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Utility of Serial Transcranial Doppler in Diagnosis of Intracranial Vasculopathy with Computed Tomography Correlation in Children with Tuberculous Meningitis

Authors
Dr Rupam Kumari[1*], Dr Suresh Kumar Toppo[2], Dr Paras Nath Ram[3], Dr Rajeev Kumar Ranjan[4], Dr Pughaz Deivigan[5], Dr Vijay Agarwal[6]
[1, 5]Junior Resident, Department of Radiology, RIMS Ranch
[2]Professor & HOD, Department of Radiology, RIMS Ranchi
[3,4]Associate Professor, Department of Radiology, RIMS Ranchi
[6]Senior Resident, Department of Radiology, RIMS Ranchi
*Corresponding Author
Dr Rupam Kumari
Add: New PG Girl's hostel, RIMS, Bariyatu, Ranchi 834009, India
Mobile No: 8674829414, Email: *rupam.rims08@gmail.com*

Abstract
Background: *Cerebral vasculopathy leading to infarct are the most serious complications of tuberculous meningitis (TBM). Transcranial Doppler (TCD) allows early diagnosis and monitoring of cerebral hemodynamics. It is real time, non-invasive and non-ionizing imaging modality.*
Aims & Objectives: *1) To describe spectrum of findings and to detect cerebral vasculopathy in pediatric TBM patients by using TCD. 2) To determine reliability of TCD by correlating its findings with computed tomography (CT) findings and stage of the disease.*
Materials & Methods: *40 children≤ 13 years with diagnosis of TBM referred in Department of Radiology of a Tertiary care Hospital, Rajendra Institute of Medical Sciences (RIMS), Ranchi from September 2017 – August 2018 underwent serial TCD imaging on day 1, day 3 & day 7 after obtaining written informed consent. Findings were analyzed and then compared with CT findings and stage of the disease.*
Results: *Out of 40 study subjects who underwent TCD imaging, 19 patients showed abnormal Doppler findings in the form of stenosis in 15, vasospasm in 4, and hyperemia in 2 children. Sensitivity and Specificity of TCD as compared to CT to detect stenosis in cerebral arteries were 91.7% & 85.7% respectively.*
Conclusion: *Serial TCD can be used as a reliable modality for early diagnosis and monitoring of intracranial vasculopathy in childhood TBM.*
Keywords: *Transcranial Doppler, Vasculopathy, Tuberculous Meningitis, Children, CT.*

Introduction

Neurotuberculosis can manifest as tuberculous meningitis (TBM), tuberculoma ortuberculous abscess.[1] TBM is the most severe form of neurotuberculosis with high rate of mortality and morbidity in children.[2] Rapid diagnosis and early commencement of treatment play a crucial role in outcome of the disease.[3]

Lumbar puncture is the cornerstone of diagnosis. Many laboratory diagnostic options are available such as CSF smear, CSF culture, MODS, Interferon Gamma Release Assays etc.[4]But clinicians have to rely on less time consuming investigations so that treatment can be started at an early stage. Neuroimaging (CT&MRI) plays a great role. Imaging features of TBM which are characteristic for the disease are presence of basal hyperdensities on NCCT, hydrocephalus usually communicating type, enhancement of leptomeninges and basal cisterns, periventricular infarcts and associated tuberculoma or abscess.[5][6] Infarcts are the result of vasculopathy which is one of the most severe complications of TBM, hence early diagnosis of vasculopathy needed.

Many imaging modalities are available to detect intracranial vasculopathy like CTA, MRA, DSA and TCD. Transcranial Doppler is also called doctor's stethoscope. It is a real time, non-invasive and non-ionizing investigational tool for assessing cerebral hemodynamics. It is cheap, widely available, reproducible and can be used for bed side evaluation in comatose patients. It provides both structural and physiological details of cerebral arteries.[7]

Many studies have investigated the role of TCD in TBM, but very few studies have been done regarding its use in TBM related vasculopathy. In our study, we tried to find out reliability of TCD in early diagnosis and monitoring of vasculopathy in pediatric TBM patients by comparing it with CT.

Materials And Methods

Study Duration: from September 2017 to August2018.

Source of Data: Children with diagnosis of TBM referred to the department of radiology, RIMS, Ranchi during the study duration. Diagnosis was based on Consensus clinical case definition of TBM as Definite, Probable and Possible case of TBM.[6]

Study Sample: 50 cases of diagnosed TBM**.**

Inclusion Criteria

- Patients of both gender ≤ 13 years of age.
- Pediatric patients with diagnosis of TBM and without any previous history of Anti Tubercular Treatment (ATT).

Exclusion Criteria

- Patients more than 13 years of age.
- Previously treated patients with ATT.
- Such patients were secondarily excluded whose final diagnosis came out to be other than TBM.
- Patients with history of allergy to contrast.

Data Collection Techniques and Tools

Patients were enrolled in the study only after obtaining written informed consent. A detailed history was taken, complete clinical examination was done and all previous investigations especially CSF based examination reports were seen.

Grading of disease severity was done based on Modified British Medical Research Council (MRC) into 3 grades.[8] Grade 1 was considered as Early stage and Grade 2 + Grade 3 were considered as Advanced stage.

Serial Transcranial Doppler (TCD) was done on day 1, day 3 & day 7 through fontanelle if open and through transtemporal window if fontanelle closed to insonate bilateral middle cerebral artery (MCA), anterior cerebral artery (ACA)&posterior cerebral artery (PCA) using Philips HD 11 XE ultrasound machine and 2-4 MHZ sector transducer. Peak Systolic Velocity (PSV), Mean flow velocity (V_m) & Pulsatility Index (PI) displayed on the screen were recorded. Lindegaard ratio (LR) was calculated after insonating bilateral terminal part of extracranial ICA. Diagnostic criteria used were:

Cerebral arterial stenosis: When persistently raised PSV with Lindegaard ratio > 3, patients with subnormal PSV were diagnosed as severe stenosis (near occlusion).

Vasospasm: When PSV raised initially with Lindegaard ratio > 3 and normalize on follow up of patients.

Hyperemia: when PSV raised with Lindegaard ratio< 3. Normal PSV range used in this study were as per the age group in a published article shown in table 1.[9]

Table 1: Age wise normal Peak systolic velocities (SD) in cm/sec

AGE	MCA	ACA	PCA
3-11.9 months	114(20)	77(15)	---
1-2.9 years	124(10)	81(19)	67(18)
3-5.9 years	147(17)	104(22)	84(20)
6-9.9 years	143(13)	100(20)	82(11)
10-18 years	129(17)	92(19)	75(16)

All patients underwent Non Contrast Computed Tomography (NCCT), Contrast Enhanced Computed Tomography (CECT) & CT Angiography (CTA) to look for any visible infarcts and cerebral arterial narrowing. Other associated findings such as leptomeningeal & basal cistern enhancement, hydrocephalus or any focal lesions were also recorded. To assess reliability of TCD, findings of TCD were then compared with findings on NCCT + CECT and CTA. TCD findings were also compared with the stage of the disease. All descriptive statistics were analyzed and p-value < 0.05 was considered statistically significant.

The study was approved by the Institutional Ethics Committee of Ranchi University.

Results

40 children with the diagnosis of TBM were enrolled in the present study. Demographic findings, patient distribution based on consensus clinical case definition along with disease severity grading are presented in table No. 2

Table 2: Demographic findings, Distribution of patients based on case definition of TBM and modified MRC grading

		Patients (n=40)
Age	Mean	6.92 years
	SD	3.88
Gender	Male	24(60%)
	Female	16(40%)
Diagnosis of TBM	Definite	3(7.5%)
	Probable	31(77.5%)
	Possible	6(15%)
Modified MRC grading	Grade 1	16(40%)
	Grade 2	16(40%)
	Grade 3	8(20%)
Stage of TBM	Early	16(40%)
	Advanced	24(60%)

Among 40 children with TBM, maximum incidence was in the age group 6-10 years (16 patients) followed by 1-5 years(11 patients) with mean age 6.92 with SD= 3.88. 24(60%) patients were male and 16(40%) patients were female. 24(60%) children were having advanced stage(Grade 2 + Grade 3) of the disease at presentation, rest presented at an Early stage of the disease.

On NCCT+CECT,31(77.5%)children were having hydrocephalus (mostly communicating type), enhancement of basal cisterns & leptomeninges were demonstrated in 27(67.5%) patients. 16(40%) children also had other manifestations of neurotuberculosis like tuberculomain 10(25%) patirnts, encephalitis in 4(10%) patients and abscess in 2(5%) patients along with features of TBM. Also 30% children were having visible infarcts in brain parenchyma mostly in basal ganglia and periventricular region in MCA territory.

CTA further revealed narrowing in one or more cerebral arteries in 12 patients. Out of all 12 patients,25.1% showed narrowing in left MCA followed by 16.67% patients having narrowing in bilateral MCA & right MCA each. Narrowing was found in 1 patient each in right MCA & bilateral PCA, left MCA & left ACA, right MCA & right ACA, right ACA only and right MCA &left ACA.

On TCD, 21(52.5%) study subjects showed normal Doppler study. Among 19(47.5%) patients with abnormal Doppler findings, 15(37%) were diagnosed as having stenosis of one or more cerebral arteries. among these 15 patients, MCA was involved in 12 patients (5 of them showed bilateral involvement and rest were unilateral either left or right), involvement of ACA was found in 7 patients and PCA was involved in only 2 patients.

When found that PSV and V_m of all arteries (Bilateral MCA, ACA & PCA) goes hand in hand

showing positive correlation. In our study we observed increment in mean PSV and V_m with increase in grade or stage of the disease. Mean PSV &V_m were on higher side in the advanced stage of the disease as compared to early stage. However, these correlations were found significant only in right MCA and left ACA. In rest of the arteries these correlations were not significant as p-value was more than 0.05.

Correlations between PSV and PI of cerebral arteries (bilateral MCA, ACA & PCA) were poor not found significant in our study.

Comparison between TCD findings and stage of the disease is depicted in figure 1. In our study out of all patients in early stage (Grade 1),about 93.8% patients did not have stenosis on TCD imaging, while, out of all in advanced stage(Grade 2+3), 58.3% patients showed stenosis on TCD imaging. This correlation was found to be statistically significant.

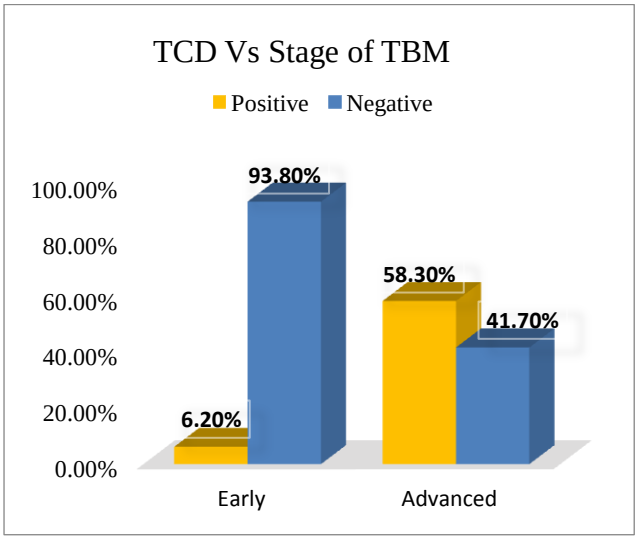

Figure 1: Comparison of Positive (presence of stenosis) and Negative (Absence of stenosis) findings on TCD with Early (Grade 1) and Advanced (Grade 2+3) stage of the disease.

Statistically significant correlation was found between infarcts on CT and diagnosis of stenosis on TCD imaging.

Correlation between TCD findings and CTA was made which is shown in figure 2.

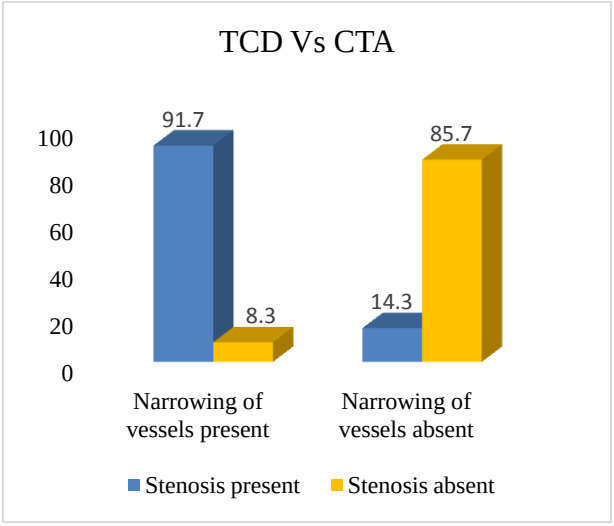

Figure 2: Comparison between TCD and CTA findings.

When comparison was made between narrowing of vessels on CTA and stenosis on TCD, the Sensitivity of TCD as compared to CTA was 91.7% and specificity was 85.7%. Also Positive Predictive Value was 73.33% and Negative predictive value was 96% and accuracy of TCD was found to be 87.5%. The correlation between TCD imaging and CTA was highly positive and statistically significant.

Discussion

Present study in 40 pediatric TBM patients describes the role of TCD in early diagnosis and monitoring of cerebral vascular complications in children with TBM and also define its reliability as compared to CTA.TCD allows rapid vessel identification and is most reliable for detecting vasculopathy related to MCA, terminal ICA & basilar artery. It detects stenotic areas of vessesls and also provides accurate blood flow velocities.

As TBM shows rapid progression in children, more than half (60%) patients presented at an advanced stage (grade 2+3) which is similar to the studies conducted by Mei-Ling Sharon Tai et al & Ronald Van Toorn et al.[10][11]

On NCCT + CECT, out of 40 TBM patients, 77.5% were found to have hydrocephalus, 67.5% children showed enhancement more in basal cisterns followed by cerebral convexities which correlates well with studies conducted by Mei-Ling Sharon Tai et al and Anil et al.[10][12] Also

30% patients had visible infarct in brain parenchyma mostly in basal ganglia region. The review article by Ravindra Kr. Garg& other stated that in a meta-analysis that included 404 patients, infarcts at the time of diagnosis were found in approximately 25% patients.[13] Study by Ronald Van Toorn et al and by Anil et al showed 40% and 45% patients having infarct respectively.[11][12]

Among 12 out of 40(30%) patients with narrowing of one or more vessels of cerebral arteries on CTA, MCA either unilateral or bilateral was involved in 11 patients and was the most common artery to be involved followed by ACA in 4 patients and PCA in one patient. These results are similar to the results of studies conducted by Mei-Ling Sharon Tai et al, Singh B et al and Jayantee K et al.[10][14][15]

In our study we concluded that mean of PSV and V_m increases with advancement of the disease. But this correlation was not found statistically significant in all arteries except Right MCA & Left ACA (p-value <0.001).Study conducted by Mei-Ling Sharon Tai et al also found the correlation statistically significant only in few arteries of circle of willis.[10]

In Transcranial Doppler studies in TBM patients, Mei-Ling Sharon Tai et al diagnosed vasculopathy in 11 out of 36 patients. Ronald Van Toorn et al found bilateral MCA stenosis on admission in 14 of the 20 TBM children.[10][11] These findings are similar to our study where 15(37.5%) out of 40 patients were found to have stenosis in one or more arteries in the brain parenchyma on TCD imaging most of them involving MCA.

In our study the correlation between cerebral artery stenosis on TCD and Stage of disease was found to be positive and statistically significant and thus it can be concluded that advance the stage of the disease, more are the chances of stenosis.

The correlation between PSV & PI in all arteries on TCD was not statistically significant and was similar to the study conducted by Ronald Van Toorn et al.[11]

Comparison of presence of stenosis on TCD was made with presence of infarct on NCCT + CECT and narrowing of vessels on CTA. Correlation between stenosis on TCD and infarct on NCCT+CECT was positive and statistically significant. Also Correlation between TCD and CTA to detect stenosis was found to be strong positive and statistically significant. Out of all patients who had shown stenosis on TCD, about 91.7% patients showed narrowing on CTA while 85.7% patients labelled normal by TCD showed normal CTA. Thus we can conclude that Sensitivity and Specificity of TCD is good when compared with CTA. Positive Predictive Value (PPV) was 73.33% and Negative Predictive Value (NPV) was 96% and the accuracy of TCD was found to be 87.5%.4 patients having stenosis on TCD did not show narrowing on CTA. Similar results were found in the study conducted by Mei Ling Sharon Tai et al.[10] This was thought to be due to earlier detection of hemodynamic changes on TCD because of small penetrating vessel involvement difficult to be evident on CTA. Another reason can be inflammatory hyperemia which often occurs in first week of the disease causing elevated PSV on Transcranial doppler.

Thus TCD imaging can play a crucial role in detecting stenosis in cerebral arteries if CT facilities are unavailable.

Conclusion

This study showed that a considerable proportion of TBM patients develop vascular complications leading to ischemia or infarct. Serial TCD can be used as a reliable modality for early diagnosis of cerebral arterial stenosis, and to differentiate from other cerebral hemodynamic changes like vasospasm and hyperemia. It can also be used as a follow – up tool as it is safe, non-invasive, non-ionizing, cheap and widely available.

Our study has certain limitations. Short study duration, relatively small sample size and few parameters (like arterial CO_2 level, body temperature, ICP) that affect cerebral hemodynamics were not considered during

Transcranial Doppler imaging. Further studies with large sample size is needed to validate our results.

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