA to RA with moderate accuracy.¹³ Our study showed 72% positivity for RF and 83% positivity for anti-CCP antibodies. Anti-CCP antibody positivity among RF positive patients was observed to be 91.7%. On comparison of RF levels between anti-CCP positives and anti-CCP negatives

groups, RF titers were higher in anti-CCP positives group. The percentage distribution of polyarticular joint involvement and joint swelling is found to be more in anti-CCP negative patients as compared to anti-CCP positive patients. On the other hand, tenderness in joints is significantly associated with anti-CCP positive patients, when compared with anti-CCP negative patients. Other immune parameters when taken into consideration, our data showed modest correlations between (changes in) anti-CCP antibodies and RF levels and the inflammatory indices, namely ESR and CRP. The correlation of changes in RF and anti-CCP antibody levels with changes in acute-phase markers was stronger for the group having both RF and anti-CCP positives as compared to RF negatives and anti-CCP positives group.

Presence of RF and anti-CCP antibodies along with immune parameters taken together should certainly not be regarded as mere epiphenomena, but should be addressed as influential diagnostic markers for RA. The identification of new autoantigens, particularly, citrullinated peptides, and the characterization of cellular and molecular processes underlying the pathological autoimmune reactions against them, can thus provide new insights into the pathogenesis of RA.^{16,17} Better understanding of the RA disease process will indeed help in developing novel therapeutic concepts, which may further allow, in proper disease treatment and management.

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Study of Stroke in Young Adults (18 to 45 years) with special reference to Hypertension as a Risk Factor

R Patil*, R P. Medhi**, S Choubey***

Abstract

Objectives: To determine the percentage of different categories of stroke patients according different epidemiological parameters. To find out major risk factors causing stroke in young adults. To find out association of hypertension with stroke as a risk factor.

Methods: The study was conducted over 100 indoor patients admitted in Aditya hospital, from age group 18-45 years with history and investigation finding suggestive of cerebrovascular disease.

Results: Among 100 patients, 63 patients were having hemorrhagic stroke and 37 with ischemic. 72 patients were males and 28 were females. Total 65% patients were having HTN in all patients studied. Hypertension was risk factor for 76 % of hemorrhagic stroke patients and 45% of ischemic stroke patients. Basal ganglion was common site for hemorrhage. Atherosclerosis was major cause for ischemia followed by cardio-embolic stroke. MCA territory was major site in ischemia. 24% hemorrhagic stroke patients expired in hospital and 8% ischemic stroke expired in hospital.

Conclusions: Stroke is common in young males. Hypertension with an irregular treatment is important risk factor for stroke especially hemorrhagic stroke in young adults. Hypertension is important for atherosclerosis related stroke. Hemorrhagic stroke was having higher mortality in hospital than ischemic stroke.

Key words: ACAs : Anterior Cerebral Arteries, AF : Atrial Fibrillation, AVM : Arteriovenous Malformation, HTN : Hypertension, IHD : Ischemic heart disease, MCA : Middle cerebral artery, PCA : Posterior Cerebral Artery, RHD : Rheumatic Heart Disease, SAH : Subarachnoid Hemorrhage, SD : Standard Deviation, SLE : Systemic Lupus Erythmatosus.

Introduction

Stroke is the leading cause of adult disability and is the second commonest cause of death, world wide. More than two-thirds of the global burden of stroke is borne by developing countries, where the average age of patients with stroke is 15 years younger than in developed countries¹. The available limited data indicate that stroke occurring in young people is more often atherothrombotic in origin in developing countries,² in contrast with developed countries where arterial

dissection and cardioembolic aetiologies predominate. There are notable differences in incidence, presentation, risk factors, and prognosis in stroke occurring in individuals younger than 45 years compared with individuals older than 45 years.³

Because of the lack of recognition of acute stroke symptoms by patients, witnesses, and the health care community, the treatment of young stroke patients may be compromised. In the last two decades, extraordinary imaging technology has been introduced that allows the physician to make physiologic distinctions between normal, ischemic, and infarcted brain tissue. Which of the sophisticated imaging techniques will contribute to improved clinical outcome is still to be determined but certain ones, such as diffusion-weighted magnetic resonance imaging, have already proved invaluable in stroke work.⁴

The present study was undertaken to determine the percentage of different categories of stroke according different epidemiological parameters and to find out major risk factors causing stroke in young adults and correlation of hypertension as a risk factor.

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Material & Method

The study was conducted in patients admitted in the departments of medicine, neurology and neurosurgery in Aditya Diagnostics and Hospitals, Dibrugarh, Assam, for period of one year from 2009 – 2010. The study was conducted over 100 indoor patients, from age group 18-45 years with history and investigation finding suggestive of cerebrovascular disease. All cases of stroke in age group 18 to 45 years supported by specific investigations were taken for study.

Patients with space occupying lesion in brain, demyelinating diseases like multiple myeloma, infections like meningitis, traumatic head injury were excluded. Clinical evaluation of a young adult presenting with acute stroke involves obtaining a detailed history, including previous medical history, recent trauma, fever, weight loss, infection including chickenpox, and drug ingestion. Certain diseases are associated with a higher risk for stroke, such as complex congenital heart disease, sickle cell disease, or coagulopathy.

A careful family history was taken, with attention to premature vascular disease, hematologic disease, and mental retardation.

Stature and build was assessed, checking for clinical signs of Marfan or Ehlers-Danlos syndrome, or the thin habitus of homocystinuria. The skin was examined for birthmarks, rash, signs of trauma, various neurocutaneous markers like Café au lait spots as well as splinter hemorrhages or embolic skin rash.

Funduscopy examination was done which is important in looking for disc elevation, hemorrhage, changes of chronic hypertension or retinal emboli. Blood pressure on right arm (average of three readings separated by one minute each) was recorded. Grading of HTN was done as per JNC7 GUIDELINES:⁵

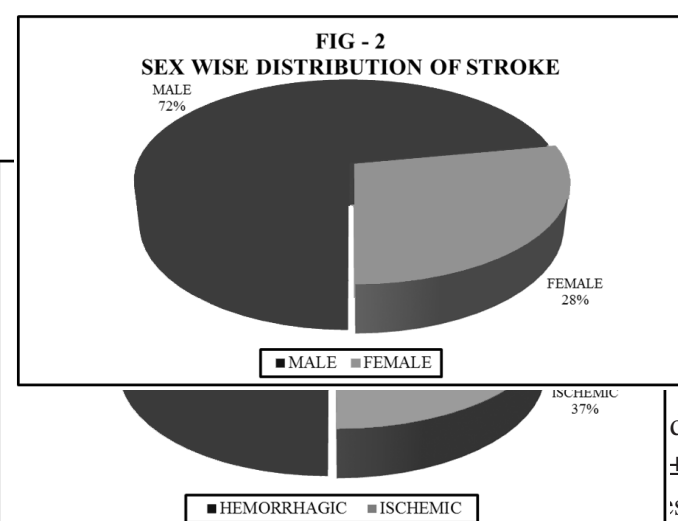
A detailed nervous system and cardiovascular examination was done. Clinical Assessment by Glasgow Coma Scale (GCS):⁶

All routine blood investigations were done including special investigations like Rh factor, ANA, antiphospholipid antibody, lupus anticoagulant, serum homocysteine level. ECG, echocardiography was done and then carotid echo Doppler was done if required. Imaging studies of brain was done initially CT brain and if required MRI Brain, CT angiography. All statistical

calculations were done from online statistical software (<http://in-silico.net/statistics>)

Results

Among 100 patients, 63 patients were having hemorrhagic stroke and 37 with ischemic. (Figure No.1). Among the total 100 patients, 72 patients were males and 28 were females. (Figure No. 2).



was 39.77 ± 5.78 while in females mean age \pm SD was 42.17 ± 4.22 years.

Fifty two percent of hemorrhagic stroke patients were from age >40 years, 67% ischemic stroke patients were from age >40 years. There was a male preponderance in both rural and urban area. (Table No.1)

Hospital statistics show that, Ahum, Kalita, Muslim, Missing, Kachari, Marwadi Bengali and some other tribes from hilly areas especially from Arunachal Pradesh are population attending our hospital. Most of stroke were from Ahum, Kalita people. Total 65% patients were having hypertension (HTN) in all patients studied. Hypertension was cause for 76% of hemorrhagic stroke, 6% were having arteriovenous malformation. Other causes were

Table-1 : Age Specific Types of Stroke.

Age Group (in years)	Hemorrhagic		Ischemic		Total	
	(n)	(%)	(n)	(%)	(n)	(%)
18-25	1	1.58	1	2.70	2	2.00
26-30	5	7.93	2	5.40	7	7.00
31-35	7	11.11	3	8.10	10	10.00
36-40	17	26.98	7	18.91	24	24.00
41-45	33	52.38	25	67.56	58	58.00
Total :	63	100	37	100	100	100.00

aneurysm, anticoagulant induced. Cause could not be established in 13 % patients. (Table No. 2).

Table-2 : Etiology of Hemorrhagic Stroke

Causes	Number (n)	Percentage (%)
Hypertension	48	76.19
AVM	4	6.34
Aneurysm	2	3.17
Anticoagulants	1	1.58
Unknown	8	12.69
Total	63	100.00

In all ischemic stroke patients 35.13% had large artery atherosclerosis, 18.91% had cardio-embolic stroke, 13.51% had small vessel occlusion (lacunae); 5.4% patients with other determined etiology like SLE (vasculitis), vertebral arterial dissection and unknown in or undetermined etiology in 27.02% patients. (Table No.3)

Table-3 : Etiology of Ischemic Stroke

Causes	Number (n)	Percentage (%)
Large-artery atherosclerosis (embolism/thrombosis)	13	35.13
Cardio-embolism	7	18.91
Small-vessel occlusion (lacunae)	5	13.51
Stroke of other determined etiology	2	5.40
Stroke of undetermined etiology	10	27.02
TOTAL :	37	100.00

In hemorrhagic stroke patients apart from HTN (76%) risk factors were Diabetes mellitus, smoking, alcoholism, past h/o stroke or TIA as a risk factor. Among all ischemic stroke patients hypertension (46%) was major risk factor. Other risk factors were Diabetes mellitus, RHD, AF, IHD, smoking, alcoholism, past h/o stroke or TIA, hyperlipidemia, positive family history and SLE. Out of all hemorrhagic stroke patients half of the patients were having GCS <13 and half were having GCS between 13-15. While in ischemic stroke patients 68 % patients having GCS between 13-15. (Table No.4)

Most common presenting complaint in the patients with hemorrhagic stroke and ischemic stroke was hemiplegia (81%) with equal in both left and right side

Table-4 : Risk Factor of Stroke

Groups	Hemorrhagic (N=63)		Ischemic (N=37)		Total (N=100)	
	(n)	(%)	(n)	(%)	(n)	(%)
HTN Total	48	76.19	17	45.94	65	65.00
(a) HTN on Rx	15	23.80	9	24.32	24	24.00
(b) HTN not on Rx or irregular Rx	33	52.38	8	21.62	41	41.00
DM	7	11.11	6	16.21	13	13.00
Rheumatic Heart disease	1	1.58	4	10.81	5	5.00
Atrial fibrillation	1	1.58	4	10.81	5	5.00
Ischemic Heart disease	1	1.58	5	13.51	6	3.00
Dyslipidemia	3	4.76	4	10.81	7	7.00
Smoking	11	17.46	6	16.21	17	17.00
Alcoholism	9	14.28	5	13.51	14	14.00
Past stroke or TIA	4	6.34	6	16.21	10	10.00
Other systemic disorder or risk factor	2	3.17	1	2.7	3	3.00
No obvious risk factor	5	7.93	6	16.21	11	11.00

with or without facial weakness. Altered sensorium, headache and vomiting was more in hemorrhagic stroke than ischemic.

In all hemorrhagic stroke (total- 63) patients - 63.49% patients were having Basal ganglia bleeding, followed by lobar bleed, thalamic bleed, pontine bleed, cerebellar bleed, subdural hematoma, subarachnoid hemorrhage. (Table No. 5)

Table-5 : CT Scan Site of Hematoma

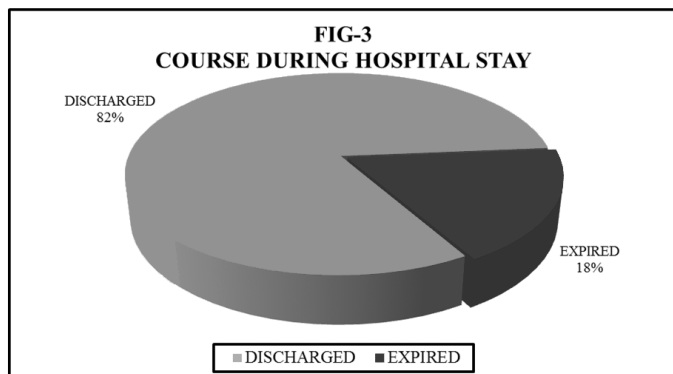
SITE	Number (n)	Percentage (%)
Basal Ganglia	40	63.49
Thalamus	5	7.90
Pons	3	4.76
Cerebellum	2	3.17
Lobar	10	15.87
SDH	2	3.17
Subarachnoid Hemorrhage	1	1.58
TOTAL	63	100.00

Area of involved in ischemic stroke (total - 37) patients – MCA territory infarct in 23 (62.16%), vertebro-basillar (PCA, Cerebellar) stroke in 6 patients. lacunar stroke was present in 5 patients, ACA territory infarct in 3. (Table No.6)

Table-6 : CT Scan Site of Ischemia

SITE	Number (n)	Percentage (%)
Lacunar Infarct	5	13.51
MCA Territory	23	62.16
ACA Territory	3	8.10
Vertebro-basillar (PCA, Cerebellar)	6	16.21

Our study hospital mortality was 18% and it was more in case hemorrhagic stroke (15%) than ischemic (3%) stroke. (Figure 3)



Discussion

Most of studies outside India and in some parts in India have shown that ischemic stroke have higher incidence than hemorrhagic stroke. In our study hemorrhagic stroke was very high as compared to ischemic. Reason might be higher incidence of HTN due high salt intake and negligence toward treatment of HTN especially by males. Health education is essential to increase the compliance of treatment. Most studies proves that stroke in young adult is common in males than females. Further detailed studies are essential in those young patients who were on regular treatment and had a stroke, to find out whether the goal of blood pressure is achieved or not and if yes then the probable causes of stroke. In our study males were having higher incidence of stroke.

Intra cerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) together constitute approximately 30-35% of all strokes in patients under the age of 50 (Awada⁷1994). Most common etiology in most of the studies are HTN, AVM, aneurysm. Hypertension (HTN) is common as both a cause and risk factor in young stroke patients (Lai *et al.*⁸ 2005). Within the young stroke population, males between the ages of 30-45 have the highest rate of HTN (Nayak *et al.*⁹1997;). This is particularly true of males living in Asian populations (Lee *et al.*¹⁰2002). In addition, young people may not always be compliant with treatment for hypertension, or are not fully aware of the risks of hypertension (Spengos and Vemmos¹¹2010). Our study also shows HTN as a commonest etiology especially in males.

Higher incidence of hypertension related stroke in our study as mentioned above may be due to ignorance of young patients toward hypertension (lack of health education) and taking irregular medication may be due to outdoor work (mostly done by males), excess intake of

salt in salad and salt containing items like khar (traditional eating habit in this region).

Cardiac embolism is a frequent cause for patients younger than 40, while advanced atherosclerosis is a common etiology in patients aged 40-49 (Mehndiratta *et.al.*¹² 2004 India). Our study also shows that atherosclerosis is common in age between 40-45 years whereas cardioembolic cases are more in cases of age <40 years.

In all ischemic stroke hypertension was major risk factors, followed by Diabetes mellitus, past h/o stroke or TIA, RHD, AF, IHD, smoking, alcoholism.

Study by Das SK *et al*¹³ 2007, shows basal ganglia and thalamus as a commonest site of hemorrhage. Study Data from Ruiz-Sandoval JL *et al*¹⁴ 1999, Shows that ganglionic bleed is more in HTN while lobar bleed is mainly by AV malformations. Our study a proves the findings of most of studies regarding site of hemorrhage.

Middle cerebral artery related stroke were more, followed by anterior cerebral artery and vertebra-basilar system strokes. Our study corresponds with S.Dinesh *et al*¹⁵ 1997 shows that middle cerebral artery stroke were more than vertebro-basillar and ACA stroke in young adults.

Marini *et al.*¹⁶ 2001 Italy shows higher mortality in hemorrhagic stroke. Our study hospital mortality was 18% and it was more in case hemorrhagic stroke (15%) than ischemic (3%) stroke (p value 0.0485). Most of the patients having ischemic stroke were discharged earlier (<7days) as compared to hemorrhagic stroke (p value 0.0097). Most of the patients having hemorrhagic stroke were discharged late (>16 days) from hospital as compared to ischemic stroke (p value 0.0126).

Conclusions

The study revealed that stroke in young adults is common in hypertensive patients especially males. Hemorrhagic stroke is more common than ischemic stroke with higher mortality in hospital. Hypertension was commonest cause for hemorrhage. Diabetes mellitus, smoking, alcoholism are other important risk factors in hemorrhagic stroke.

In ischemic stroke HTN, diabetes mellitus, RHD, AF, IHD, smoking, alcoholism, past h/o stroke or TIA, hyperlipidemia, positive family history and SLE are

important risk factors.

Basal ganglia as a common bleeding site and then lobar, thalamic, pontine, cerebellar, subdural and subarachnoid hemorrhage in descending order of incidence. MCA territory infarct was most common site of lesion in ischemic stroke, followed by vertebro-basillar, lacunar strokes and ACA territory infarct in descending order of their incidence. It appears that ischemic stroke due to atherosclerosis is more common than cardio-embolic stroke possibly because of poorly controlled blood pressure.

Hence to avoid both hemorrhagic and ischemic stroke in young adults (18-45 years), it is very essential to control blood pressure by increasing the patient compliance. Health education regarding hypertension and its possible complications like stroke should be given. Importance of doing regular blood pressure check up to achieve blood pressure goal should be told to every patient. Patient compliance can be increased by prescribing cheap and easily available antihypertensive.

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A Study of Liver Function Abnormality in Enteric Fever

G. C. Deka*, U. K. Nath**

Abstract

Objectives: To study the relationship between the liver function and enteric fever admitted in the medicine ward in Jorhat Medical college & Hospital, Jorhat

Methods: Total 51 cases of enteric fever (male=31 and female=20) aged >12 years were taken in this study based on clinical features, blood culture and agglutination test. Liver function and other biochemical tests were done accordingly.

Results: Out of 51 cases of enteric fever 31 cases were male (58.82%) and 20 cases were female (41.17%) indicating male predominance.

49.02 % patients had elevated serum bilirubin level above the normal range with elevated direct bilirubin in 21.56% and indirect bilirubin in 27.45% of cases. AST, ALT and ALK Phosphatase were elevated in 52.94%, 47.04 % and 39.21% of patients respectively.

Conclusion: Liver function abnormality is a common association in enteric fever. Therefore enteric fever could be a differential diagnosis in case of fever with jaundice.

Key words: enteric fever, *s.typhi*, liver function tests.

Introduction

Enteric fever is caused by *S. Typhi*, a gram negative bacteria with different strains, prevalent worldwide especially in the developing countries. It involves almost all the major systems in the body including liver in the form of hepatomegaly, jaundice, biochemical alterations and histopathological changes. Its occurrence with jaundice indicates liver involvement as a result of generalized toxemia or invasion by salmonella organisms.

Enteric fever is one of the most common infectious disease in our part of the country due to lack of proper hygienic condition, poverty, illiteracy and health care unawareness. Jorhat Medical College being a newly established college, no scientific studies as such has been published yet from our department. We encounter lots of patient in day to day practice with enteric fever along with jaundice in our institute coming from the surrounding areas of Jorhat including Majuli, which is the biggest river island of the world. Considering all these facts we have

done this study to find out the relationship between the enteric fever and hepatic dysfunction.

Material and Methods

This is a hospital based prospective study which was aimed to find out the correlation between liver function and enteric fever. We included all the patients presented with fever and jaundice excluding the cases with past history suggestive of chronic liver disease, alcoholic liver disease, recent jaundice, malaria, use of drugs causing jaundice including, NSAIDS (Paracetamol) herbal medication, viral hepatitis & immunocompromised patients like HIV/AIDS.

On admission, after gathering clinical history as per proforma and recorded symptoms and signs, we collected blood for culture and agglutination test according to the duration of fever along with liver function and other biochemical tests. We excluded malaria and viral hepatitis by doing rapid test for malaria and viral hepatitis profile. In few suspected cases we excluded HIV/AIDS by doing ELISA. Enteric fever was diagnosed by serology and culture.

Objectives

To study the relationship between the liver function and enteric fever admitted in the medicine ward in Jorhat

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Medical college and Hospital, Jorhat

Place of study: Jorhat Medical College and Hospital, Jorhat

Duration: One year from November 2011 to November 2012

Sample Size: Total 51 cases were studied

Inclusion criteria:

1. All cases admitted with the diagnosis of enteric fever.

Exclusion criteria:

1. Chronic liver disease
2. Alcoholic liver disease
3. H/o recent jaundice
4. Malaria, Leptospirosis
5. H/o use of drugs causing jaundice including herbal medication/ NSAIDS
6. viral hepatitis
7. immunocompromised patients like HIV/AIDS

Results and observations

Out of 51 cases of enteric fever 31 cases were male (58.82%) and 20 cases were female (41.17%) (Table 1.) indicating male predominance.

Table 1. Sex distribution

Sex	No(n=51)	%
Male	30	58.82
Female	21	41.17

Younger age group are more vulnerable to enteric fever especially 21-30 years of age group(25.49%) (Table 2).

Table 2. Agr distribution

Age	No of Cases (n=51)	%
12-20	12	23.52
21-30	13	25.49
31-40	11	21.56
41-50	7	13.72
51-60	7	13.72
>60	1	1.96

The most common presenting symptoms were fever (100%),headache (70.58%),abdominal pain(68.62%) followed by anorexia and myalgias (62.74%). 37.2 % patients presented with diarrhea and 29.41% with jaundice.(table 3).

On examination, we encountered fever (100%) with abdominal tenderness (68.62%) followed by hepatomegaly (39.21%), anaemia (37.25%) and jaundice

Table 3. presenting symptoms of 51 cases of typhoid fever

Symtoms	Cases (n=51)	%
Fever	51	100
Headache	36	70.58
Anorexia	32	62.74
Myalgia	32	62.74
Abdominal pain	35	68.62
Nausea/vomiting	10	19.6
Diarrhea	19	37.2
Jaundice	15	29.41
Epistaxis	2	3.9
Cough	9	17

(35.29%). Splenomegaly was found in 13.72% of patients.(Table 4).

Table 4. Signs of 51 cases of typhoid fever

Signs	Cases (n=51)	%
Fever	100	100
Abdominal tenderness	35	68.62
Anaemia	19	37.25
Hepatomegaly	20	39.21
Splenomegaly	7	13.72
Jaundice(icterus)	18	35.29
Rose spot	0	0

On biochemical evaluation, we found that, out of 51 patient 49.02 % patients had elevated serum bilirubin level above the normal range with elevated direct

Table 5. Haematological and biochemical profile of 51 cases of typhoid fever

Alteration in hepatic and other biochemical function	Total cases no (n=51)	%
ALT	24	47.05
AST	27	52.94
ALK Phosphatase	20	39.21
S.bilirubin	25	49.02
Direct	11	21.56
Indirect	14	27.45
Albumin	15	29.41
Hb%	19	37.2
WBC>	5	9.8
WBC<	2	3.9
Platelet	0	0
PT	7	13.7
S.creatinine	2	3.9
Urea	2	3.9
S.Na+	5	9.8
S.K+	7	13.7
RBS 0	0	0

bilirubin in 21.56% and indirect bilirubin in 27.45% of cases. AST ,ALT and Alkaline Phosphatase were elevated in 52.94% ,47.04 % and 39.21% of patients respectively.

Male : 58.82%

Fig.1. Sex distribution in enteric fever

Discussion

We studied 51 cases of enteric fever during our study period since Nov.2011 to Nov 2012.We have found that males are more commonly infected with enteric fever than female (58.82% vs 41.17%) which is probably due to fact that males are involved more in outdoor activities most of the time and use to take food/water outside which is the most common source of typhoid fever transmission.

We also found that younger age group(21-30 years) are most susceptible to enteric fever as compared to older age(>50 years) group(25.49% vs 13.72%) which is might be also due to increase outdoor activity and tendency to take food outside home. Khosla et al.¹ in his study on typhoid hepatitis also noticed predominance of male (60%)with younger age group 15-45 years(mean 26.2 years).

In our study,on evaluation of signs and symptoms we have found fever in 100% of cases with headache (70.58%),abdominal pain(68.62%) followed by anorexia and myalgias(62.74%). 37.2 % patients presented with diarrhea and 29.41% with jaundice.

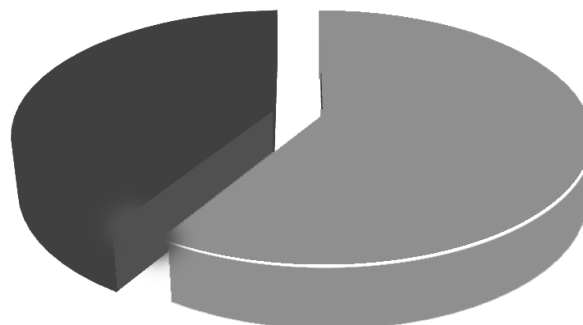
Osler² first described hepatic involvement in typhoid fever who documented enlarged tender liver with clinical jaundice in 8 out of 1500 cases. Stuart and Pullen³ observed hepatomegaly in all cases of typhoid,but Ayhan et al.⁴ in their study of 16 cases of typhoid found hepatomegaly in 7 cases(43.75%). Hepatomegaly was revealed in 14% of the cases in a study done by Mirsadraee M et al⁵. In our study we documented hepatomegaly in

20 cases(39.21%) out of 51 cases of enteric fever which is consistent with the observation by Ahmet et al (42%)⁶ and Ayhan et al.

Morgestrn et al⁷, has reported incidence of jaundice in 9% of cases of typhoid fever, where as Giltin⁸ has reported jaundice in 33% cases. In our study we have found clinical jaundice in 29.41% of cases. 49.02% patient had biochemical evidence of elevated bilirubin which is mostly of indirect bilirubin in our study.Raised bilirubin level was found in 13(25%) patients in a study done by Ali Hassan Abro et al.⁹

Abnormal AST and ALT in combination are indicative of a hepatocyte disorder. Many investigators used these enzymes for evaluation of hepatic involvement during typhoid fever. The frequency of elevated serum enzyme have been reported by Van den Bergh et al¹⁰ in 26% of cases, Alanine aminotransferase (ALT) elevated in 22 % of cases in a study done by Mirsadraee M et al. Morgenstrn et al⁷ and Mirsadraee et al⁵found elevated ALT in 52% and 22% cases respectively , whereas in the study done by Ali Hassan Abro at el found that the alanine aminotransferase levels was elevated in 85% of patients.

ALT and



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ed high

P1 (prothrombin time) in 63.5% and Ali Hassan Abro at el found increased prothrombin time in 53.8% of patients whereas we found 13.7% with elevated PT .

Serum albumin level was 38% cases in the study of Ali Hassan Abro at el and (41.9%) in Ahmet et al but we found low albumin level(29.41%) in our study in cases of typhoid fever.

Conclusion

In addition to other common presenting features , hepatic dysfunction is closely associated with enteric fever and presence of high grade fever, jaundice and tender hepatomegaly should arouse suspicion of typhoid hepatitis and it has to be differentiated from other common infectious diseases like malarial , amoebic and viral hepatitis in

tropical country . Recognition of typhoid hepatitis is very important as a correct diagnosis and early institution of

specific therapy will improve the prognosis of this common hazardous public health problem.

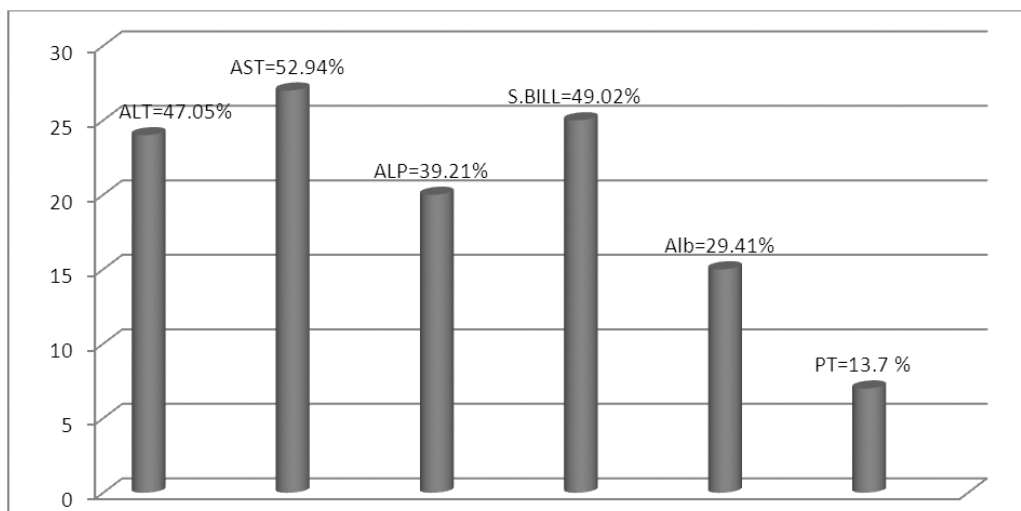


Fig.2. Liver function abnormality in enteric fever

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To study the co-relation of pulmonary hypertension and interstitial lung disease in systemic sclerosis

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Abstract

Introduction : Pulmonary hypertension (PHT) occurs as a manifestation of systemic sclerosis (SSc) and can be due primarily to pulmonary vascular abnormalities, or secondary to interstitial lung or cardiac involvement. This study was conducted with aims to study association of systemic sclerosis with pulmonary hypertension, to study association of systemic sclerosis with interstitial lung disease and to study association between systemic sclerosis with interstitial lung disease and pulmonary hypertension.

Methods and Materials : This was a hospital based, observational study, conducted in Assam Medical College & Hospital, Dibrugarh from 1st September 2010 to 31st August 2011. All confirmed cases of systemic sclerosis male and female, 13 years and above, were selected during study period. Patients with Primary cardiac disease obstructive lung disease were excluded from study. After history, detailed physical examination of the patient routine investigation, skin biopsy, ECG, Echocardiography, chest x-ray, HRCT thorax were done in every cases.

Results and Observations : Mean age at diagnosis SSc was found to 50 ± 11.2 years and diagnosis of pulmonary hypertension is 52 ± 11.2 years. Of 30 systemic sclerosis patient 12 patient (40%) has found to be associated with pulmonary hypertension and 22 patient (73.3%) has found to be associated with interstitial lung disease. Of 22 patient of systemic sclerosis with interstitial lung disease 12 patients (54.5%) are associated with pulmonary hypertension.;

Conclusion : The current study has revealed that in systemic sclerosis is commonly associated with interstitial lung disease and pulmonary hypertension.

Key Words : Systemic Sclerosis, Interstitial-lung disease, Pulmonary Hypertension

Introduction

Pulmonary hypertension (PHT) occurs as a manifestation of systemic sclerosis (SSc) and can be due primarily to pulmonary vascular abnormalities, or secondary to interstitial lung or cardiac involvement. The former is usually found in patients with limited scleroderma and minimal or no pulmonary fibrosis^(1,2). In contrast, patients with diffuse scleroderma may develop PHT on the basis of severe pulmonary fibrosis, but this is uncommon⁽³⁾. The frequency of PHT in SSc is uncertain, but was clinically detectable in 9% of patients in a large prospectively followed cohort⁽²⁾; in another study, 33% were diagnosed on right heart catheterization⁽¹⁾ and autopsy

evidence was found in 65% of CREST patients⁽⁴⁾. In a previous study, we found pulmonary disease to be the most frequent cause of death in SSc⁽⁵⁾.

Aims and Objectives

- To study association of systemic sclerosis with pulmonary hypertension.
- To study association of systemic sclerosis with interstitial lung disease.
- To study association between systemic sclerosis with interstitial lung disease and pulmonary hypertension.

Methods and Material

This was a hospital based observational study carried out in adult patients admitted in different units of Medicine department, Assam Medical College and Hospital, Dibrugarh, during a period of one year from 1st September 2010 to 31st August 2011.

Selection of Cases :

- All confirmed cases of systemic sclerosis irrespective

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of sex. Each patient fulfilled the American College of Rheumatology preliminary criteria for the diagnosis of SSc⁽⁶⁾.

- Age group : 13 years or above.

Exclusion Criteria :

- Primary cardiac disease
- Obstructive lung disease

30 confirmed cases of systemic sclerosis during study period were interviewed. After history, detailed physical examination of the patient routine investigation (urine routine, Hb%, WBC, ESR, DD), RBS, serum creatinine, blood urea, skin biopsy, ECG, Echocardiography, chest x-ray, HRCT thorax were done in every cases. Pulmonary hypertension was diagnosed according to the presence of one of the following three criteria: (1) a resting mean pulmonary artery pressure (MPAP) of >25mmHg with a pulmonary capillary wedge pressure of <12mmHg on right heart catheterization; (2) a right ventricular systolic pressure of >35mmHg estimate by Doppler echocardiography; (3) echocar-diographic evidence of right ventricular dilatation, pulmonary and/or tricuspid regurgitation or paradoxi-cal interventricular septal motion⁽⁷⁾. The statistical analysis was done by using SPSS software version 16.

Results and Observations

The results and observations found in patients were as follows :

Table : 1.1

Mean age of the patients

	Systemic Sclerosis	Pulmonary Hypertension
Age (years) (Mean±S.D.)	50±11.2	52±11.2

Mean age at diagnosis SSc was found to be 50±11.2 years and diagnosis of pulmonary hypertension is 52±11.2 years.

Table-1.2

Sex Distribution of the patient

Sex	Number of cases	Percentage (%)	Ratio (Male : Female)
Male	8	26.67	1 : 2.75
Female	22	73.33	
Total	30	100.00	

It was observed that there was an overall female preponderance.

Table-1.3
Clinical Presentation

Clinical Presentation	Number of Cases	Percentage (%)
Raynaud’s Phenomenon	27	90
Telangiectasia	27	90
Calcinosis	9	30
Finger-Up pits or scars	12	40
Gastrointestinal	23	76.7
Arthritis	6	20
Myositis	2	6.7
Renal insufficiency	1	3.3

In 30 patients with SSc most common clinical presentation was Raynaud’s phenomenon, telangiectasia followed by gastrointestinal manifestation.

Table-1.4

Systemic Sclerosis and pulmonary hypertension

	Systemic Sclerosis	Pulmonary Hypertension	Percentage %
No. of Cases	30	12	40

Of 30 systemic sclerosis patient 12 patient has found to be associated with pulmonary hypertension, that is around 40% of the patients are associated with pulmonary hypertension.

Table-1.5

Systemic Sclerosis and Interstitial lung disease

	Systemic Sclerosis	Interstitial Lung Disease	Percentage %
No. of Cases	30	22	73.3

Of 30 systemic sclerosis patient 22 patient has found to be associated with interstitial lung disease, that is around 73.3% of the patients are associated with interstitial lung disease.

Table-1.6

Interstitial Lung Disease and Pulmonary Hypertension

	Interstitial Lung Disease	Pulmonary Hypertension	Percentage %
No. of Cases	22	12	54.5

Of 22 patient of systemic sclerosis with interstitial lung disease are 12 patients (54.5%) associated with pulmonary hypertension.

Discussion

In the present study, we analysed the clinical and

laboratory features of 12 SSc patients with PHT. The frequency of PHT amongst 30 SSc patients at this centre was 40%, which is comparable to the reported prevalence of 33%, Ungerer et al.⁸ But more than the prevalence of 9% reported by Stupi et al.³ Sackner et al.⁹ noted that one half of their patients with PHT only had evidence of this complication on catheter studies. Prevalence figures for PHT in SSc are therefore heavily influenced by the extent of the investigations carried out.

Mean age at diagnosis SSc was found to be 50±11.2 years and diagnosis of pulmonary hypertension is 50±11.2 years while D Mukerjee et reported mean age of at diagnosis of 66 years.¹⁰ It was observed that there was an overall female preponderance. Female preponderance also noted in study conducted by the D Mukerjee et.¹⁰

In 30 patients with SSc most common clinical presentation was Raynaud's phenomenon (30%), telangiectasia (30%) followed by gastrointestinal manifestation. (76.7%). E.T. KOH et al in 1996 reported in patients with systemic sclerosis with pulmonary hypertension that more common manifestation as Raynaud's phenomenon (94%), telangiectasia (94%) followed by the gastrointestinal manifestation (82%) which is comparable to our study.

Of 30 systemic sclerosis patient has found to be associated with systemic sclerosis, that is around 40% of the patients are associated with pulmonary hypertension. Of 30 systemic sclerosis patient 22 patients has found to be associated with interstitial lung disease, that is around 73.3% of the patients are associated with interstitial lung disease. Of 30 patient of systemic sclerosis with interstitial lung disease are 12 patients (54.5%) associated with pulmonary hypertension. In this study it is seen that, those patient having systemic sclerosis with interstitial lung disease is having more chance of pulmonary hypertension (54.5%) than those without interstitial lung disease.

Conclusion

The current study has revealed that systemic sclerosis is commonly associated with interstitial lung disease and pulmonary hypertension. Since the study is conducted in limited no of patients further study with larger sample size is needed.

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Review Article

Current Status of Allogeneic Hematopoietic Cell Transplantation

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Summary

Allogeneic hematopoietic stem transplantation is currently a standard treatment for a number of non-malignant and malignant disorders. Advances in the field of transplantation immunology, expansion of donor pools, improved supportive care, application of reduced intensity preparative regimens allowing older patients to be eligible, are some of the factors responsible. Nevertheless, our understanding of graft versus host reaction leading to a iatrogenic condition called graft versus host disease (GVHD), the most unique complication of an allogeneic transplantation remains incomplete.

History

Replacing a defective bone marrow in hematological disorders with normal hematopoietic cells from another person was attempted in middle of 20th century. After the Second World War II the grave consequences of nuclear radiation to living beings became apparent. One such recognized complication was irreversible damage to the hematopoietic stem cells in the bone marrow. A small number of US physicians, led by E.D. Thomas in Cooperstown first and Seattle later and George Santos in Baltimore became involved in the area of stem cell transplantation which was called bone marrow transplantation (BMT) then. The knowledge of existence and renewal capacity hematopoietic stem cell was already evident by this time. In 1950s the knowledge of transplantation immunology was rudimentary, the process of transplantation arduous and failure was inevitable. Only perseverance of this small number of physicians could bring

the field to present day highly successful method of treatment for some otherwise potentially fatal malignant and non-malignant conditions. The understanding of human leukocyte antigen (HLA) improved rapidly following the work of the team led by Jon Van Rood in Netherland. This facilitated durable engraftment and reduced rejection of donor marrow. By late 1960s several groups in the US reported successful BMT for non-malignant conditions like severe combined deficiency (SCID) and advanced acute leukemia. E.D. Thomas was awarded Nobel Prize in medicine in 1990 for his contribution in the field. George Mathe in Europe did pioneering work around the same time. Since early 1980s there has been exponential increment in BMT across the globe. Currently more than 100,000 such procedures are carried out.

Initially myeloablative (MA) chemotherapy and total body irradiation (TBI) were considered to be primary requisite for successful outcome. However, in subsequent years it became clear that an immunological phenomenon known as graft versus leukemia/tumor (GvL or GvT) was significantly responsible for eradication of residual diseased cells (ref). This has led to development of reduced intensity (RIC/RIST) preparative/conditioning regimens that minimized initial morbidity and mortality (ref). Nevertheless, such an approach has not been able to significantly reduce the bugbear of allogeneic transplants - graft versus host disease (GVHD), both acute and chronic ones.

In last two decades we have been witness to many changes in regards to choice of donors, source of stem cells, conditioning regimens, post-transplant immune system manipulation and supportive care. These have helped to include older patients and advanced stage

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diseases with improved results. Better understanding of various T cell subsets and other players of the immune system at the molecular level should lead to more improved results in coming years.

With the technical feasibility of collecting hematopoietic stem cells and its progenitors from peripheral blood, umbilical cord blood, it became necessary to change nomenclatures. BMT now stands for blood and marrow transplantation. More commonly used term is hematopoietic stem cell transplantation (HSCT or SCT).

Types of HSCT

1. Allogeneic Stem Cell Transplantation. The source of stem cells is from another individual who acts as a donor.
2. Autologous Stem Cell Transplantation. The source of stem cells is from the patient self.

Stem Cell Sources

1. Bone marrow (BM)
2. Peripheral blood (PBSC); collected following mobilization of stem cells to the peripheral blood with hematopoietic growth factors like G-CSF. Chemotherapy or newer molecules like plerixafor, a CXCR4 antagonist can be used with G-CSF for autologous transplantation.
3. Umbilical cord blood (UCB)

Types of allogeneic transplantations according to donor types

1. Sibling donor transplantation; a full HLA or near full HLA match
2. Matched unrelated donor (MUD) transplantation; usually with a full or near full match
3. Haploidentical donor transplantation; the donor is either a parent or one of the sibling who has partial match with the patient (recipient).

In all these of types of transplantations, the stem cell source could be bone marrow, peripheral blood or umbilical cord.

Types of allogeneic transplantation according to conditioning regimens

1. Myeloablative transplantation (MA)
2. Non-myeloablative transplantation (NMA)
3. Reduced intensity conditioning transplantation (RIC or RIST)

Identification and quantification stem cells

In humans, the hematopoietic stem cells and some of its progenitors express CD34 antigen on its surface and is identified in laboratory by CD34 antibody. For a rapid

and sustained successful engraftment the minimum required CD34+ cells is $2 \times 10^6/\text{kg}$ (2 million) of the recipient. At a more gross quantification (if CD34+ cells identification facilities are not available) one collects minimum mononuclear cells (MNC) $3 \times 10^8/\text{kg}$ (300 million) of the recipient. Collected cells could be kept frozen for many years at -180°C or about 6 months at -70 to -80°C . At room temperature they could remain viable up to 4-7 days. In sibling donor transplantation usually collected and infused on the same day, manipulated or unmanipulated; some manipulation is necessary depending on ABO mismatch or need for T cell removal.

Rationale

In allogeneic SCT, a successful engraftment of donor cells depends on 1) effective immunosuppression of the recipient (host) by chemotherapeutic drugs and/or total body irradiation (TBI). In some centers total nodal irradiation (TLI) is used in place of TBI.

High dose chemotherapy and irradiation also destroy a significant number of malignant or residual immunocompetent hematopoietic cells. This was considered a prime requirement in earlier days but current understanding has made it dispensable.

Works done in last 3 decades have shown that donor's immune cells (T cells, NK cells and possibly some other like dendritic cells) effectively destroy diseased cells in the host through a mechanism known as graft versus leukemia (GvL) or graft versus tumor (GvT) effect. Such biological phenomenon occurs more frequently in CML, CLL and low grade lymphomas and less frequently in AML, ALL, MDS and myeloma. This has opened up an exciting field of non-myeloablative or reduced intensity transplantations. Elderly patients with hematological malignancies, younger ones with significant co-morbidities, who would have been ineligible for myeloablative cytotoxic therapy, have now become eligible.

In autologous transplantation, only high dose chemotherapy and/or TBI are used. As a result in such transplants, cytotoxic therapy should have ability to eradicate the disease on its own.

Indications for allogeneic SCT

Non-malignant conditions

- Severe aplastic anemia in young
- Hemoglobinopathies like thalassemia major, sickle cell disease

- Inborn errors of metabolism
- Others like Wiskott-aldrich Syndrome

Malignant conditions

- Acute leukemia of various stages like in remission or at relapse
- Chronic leukemia in advanced stage or failure to other standard treatment
- Malignant lymphomas after failure to standard care and/or autologous transplant
- Myelodysplastic syndrome (MDS) at certain stage

Recipients

In last one and a half decade, the number of patients undergoing allogeneic SCT has increased despite fewer patients with CML undergoing SCT. At one time, before the advent of targeted molecules, highest number of CML patients underwent SCT. This increase has been due to availability of unrelated donors, cord blood, inclusion of older patients, increasing use of RIST and newer centers opening in developing world.

Nevertheless, it should be imperative on parts of the transplant teams to select recipients carefully, particularly those with advanced disease and significant co-morbidities. Efforts are on to develop guidelines for selection of recipients.

Donors

As anyone can be a donor at present due to functional donor registries in developed world, large banks of umbilical cord blood, the age is not an absolute issue. However, people at extremes of age are not preferred. Importantly, the donor should not be a carrier of a communicable disease. HbsAg and HCV carriers are relative contraindication. Also, the severity of non-communicable diseases in them should not be risky enough for stem cell collection.

Unrelated donors could be a real problem at times. Donor attrition rate remains high, with some backing off at last moment. This being a voluntary program, there is no legal binding on them. Keeping privacy of the donor to the recipient and its family is also of paramount importance, at least for first couple of years.

The issue in umbilical cord blood transplant is lower number of CD34+ cells. Hence, adults with more than 70 kg body weight are not suitable recipient. Engraftment is relatively slower. Currently, double cord blood transplants are used in some centers.

Procedure :

Technically HSCT is a fairly simple procedure. The team collects the cells from bone marrow, peripheral blood or umbilical cord of the mother/new born, transfuses through a vein same day or freeze for future use. The preparative or conditioning regimen comprised of myeloablative or reduced intensity cytotoxic therapy is administered over a few days prior to stem cell infusion. A wash out period of 24 hours or longer, based on half-life of the drugs is required before the infusion. Manipulation of the collected material is needed if there is ABO group mismatch between recipient and donor or mature T cell are to be removed to prevent graft versus host (GVHR/GVHD) reaction/disease. Infused cells home in marrow microenvironment and start proliferating immediately. Evidence of engraftment in peripheral blood is noted by 2nd or 3rd week with rising donor origin blood cells. The donor origin cells are identified by molecular techniques (VNTR/STR) in myeloid and lymphoid cells. Traditional BMT involves collection of marrow cells from bilateral iliac crests under general anesthesia. A gross collection measures approximately 10 ml/kg of the recipient without jeopardizing donor's health. We have mentioned earlier about specific numeric collection.

At present time use of peripheral blood stem cells has become popular due to ease of the procedure. It involves subcutaneous administration of G-CSF (10-16 mcg/kg/day) to the donor for 4 days and collection of CD34+ cells on 5th day using an apheresis machine from a peripheral vein. These machines are ubiquitous in present day blood banks.

Umbilical cord blood stem cells are collected with the helps an experienced obstetrical team at child birth (normal or LSCS); health of both new born and mother ascertained. Using aseptic closed procedure, blood is squeezed out from cord vessels to bag, frozen and banked for future use. The number of stem cells required for such transplants is lower than marrow or peripheral blood stem cells due to their proliferative potential and used mostly in children. Surely, a limited number of adults also have received such transplants.

Complications: Their prevention and treatment

Successful outcome of allogeneic HSCT depends on careful recipient/donor selection by HLA typing, preparative cytotoxic therapy, age, disease status, GHVD

prophylaxis, timely prevention /control of infection.

The unique complication of HSCT is graft versus host disease (GVHD). It results from donor T cells recognizing host tissues as foreign (alloreactivity). Attempts to prevent this by removing offending T cells prior to infusion minimizes the incidence but leads to increased rejection, relapse and post-transplant infections, thus nullifying the benefit. It is not routinely practiced these days. The standard practice is prophylaxis with immunosuppressive agents like methotrexate, calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, corticosteroids, etc.

There are two types of clinico-pathological GVHD, acute (occurring within first 100 days) and chronic (usually after 100 days), arbitrarily defined by time of manifestation. GVHD targets host tissues like skin (rash, desquamation), gut (mucositis, colitis) and liver (intrahepatic cholestasis and cellular damage) that express MHC (Major Histocompatibility Complex). Rarely, GVHD may affect tissues in urinary bladder, kidney or pancreas. Acute GVHD is graded I-IV depending on severity.

GVHD or GVHR at a low biologic activity could be beneficial for GvL/GvT in hematological malignancies, but totally unwanted in non-malignant conditions. More than 40% patients will develop acute GVHD despite prophylactic immunosuppression. The mainstay of management is corticosteroids. Majority will achieve complete or partial response. Severe acute GVHD is fatal in about 10% of cases. For chronic GVHD that develops in 50%-60% of cases (increasing due to PBSCT) too, oral corticosteroid, prednisone remains the mainstay of treatment. Some patients may need prolonged therapy. For refractory GVHD, attempts are on to develop newer methods of management.

Other complications are – neutropenic fever resulting from various opportunistic infections (a CMV infection being most significant), thrombocytopenia, anemia, rejection (usually quite low), red cell aplasia following ABO mismatch transplants, post-transplant lymphoproliferative disorders. Supportive care pancytopenia is continued until a safe engraftment, prophylactic antimicrobials for bacterial, fungal and viral infections.

Quality of life remains an unresolved issue for a good number of long term survivors. It is certainly inferior in matched-pair analysis with normal people. However, about 90% patients without ongoing GVHD, live an active life.

A significant number of survivors developed chronic non-communicable metabolic diseases, specially those who received prolonged steroid-based immunosuppressive therapy.

Results

Successful outcome of allogeneic transplants depend on many factors, the most important ones being type and stage of the disease, HLA match and severity of GVHD. For example, in AML, results are best for young patients with HLA matched sibling donor and inferior in other settings like relapsed disease, unrelated donor who are less than full molecular match, haplo-identical donor, and elderly patients.

At the present time, the results of allogeneic transplant of sibling donor and 10/10 matched unrelated donor getting closer in malignant diseases. However, sibling donor and marrow source remain first choice in non-malignant diseases like severe aplastic anemia and thalassemia major. The issue of reduced intensity transplant in young people remains an unresolved; whereas the transplant related mortality is higher in myeloablative procedures, the relapse is higher in reduced intensity preparations. In older patients, reduced intensity approach has become an accepted one. If transplants are done early in the phase of the disease, better the outcome. The results in severe aplastic anemia are close to 80%-90%, falling to 60% in late cases. The case is similar in thalassemia major. In acute myeloid leukemia in first remission, 50%-65% are cured, but if done at relapse or second remission, only 25%-30% become survivors.

Indian Transplant Scenario

First allogeneic BMT in India was done for child with AML in first remission in March 1983 at the Tata Memorial Hospital, Mumbai. It was a successful transplant with very long survival. CMCH, Vellore, began its program in 1986 and it has done maximum number of transplants till date. Since early 2000, there has been rapid increase in number of transplant centers across the country; currently there are at least 30 centers performing regular procedures. This has been possible due to availability of locally trained transplant physicians, improving results, willingness of patients/families to accept a transplant, and increasing affordability. There is an active Indian Stem Cell Transplant Registry (ISCTR) with its central office at Vellore. Major centers are performing all presently possible types

of transplants, like sibling donor, matched unrelated donor, haplo-identical donor and umbilical cord blood. The Indian marrow donor registries only a small number of voluntary donors registered. This needs to grow rapidly.

The results from published studies show equivalent outcome compared with that of most international centers. Nevertheless, there are many in the country who have not been able to undergo the procedure due to lack of funds, non-referral by inadequately informed physicians, non-availability of suitable donors, etc.

Conclusion

In recent years, allogeneic SCT for various diseases has expanded progressively. It is now an accepted standard of treatment for certain conditions. Availability of unrelated donors, umbilical cord blood, inclusion of elderly patients, patients with co-morbidities and to some extent expansion of transplant centers in the developing world have been the factors for this progress. Chronic phase CML patients are not offered allo SCT until it advances to accelerated or blast phase or new molecules fail. The results have been improving steadily due to improved HLA typing with high resolution molecular typing, better supportive care to prevent and manage some infections, less damage to vital organs and reduction in severity of acute GVHD. However, relapse rate has increased due to inclusion of advanced stage diseases and reduced intensity conditioning regimens. Our understanding of biology of GVHD which revolves around immuno-competent T cells, needs to improve for better prevention and treatment of acute and chronic GVHD. If this hurdle of SCT could be more easily handled, allogeneic transplant will not remain the preserve of a select group of health care providers.

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Case Report

Successful Percutaneous Transluminal Balloon Angioplasty of Descending Thoracic Aorta in Takayasu's Arteritis - Case Report

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ABSTRACT :

Percutaneous transluminal balloon angioplasty has been successfully used during the chronic phase of Takayasu arteritis for significant short segment stenosis of aorta in symptomatic patients. Balloon angioplasty offers a minimally invasive, cost effective and safe approach for relief of significant localized stenotic lesions in such patients. In this case report, we have successfully performed Percutaneous transluminal balloon angioplasty (PTBA) of localized stenosis of descending thoracic aorta in a 19 year old girl with satisfactory immediate results (hemodynamic, angiographic and clinical) and without any major or minor complications.

KEY WORDS : *Takayasu's arteritis, Balloon angioplasty, Descending thoracic aorta.*

Takayasu Arteritis is a rare, idiopathic, chronic inflammatory cause of transmural fibrosis of the aorta and its major branches⁽¹⁾ Preponderance amongst females of Asian origin in the second decade of life is usually seen. Etiology is unknown; no infectious agent has been identified, and identification of endothelial antibodies in patients with this disease supports an autoimmune mechanism⁽²⁾.

An acute phase of constitutional symptoms is followed by a chronic phase months to years later, during which arterial complications occur. Ultimately, all three layers of the aorta fibrose. The disease causes stenosis, occlusion and aneurysm formation in a patchy distribution, resulting in characteristic 'skip' lesions⁽³⁾ Due to non-specific nature of symptoms at presentation and the initial absence of clinical signs, most patients remain undiagnosed until the chronic or 'pulseless' stage of the disease. The two stages are not always distinct and may coexist at different sites⁽⁴⁾. Hypertension and claudication are common. Hypertension is observed in > 50% cases and suggest narrowing of aorta proximal to renal arteries or renal artery stenosis itself. It also indicates reduced aortic distensibility as well as baroreceptor reactivity. Mortality is upto 30% at 5 years. In 50% of such cases this is due to congestive heart failure

or aortic regurgitation. Only 28% of patients achieve sustained remission⁽⁵⁾.

Angiographically, the left subclavian artery is narrowed in approximately 90% patients. Thoracic aortic lesions occur in 66% of patients and abdominal aorta is involved in 50%. Descending thoracic aorta involvement in different Indian series varies from 40 to 80%. In the aorta, distribution of lesions shows one of the following patterns : localized involvement (from 2 cm to 7 cm), involvement of multiple short segments with normal or "skipped" areas in between and diffuse involvement of the aorta⁽⁶⁾

Therapy during the acute phase of Takayasu arteritis is usually medical and consists of corticosteroids and sometimes immunosuppressive therapy. Surgical bypass grafting is one modality of treatment for obstructive arterial disease in the chronic phase especially for long segment involvement. Grafts must be anastomosed to healthy tissue. Surgical mortality is <5% provided the disease is in the chronic phase. However, mortality can nevertheless be high. Complications include anastomotic site aneurysms (in upto 10% cases) and graft occlusion, potentially resulting from flare-ups of "inactive" lesions. Surgery during the acute phase results in higher incidence of anastomotic stricture and pseudoaneurysm formation. Progressive inflammation and uncertainty regarding disease stage can limit surgical management.

Endovascular management (Balloon angioplasty or stenting) is minimally invasive, cost effective and safe. Serious complications following endovascular intervention

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are rare. It avoids the morbidity associated with surgical exposure of large vessels in the abdomen and thorax. Although long term durability of endovascular treatment remains unestablished, few Indian series have demonstrated that it is highly effective in relieving stenosis of the aorta, particularly in short segment lesions, and relief of obstruction appears long lasting. It is clear that angioplasty or stenting is most effective for short lesions, but there are no clear guidelines for selecting endovascular therapy over surgery.⁽⁵⁾

Case report

This 19 year old girl hailing from North Lakhimpur presented to a private hospital in Guwahati (in Dec, 2011) with chief complaints of headache, giddiness and back pain of 1 year duration. She was detected to be hypertensive 3 months back by a local doctor. MR angio of thoraco-abdominal aorta was advised by the attending physician in view of absent femoral pulses and upper body hypertension to rule out Coarctation of aorta. MR angio (Fig. 1&2) done

(Takayasu disease), she was referred to us for further evaluation and management.

Upon admission in Cardiology department of GMCH, the girl was in good general condition. Detailed history disclosed additional symptoms of intermittent claudication of lower extremities and dyspnoea on exertion for last one to one and half years apart from complaints of headache, giddiness and high blood pressure. There were no symptoms of upper extremity claudication. Relevant findings on general physical examination revealed unequal upper extremity pulses (left upper limb 1+; right upper limb 4+) and absent lower limb pulses. Blood pressures in right upper limb was 180/90 mmHg; left upper limb 120/90 mmHg. Audible bruit at the base of the neck and over clavicular area on the left side was noted. The chest x-ray showed mild cardiomegaly. The ECG showed normal sinus rhythm. On admission, her abnormal hematological and biochemical values were erythrocyte sedimentation rate (ESR) 110 mm/hr, C-reactive protein (CRP) 44.6 mg/L (normal, 0-10 mg/L), TSH 14 mIU/L and Hemoglobin 8.5 gm%. The urinalysis was normal. The 2-D transthoracic echocardiography showed mild left ventricular dilatation and a left ventricle of 45%. In view of her disease hypertension, mild LV systolic dysfunction and hyperthyroid state she was started on antihypertensive medications, thyroid replacement, beta-blockers and iron supplementation and followed up in OPD. Following the treatment she had two more hospital admissions for chest pain and dyspnoea and on both occasions was treated conservatively.

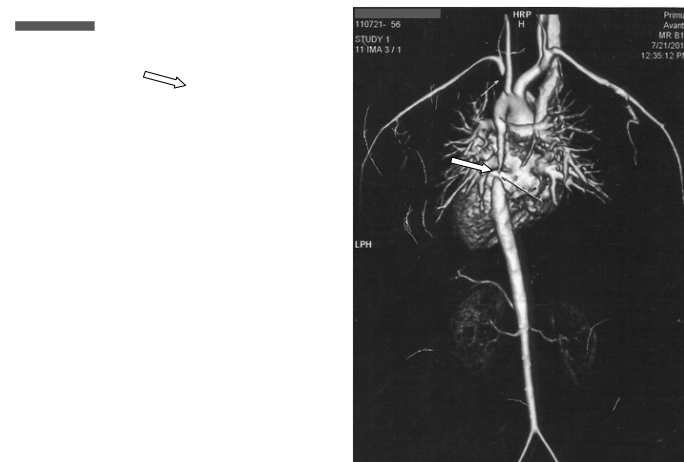


Figure 1 : MR Angio showing stenosis of left subclavian artery just after origin

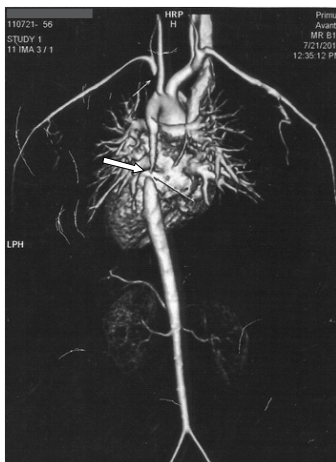


Figure 2 : MR angio showing segmental narrowing of descending thoracic aorta

in a different centre revealed segmental narrowing of the proximal descending thoracic aorta measuring approximately 5 cm in length, mild narrowing of the distal part of the arch and rest of the descending thoracic aorta. There was focal narrowing in the proximal part of left subclavian artery (1.4 cm in length) along with small short segment narrowing in the 2nd part of right subclavian artery. The origin of the brachiocephalic and left common carotid arteries were normal. The abdominal aorta, both renal arteries, superior and inferior mesenteric arteries including the aortic bifurcation were normal. So with features suggestive of aorto arteritis

she was admitted for cardiac catheterization and percutaneous transluminal balloon angioplasty (PTBA) of descending thoracic aorta in view of dyspnoea on exertion, severe uncontrolled hypertension and lower limb claudication. Her hematological and biochemical parameters were ESR 07 mm AEFH, CRP 04 mg/L, TSH 3.44 mIU/L and Hemoglobin 10.3 gm%. Cardiac catheterization performed under local anaesthesia with vascular access from the left femoral artery revealed: normal origin and course of coronary arteries on aortic root angiogram; Aortic arch angio and selective angiogram showed normal brachiocephalic trunk (right subclavian, right common carotid), left common carotid artery and bilateral internal and external carotid arteries. The left subclavian

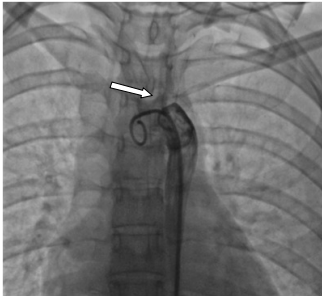


Figure 3: Angio showing Left subclavian artery stenosis

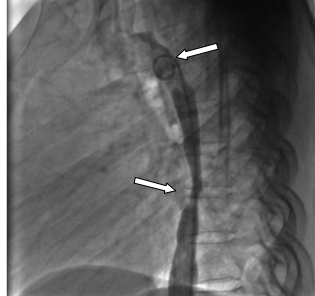


Figure 4: Descending aortogram showing stenosis of descending thoracic aorta with luminal irregularities as well as stenosis of left subclavian artery after origin (arrows)

artery revealed critical stenosis just after origin (Fig.3). Descending aortogram revealed tight localized stenosis of the descending thoracic aorta (Fig.4) of approximately 4 cms length and diameter at the tightest point of 2.7 mm. The gradient across the stenosed segment was measured to be 100 mmHg. The diameter of the normal segment of Aorta was 12.6 mm. Bilateral renal arteries were normal (Fig. 5 & 6).

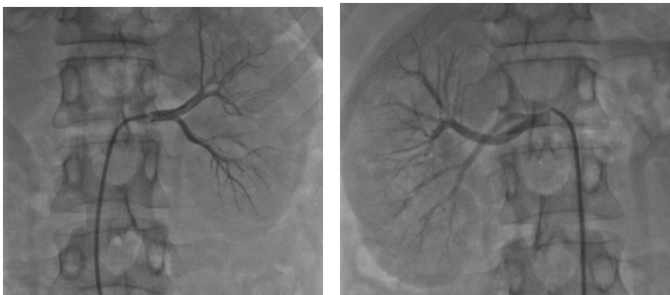


Fig 5 & 6 : Normal bilateral renal arteries

In view of significant and symptomatic stenosis of descending thoracic aorta, she was taken up for PTBA. Unfractionated heparin 2500 U was given intravenously. The angiography catheter was replaced by a balloon dilatation catheter over 0.035 inch exchange guidewire. Graded dilatation (i.e. initial dilatation by a smaller balloon followed by dilatation with a balloon of larger diameter) was done because of severe stenosis (<4 mm). The balloon size selected was 60% of normal aortic segment and not more than three times the constricted segment (i.e. maximum of 7 mm). The initial balloon used was AVIATOR PLUS (Cordis) 5 mm dia. X 20 mm length followed by a second balloon OPTA PRO (Cordis) 7 mm dia. X 40 mm length. The balloon was positioned across the area of stenosis and inflated with diluted contrast medium. Balloon position was confirmed with fluoroscopy by the appearance of “waist” at the site of constriction (Fig.7). The balloons were inflated

sequentially to higher pressures until the “waist” disappeared (Fig. 8). Balloon inflation pressure of 4 to 6 mmHg was

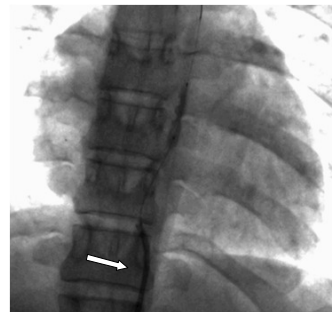


Fig 7 : Balloon position confirmed by fluoroscopy by appearance of “waist” at the site of constriction (arrow)

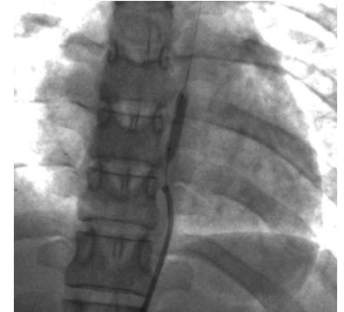


Figure 8 : Disappearance of “waist” after sequential balloon dilatation

required for successfully dilating the stenosed segment. Inflations were performed 1 to 2 times for 10 seconds each. The balloon catheter was then replaced by pigtail catheter and an aortogram was performed. There was an increase in aortic diameter at the site of stenosis from 2.7 mm to 5.4 mm (an increase in diameter of the stenosed aorta by 100 %). After 15 to 20 minutes of the last balloon dilatation when the heart rate settled to near pre balloon angioplasty level, pullback pressure tracing was recorded across the site of stenosis which revealed a decrease in peak systolic pressure gradient (PSG) from 100 mmHg to 30 mmHg (fall in PSG by 70%) . Successful PTBA of descending thoracic aorta stenosis in this young female patient was performed without any major or minor complications. Stent implantation in this patient was not considered due to her young age and satisfactory angiographic and hemodynamic results after PTBA alone. She was started on dual anti platelet therapy(DAPT) 2 days prior to the procedure and advised to continue same for at least 3 months post procedure along with prednisolone and other medications. After the procedure she was observed for 5 days in the hospital. Clinically, her femoral pulses which had been absent before the procedure became palpable with increased pulse volume after successful angioplasty. There was marked improvement of her symptoms. Her blood pressure normalized and was in the range of 140/70 mmHg in the right upper limb and 110/70 in the left upper limb. Lower limb blood pressure recorded was 110/70 mmHg.

On the first follow up visit after 3 months, symptoms of dyspnoea on exertion, headache and lower limb claudication improved significantly. Blood pressure was maintained at 140/ 80 mmHg in right upper limb on single anti-hypertensive

medication. Lower limb pulses were palpable with blood pressure record of 110/70 mmHg. 2D Echocardiography showed normal LV function with Ejection fraction of 60%.

Discussion

First reports of use of balloon angioplasty in patients with Takayasu's arteritis were published in 1980 by Martin, Diamond and Casarella, who performed successful dilatation of subclavian and renal artery stenosis. The first case of use of balloon angioplasty for treatment of stenosis of the aorta that was due to Takayasu's arteritis was reported by Yagura et al.

The indications for balloon angioplasty of aortic lesions include presence of ischemic symptoms (such as claudication, renovascular hypertension), focal rather than long segment stenosis of over 70% to 75% and clinically chronic disease phase. In comparison to coarctation of aorta, it is generally recommended that the gradient across the stenotic area should be at least 50 mmHg. Severe lesions require graded dilatation. Balloon diameter of 60% to 100% of adjacent normal vessel diameter, but no more than three times the stenotic segment, reliably results in significant reduction in gradient and increase in mean luminal diameter⁽⁵⁾. Successful PTBA of aorta has been labeled as those that resulted in an increase in diameter of the stenosed aorta by more than 30% and in a gradient of less than half that before dilatation⁽⁸⁾. Stent implantation has been effectively used in patients with unsatisfactory or sub optimal results after PTBA alone (flow limiting or obstructive dissection, failure to reduce PSG by 50%).

From India, Tyagi et al. has a long term follow up series of 36 patients with Takayasu's arteritis who have undergone balloon angioplasty of the aorta. Results from this series have shown that balloon dilatation is highly effective in relieving stenosis of the aorta, particularly in patients with discrete lesions. There was an immediate decrease in the peak systolic pressure gradient (PSG) of 67% (from 75.2 +/- 29.1 mm Hg to 24.8 +/- 19 mm Hg; p less than 0.001) with an increase of 113.3% in diameter of the constricted segment (from 4.5 +/- 2.2 mm to 9.6 +/- 3.8 mm; p less than 0.001). Except for one patient with restenosis, persistent relief was observed during follow up hemodynamic and angiographic restudies. Further decrease in PSG has been noted by other investigators also. This beneficial late remodeling may be due to slow retraction of ruptured fibrous bands and release of superimposed spasm. Aneurysm formation at the site of

angioplasty was not observed in the the series by Tyagi et al. which could be due to markedly thickened aortic wall because of fibrosis of all three layers as observed in this disease. Balloon angioplasty was also highly effective in relieving hypertension which may be due to relief of mechanical obstruction in the aorta and an increase in renal blood flow, which lead to relief of renovascular component of hypertension. In few young patients, cardiac failure improved after angioplasty, and this may be due to reduced afterload after relief of aortic obstruction⁽⁷⁾.

Conclusive evidence for use of anti - platelet agents before and after balloon dilatation is lacking. However, most operators prescribe aspirin indefinitely following intervention. It has been suggested prednisolone should be given for 6 months following intervention to prevent flare up of disease⁽⁵⁾.

Conclusion

Balloon angioplasty of aorta in patients with Takayasu's arteritis is a safe and cost effective alternative to surgical bypass grafting for short segment stenotic lesions. This procedure is highly effective in relieving stenosis of the aorta resulting in marked improvement of symptoms, control of hypertension and improvement of cardiac failure and left ventricular function. Serious complications following PTBA are rare.

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Takayasu Arteritis Presenting With Stroke : A Case Report

A. Pal*, J. Thakuria**, S. M. Baruah***

ABSTRACT:

A 22 year old lady presented with a history of sudden onset inability to move right upper and lower limbs with dimness of vision. There was history of headache for one month and a non healing ulcer over the scalp for three months. No previous history of fever, joint pain, or other systemic manifestations was present. Magnetic resonance angiography revealed bilateral lacunar infarcts and significant long segment narrowing of bilateral common carotid arteries with near complete occlusion of left internal carotid artery. The patient was improved with corticosteroids.

Introduction

Takayasu's arteritis is an inflammatory arteritis of unknown cause, involving the aorta and its major branches (ie, the subclavian, carotid, and renal arteries). Arterial inflammation leads to stenosis or occlusion of the involved artery, aneurysm formation, or both.^{1,2,3} The first report of TA was by R Yamamoto in 1830, while the first presentation on TA was in 1905 by Mikito Takayasu at the 12th annual meeting of the Japan Ophthalmology Society, describing a patient with a peculiar optic fundus abnormality, characterized by coronal anastomoses.⁴

Case report

A 28 year old lady, right handed, presented with history of sudden inability to move her left upper and lower limbs with dimness of vision. There was history of headache with occasional vomiting for one month. There was also history of non healing ulcer over the scalp on the left parietal region for three months. There was no past history of fever, joint pain, or other systemic manifestations.

On examination, the patient was irritated, moderately pale, average built with average nutrition. She was afebrile. Her bilateral common carotid, radial and brachial pulses were absent. All the lower limb pulses were palpable. There was a bruit over both the carotid arteries. Blood pressure

in right upper limb was 104/60 mm Hg and left upper limb 112/68 mm Hg. Blood pressure recorded in the lower limbs 160/90 on both the sides. The patient had only perception of light and projection of rays in both eyes. Ophthalmoscopy examination showed macular edema, micro aneurism and cattle track appearance in central retinal arteries in both eyes. There was right sided hemiplegia (power- grade 0/5) and left sided hemiparesis (power- grade 4/5) with extensor plantar response and clonus. Cardiovascular and other system examination were normal. There was no bruit over the renal arteries. Her Hemoglobin was 7.9 g/dL (55%), total counts 5,800 cells/cmm and ESR was 120 mm/hr, C-reactive protein 18 microgram/ml. Her Electrocardiogram was normal. Anti nuclear antibody (Immunofluorescence), lupus anticoagulant, and anticardiolipin antibodies were absent. Echocardiography revealed normal LV function. Carotid doppler showed 70% stenosis of proximal right common carotid artery and 60% of whole of left common carotid artery. Magnetic resonance imaging of brain showed diffuse bilateral lacunar infarction of varying stages with cortical laminar necrosis in the left superior frontal gyrus (Fig 1). Magnetic resonance angiography revealed concentric mural thickening involving bilateral common carotid arteries with 60% narrowing of luminal diameter which is extending superiorly on the left side to cause near complete occlusion of the petrous portion of the left internal carotid artery. On the right side the internal carotid artery was normal (Figure 2). The patient was diagnosed as Takayasu arteritis. She was improved with steroids (power of both upper and

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lower limb bilaterally was 4/5 after initial intravenous followed by oral corticosteroid therapy).

the 1st case of a 21 year old woman with characteristic fundal arterio-venous anastomosis.⁵ This is a rare disease, but commonly seen in Japan, South East Asia, India, and Mexico. Takayasu's arteritis is characterised by two stage disease "pre pulseless" with non-specific inflammatory features followed by a chronic phase characterised by vascular insufficiency. The disease presents in the 2nd or 3rd decade of life. A study in India gave a mean age of symptom onset of 24 years and age at diagnosis of 28.3 years.⁶ Non-specific features include fever, weight loss, arthralgias, myalgia, malaise, and anaemia. As inflammation progresses, stenotic lesions develop and patients develop associated symptoms. Diminished or absent pulses, vascular bruits, hypertension, retinopathy, aortic regurgitation, congestive cardiac failure, neurological manifestations, and pulmonary artery involvement are some of the common manifestations of these patients. Panja's series of 650 cases of Takayasu's arteritis, the largest series in India, reported an incidence of stroke as 22%.⁷ 1990 American College of Rheumatology (ACR) proposed the criteria for diagnosis of Takayasu's Arteritis⁸ :

1. Age of onset < 40 years

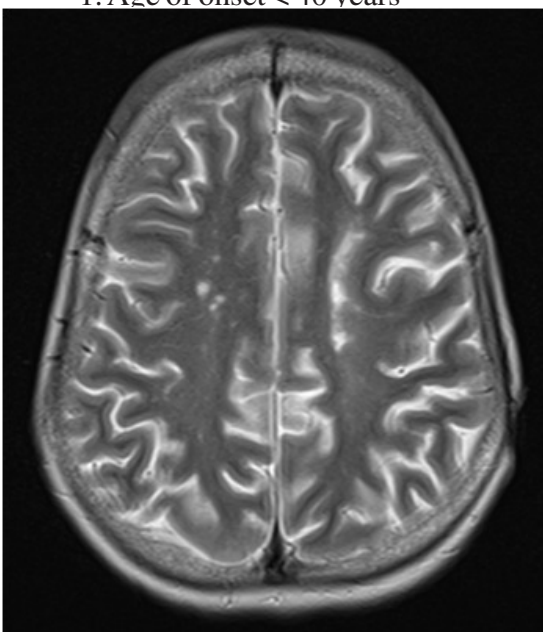
Figure 1: Bilateral lacunar infarct in varying stages



Figure 2: Near complete occlusion of petrous portion of (Block arrow) left internal carotid artery (Block arrow)

Discussion

Takayasu's arteritis also known as "pulseless disease" or thromboangiopathy is characterized by chronic vessel inflammation leading to wall thickening, fibrosis, stenosis, and thrombosis. It affects predominantly aorta and its branches. Symptoms depend on end organ ischaemia.² In 1905, Takayasu, Professor of Ophthalmology presented



may contribute to vasculitis. Chaturvedi, et al, and recently magnetic resonance angiography (MRA) has shown promise in the diagnosis of Takayasu's arteritis.⁹ MRA provides high resolution detail of vessel wall thickness and lumen configuration. It allows the measurement of wall enhancement as a reflection of oedema and inflammation. Compared to the gold standard of angiography, 2% of stenosed vessels are over estimated as occluded on MRA.

By reduction of enhancement on follow-up MRA also serves as a surrogate marker for disease activity. Steroids are the mainstay of treatment for Takayasu's arteritis. Approximately half of the patients respond to steroids. Steroid unresponsive patients can be treated with cytotoxic drugs including cyclophosphamide, azathioprine, and methotrexate. Treatment should aim to control disease activity, preserve vascular competence with minimal long term side effects. Surgical treatment is offered to those with severe stenosis of renal artery, extremity claudication, stenosis of 3 or more cerebral vessels, or evidence of coronary artery involvement. Cumulative survival at 5 years after disease onset was 91%, and after 10 years the figure was 84%.

Our patient had no past history of systemic manifestations like fever, joint pains, and weight loss. Non healing ulcer over the scalp and acute neurological deficit heralded the onset of disease. Patient showed good response to steroids, with return of limb power to grade 4/5. Also the role of magnetic resonance angiogram needs to be highlighted. It is a non-invasive procedure, provides high resolution detail of vessel wall thickness and lumen configuration. In our patient, MRA revealed bilateral common carotid artery occlusion with bilateral pyramidal signs and there was no involvement of thoracic or abdominal aorta and renal arteries – an uncommon presentation.

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Splenic Infarction in A Patient with Plasmodium Falciparum Malaria : A Case Report

A Datta*, A K Bhattacharyya**

ABSTRACT:

Splenic infarct is usually seen in large spleens of haematological disorders, cardiac diseases, trauma etc. Malarial fever has also been reported to be associated with this splenic complication. But the number of such cases are reported very few in the literature. We also report such a rare case of splenic infarct in a patient with plasmodium falciparum malaria. The case was diagnosed considering the clinical presentation, positive blood report for plasmodium falciparum malaria, radiological features of splenic infarction, clinical response to anti malarial treatment and absence of any other condition responsible for splenic infarct.

Key words : *PF malaria, Splenic infarct.*

Introduction

Malaria is the most important parasitic disease prevalent many countries of the world especially in tropical areas. According to the latest WHO estimates, there were about 219 million cases of malaria in 2010 and estimated 660000 death.⁽¹⁾ Acute malarial fever especially PF malaria can present with different complications like cerebral malaria, thrombocytopenia, ARF, intravascular haemolysis, DIC, hypoglycemia, ARDS etc.⁽²⁾ Besides these splenic complications such as splenic infarct, rupture, haemoperitonium, ectopic spleen, hyper-splenism, torsion, cyst or abscess formation are also mentioned in the literature.⁽³⁾ The number of these splenic complications especially splenic infarct are reported very few in the literature. Recently we came across a case of splenic infarct with falciparum malaria and due to its rarity we are reporting this case.

Case report

A 50 years old female was admitted in our Hospital in the month of June (09/06/13) with the complaints of severe left sided upper abdominal pain, nausea & vomiting.

Initially she was admitted in surgical ward assuming a case of acute abdomen and started conservative management with i/v fluids, PPI, antibiotics and analgesic. The pain abdomen was so intense that the patient could not lie down. Initial investigations of blood RE, S.creatinine, blood sugar random, urine RE, revealed anaemia (Hb-5.5gm%), hypokalemia (S.k+-2.7), others were all within normal limits. CXR (PA view) and straight X ray abdomen in erect position revealed nothing. The patient was taken care of with blood transfusion and potassium supplementation.

Patients condition was worsening and medicine consultation was asked for. On query we came to know that the patient had fever with cold and cough like viral fever 2-3 days prior the onset of pain abdomen. Patient was having pallor and on per abdomen examination which was done with great difficulty revealed hepatomegaly and massive splenomegaly which was tender. No splenic rub could be detected. There was no history of RHD and patient did not have any cardiological findings like murmurs, pericardial rub etc. Patient was transferred to the medicine ward and asked for complete haemogram, blood for MP by optimal method and USG whole abdomen. MP optimal was positive for PF malaria and the patient immediately was put on injectable Artesunate along with blood transfusion. Complete haemogram report revealed no abnormal cell and USG report showed moderate hepatomegaly and huge splenomegaly (20cm in length). Multiple irregular hypo echoic areas in the spleen

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(? splenic infarct) was seen in USG. To confirm that the patient was asked for CECT abdomen which showed two areas of infarct in the spleen. Second day onwards after starting the artesunate regimen patient showed signs of improvement with decrease both in fever and pain abdomen. At the completion of 07 days therapy of artesunate and antibiotics with supportive therapy, patient was asymptomatic completely with complete regressive on the size of spleen. The patient was discharged on 18/06/13.

Considering the area where the patient is from and which is a malarial endemic area, clinical features of fever with hepatosplenomegaly, positive blood test for Plasmodium Falciparum malaria with absence of other causes of splenomegaly and clinical response of the patient to anti malarial treatment, the splenic infarct in this patient was attributed to Falciparum malaria.

Discussion

The disease burden of malarial fever is very high especially in African and south east Asia including India⁽¹⁾ and in India, north-eastern states along with some other few states like Orissa, Rajasthan, Jharkhand etc are having API>5⁽⁴⁾, but Splenic infarction as a complication of Malaria has been reported not so frequently in literature. However maximum of the reported splenic infarct cases were due to Falciparum malaria.⁽⁵⁾ Few cases were reported due to vivax malaria^(5,6,7) and only one case has been reported due to plasmodium ovale malaria.⁽⁸⁾ Splenic infarction occurs mostly due to haematological disorders as mentioned by Lawrence YR et al.⁽⁹⁾ Except haematological malignancies, they also found, solid tissue malignancy, infections mononeucleosis, intracardiac thrombosis, bacterial endocarditis, sickle cell disease, wandering spleen, thrombotic, liver disease, dislodged aortic plaque, infected vascular graft, sepsis and unknown causes as the etiological factors of splenic infarct. Gruth AA and Pachter HL has mentioned malaria as a rare cause of splenic infarct, besides the several haematological disorders, hyper coagulable states, embolic disorders & trauma as the common cause of the same.⁽¹⁰⁾

The occurrence of splenic infarct in plasmodium falciparum can be explained by the ability of its mature trophozoite and schizont forms to sequester in the deep venous micro vasculature. But spleen acts as a principal

host defence against malarial parasites by destroying and filtering of both parasitised and uninfected erythrocytes for accumulation of malarial parasite in the spleen itself and causing infarction is very unusual and rare manifestation.⁽¹¹⁾ Most of the reported case of splenic infarct presented with Lt. upper quadrant abdominal pain, Lt. pleuritic chest pain and tender splenomegaly. The diagnosis of splenic infarct was confirmed either by USG or by abdomen.⁽¹¹⁾ In this case, we used both the modalities.

The treatment of splenic infarct in most of the cases including ours was done conservatively with good outcome which includes anti malarial with other supportive medications.⁽⁵⁾ Patients had to be followed up very carefully for early identification of possible complications like splenic rupture, hemorrhage and abscess formation which may require surgical management.

Conclusion

Splenic infarction in malaria is a rare diagnosis which may be under diagnosed or under reported as the diagnostic tools like USG and CT scan are not freely available in the areas where malaria is highly prevalent. Any patient who presents with fever with hepatosplenomegaly with Lt. sided upper abdominal pain and Lt. sided pleuritic chest pain should be evaluated for splenic infarct by USG/CT scan abdomen.

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Unexplained Hemorrhagic Stroke in Thirteen Years Old Girl

Dear Sir,

The article “Unexplained Hemorrhagic Stroke in Thirteen Years Old Girl” published in Volume- 3 Issue -2 of your journal is very well compiled and informative. With take this opportunity to congratulate the Authors for the nice article.

In this context we want to highlight the fact that MR Angiography is not an ideal choice for investigating a patient of unexplained ICH. A systematic review of a large trinational survey¹ concluded that “Until further studies of the diagnostic accuracy of noninvasive investigations such as CT angiography or MRA have been performed, these techniques cannot replace IADSA for the investigation of ICH”. There are other series too which confirm that conventional angiography/DSA is the gold standard investigation for evaluation of a patient with spontaneous ICH, particularly in young individuals²³.

A Mahanta*
A. K. Kayal**

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