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# Utility of transcranial Doppler ultrasonography in the diagnosis and follow-up of tuberculous meningitis-related vasculopathy

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**Abstract** *Introduction:* This prospective clinical study tested the hypothesis that transcranial Doppler ultrasonography (TCD) can be efficiently utilized in the diagnosis and management of tuberculous meningitis-related vasculopathy.
*Patients and methods:* Twenty patients with tuberculous meningitis were assessed with serial TCD examinations. Blood flow velocity (Vm) and pulsatility index (PI) were measured, and findings were correlated with patient prognosis and with clinical and radiological findings.
*Results and conclusions:* The TCD data allowed us to distinguish three phases of tuberculous meningitis-related vasculopathy. In phase I vasculopathy TCD reveals increased Vm and normal to moderately decreased PI. In patients in this phase reversible ischemic deficits are seen clinically and radiologically. Phase II is associated with decreased Vm and decreased PI. At this stage patients reveal radiological and clinical signs related to proximally evolving vasculopathy in the basal main arteries. Phase III is characterized by almost absent blood flow in one or more basal arteries and, accordingly, by associated brain tissue infarction and permanent severe neurological deficit or fatal outcome.

**Keywords** Tuberculosis · Vasculopathy · Meningitis · Hemodynamics · Transcranial Doppler ultrasonography

## Introduction

Tuberculous (TBC) meningitis has a major vascular component that is often overlooked clinically. The inflammatory reaction surrounding the vessels in the basal subarachnoidal cisterns may lead to obliterative endarteritis [13]. This results in ischemia and infarction in the brain tissue normally supplied by the affected vasculature. Depending on which vessel is affected, the clinical consequences can be catastrophic.

Transcranial Doppler sonography (TCD) has been available as a diagnostic tool since 1982 [1]. The technique has advanced rapidly, and is currently a simple, noninvasive, and reliable method of evaluating intracranial hemodynamics [9, 10]. We designed a study to assess the utility of TCD in the diagnosis and management of TBC meningitis-related vasculopathy.

## Materials and methods

Twenty tuberculous meningitis (TBCM) patients who exhibited cerebrovascular symptoms were prospectively evaluated in the Transcranial Unit in Marmara University Department of Neurosurgery between January 1997 and February 1998. All the patients were examined daily with TCD and were diagnosed and treated by staff of the Departments of Infectious Diseases and/or Pediatrics. In order to obtain a more homogeneous sample group, we set the following criteria for patient selection:

1. The causative microorganism, *Mycobacterium tuberculosis*, was identified or isolated in each case.
2. Only TBCM patients who were referred to our unit and received medical care from the start of their illness were included. We excluded individuals with this disease who were referred from another health center for treatment of any complication.
3. In assessing the data, we accounted for the baseline TCD measurements taken at the time each patient's clinical status first changed.

4. Computerized tomography and/or magnetic resonance imaging were performed each time there was a change in a patient's neurological status.
5. Patients who had undergone surgery for any intracranial problem (e.g., shunt placement for hydrocephalus) were excluded.
6. Patients with pre- or postoperative hematocrit values below 28 g/dl or above 44 g/dl were excluded.
7. Patients who died primarily due to causes other than neurological conditions, and immunocompromised patients who died from primary disease were excluded.

The selected group ranged in age from 2 to 24 years, with a mean age of 9 years. Thirteen of the patients were female, and 7 were male. Seven patients were immunocompromised owing to other primary nonneurological diseases.

We used a 2-MHz pulsed TCD system (EME 2000, Eden Medizinische Elektronik, Überlingen, Germany) for all ultrasound examinations. At each assessment, we measured the systolic, diastolic and mean blood flow velocity (Vm) and the pulsatility index (PI) for the basal arteries via the temporal and transorbital routes. Vm was measured as an absolute value on TCD, and is expressed in cm/s. PI was calculated and displayed on the TCD unit during the examination, and is derived using the following formula:

(Peak Systolic Velocity
− End Diastolic Velocity) ÷ Mean Velocity

We used StatView PC software to perform the statistical analysis. *P*-values smaller than or equal to 0.05 were considered statistically significant. Error bars for 95% confidence interval were used in cell line charts.

Once the prospective data were generated, we tested correlations between phase of TCD and the respective clinical and radiological findings. The following three phases of the disease were identified based on clinical and radiological findings:

- Phase I (Figs. 1, 2) featured temporary focal neurological deficits that clinically and resembled transient ischemic attack (TIA), and the Glasgow Coma Scale (GCS) score was 15.
- Phase II (Figs. 1, 3) involved focal neurological deficit(s) but no loss of consciousness, and the GCS was 12–14.
- Phase III (Figs. 1, 4) featured impaired consciousness, and the GCS was below 12.

## Observations and results

### Phase I

All 20 patients experienced transient focal neurological TIA-like symptoms. Eighteen developed motor deficits, and 2 patients had visual symptoms. The mean Vm in the middle cerebral artery (MCA) ipsilateral to the symptoms on the day each patient was diagnosed with phase I TBCM vasculopathy was 180 cm/s. The mean PI at this stage was 0.50. In all cases, audible vascular turbulence was noted during the examination. All 8 patients who did not progress to phase II were discharged from hospital with no neurological deficits.

### Phase II

Although all 20 patients received appropriate treatment in phase I of the condition, 12 developed permanent fo-

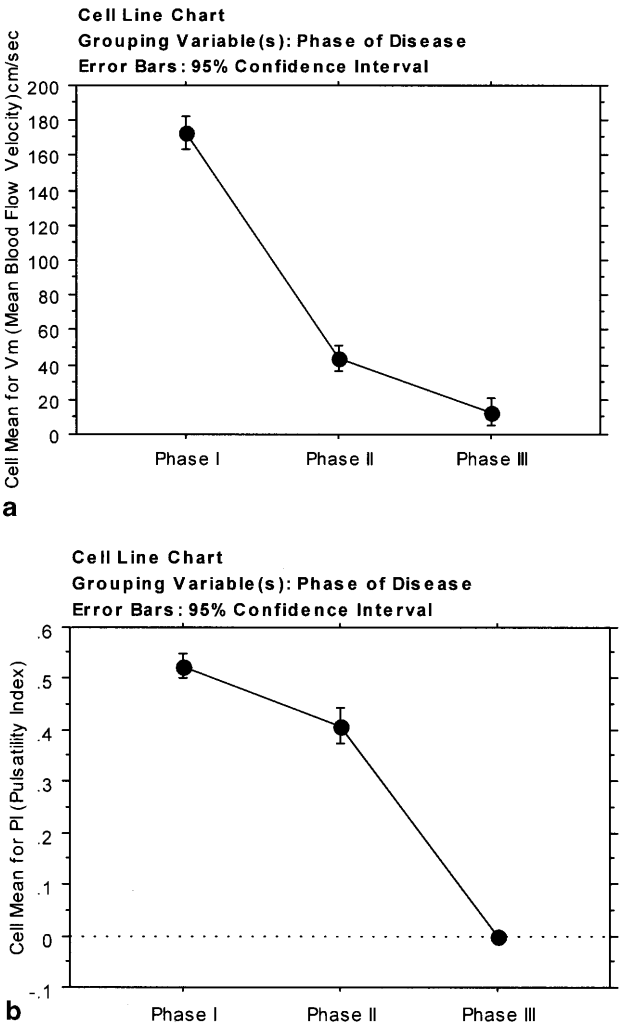


**Fig. 1 a** This graph shows the changes in mean velocity (Vm) of the affected middle cerebral artery (MCA) as a function of the phases of tuberculous meningitis related vasculopathy. Vm on the MCA in the normal population changes between 60–90 cm/s [7]. Vm increases in phase I of the vasculopathy. Symptoms and signs in this phase are reversible. As the inflammatory reaction around the affected MCA progresses, i.e. in phase II, Vm starts to decrease and falls to subnormal values. In phase II, neurological focal deficits are determined and they may be irreversible. So decrease in Vm after phase I of vasculopathy, may be an ominous sign of irreversible anatomical damage caused by the vasculopathy. If disease further progresses and the blood flow is severely impaired, Vm decreases to 0–20 cm/s. This TCD transcranial Doppler ultrasonographic sign of phase III indicated poor prognosis with a high mortality rate. **b** This graph shows the changes in pulsatility index (PI) of the affected middle cerebral artery (MCA) as a function of the phases of tuberculous meningitis TBCM-related vasculopathy. PI on the MCA in the normal population changes between 0.6 and 0.9 [3, 6, 9]. PI is usually within normal to moderately decreased limits in phase I of the vasculopathy. Symptoms and signs in this phase are reversible. As the inflammatory reaction around the affected MCA progresses, i.e. in phase II, PI starts to decrease and falls to subnormal values. In phase II, neurological focal deficits are determined and may be irreversible. If disease further progresses and the blood flow is severely impaired, PI decreases to almost 0. This TCD sign of phase III indicated poor prognosis with a high mortality rate

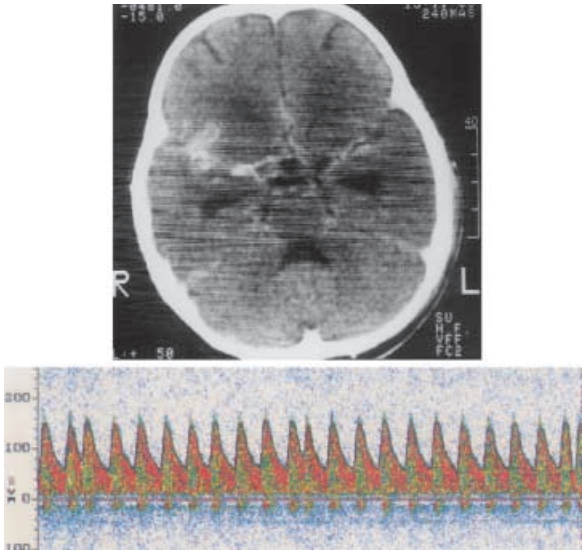

**Fig. 2** Radiological and TCD findings in phase I: computerized tomographic (CT) examination (with contrast) reveals contrast enhancement in the basal cisterns, indicating inflammatory reaction due to TBCM. TCD examination of the right MCA shows increased Vm (125 cm/s in this case), with normal to moderately decreased PI (0.50 in this case), which are signs of phase I disease. Symptoms and clinical signs in this phase mimic transient ischemic attacks, and they are reversible if the disease does not progress

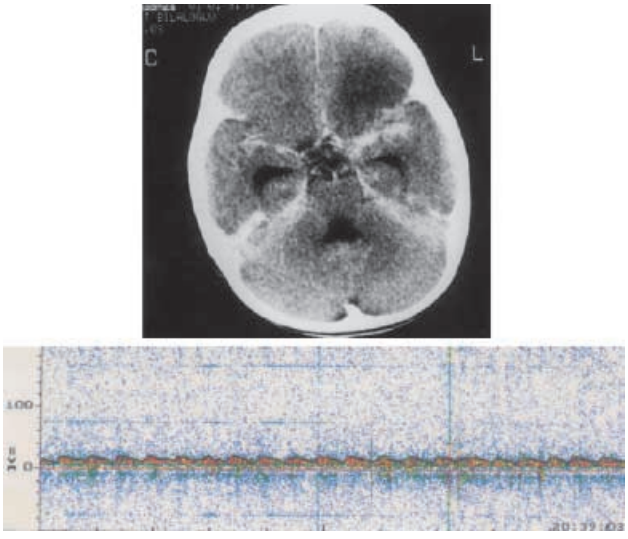

**Fig. 4** Radiological and TCD findings in phase III: computerized tomographic (CT) examination (with contrast) reveals out contrast enhancement in the basal cisterns, indicating inflammatory reaction due to tuberculous meningitis. Although the contrast enhancement is not as severe as in the case illustrated in Fig. 3, TCD examination of the left MCA shows severely impaired Vm (15 cm/s in this case) and undetectable PI, which are signs of phase III disease. Usually cerebral infarction is detected (as the evident infarction in the frontal lobe in this CT section), and the prognosis is poor

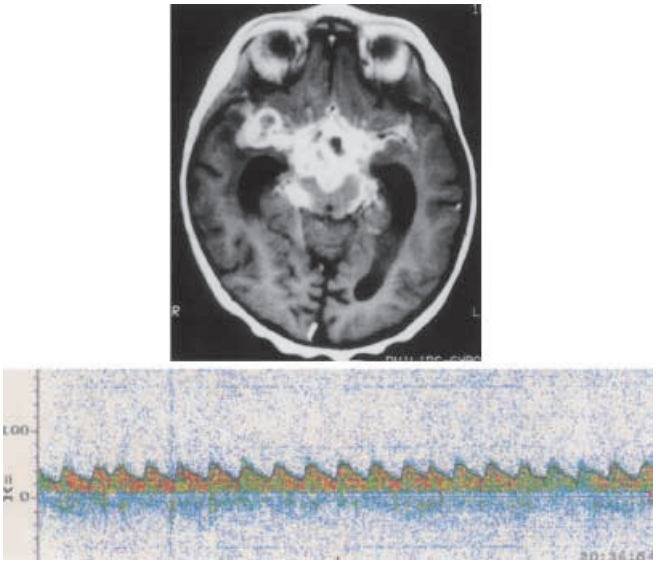

**Fig. 3** Radiological and TCD findings in phase II: T1-weighted magnetic resonance examination (with contrast) reveals out severe contrast enhancement in the basal cisterns, indicating progressed inflammatory reaction due to tuberculous meningitis. After an initial increase in phase I, transcranial Doppler examination of the right MCA shows decreased Vm (45 cm/s in this case), with decreased PI (0.40 in this case), which are signs of phase II disease. Symptoms and clinical signs in this phase reveal usually focal neurological deficits, which may be irreversible

cal motor neurological deficits, such as hemiparesis. The mean Vm in MCA ipsilateral to the symptoms on the day each patient was diagnosed with phase II TBCM vasculopathy was 46 cm/s, and the mean PI at this examination was 0.42. Again, audible vascular turbulence was noted at this stage. Of the 7 patients who did not progress to phase III, 5 left hospital with permanent neurological deficits.

### Phase III

Five of the 12 patients who progressed to phase II also lost consciousness in the course of their illness. In these cases, there was severely impaired blood flow in the MCA ipsilateral to the deficit. Four of the 5 patients died as a result of the vascular compromise, and all those who died during hospitalization were in this group.

## Discussion and conclusions

### Vasculopathy in TBCM

Although it has been recognized for many years, TBCM is still an important disease in various parts of the world. It remains one of the most common causes of chronic

meningitis in some developing and industrialized nations, and the incidence continues to rise in parallel with the growing numbers of immunocompromised patients worldwide [16]. In addition, the clinical presentation of TBCM is changing, which complicates diagnosis and management.

One of the most seriously underestimated effects of this disease is TBCM-related vasculopathy [13]. In pathological terms, the inflammatory reaction surrounding the vessels in the subarachnoid space may cause obliterative endarteritis [8, 13] (Figs. 2, 3, 4). Vascular blockage can result in ischemic changes in the corresponding brain tissue. The clinical consequences depend on which structure is involved, but they can be lethal if a vessel such as the middle cerebral or anterior spinal artery is affected [13].

## Value of TCD in management

TCD is an effective means of assessing the main arteries at the base of the brain, which are also the vessels most severely affected by TBCM-related vasculopathy [5]. The noninvasive nature of TCD and the ease with which it can be repeated (even in severely ill patients) make it valuable for diagnosing, staging, and following up a number of cerebrovascular diseases [3, 6, 7]. TCD is of particular benefit in these conditions, because obliterative endarteritis is considered a progressive pathologic process; early detection and assessment of changes during treatment can facilitate more efficient management of the debilitating consequences of the disease [15].

Cerebral angiography is currently the gold standard for anatomical diagnosis and follow-up of cerebrovascular diseases; however, the invasive nature of this technique restricts its use as a decision-making tool when rapid changes need to be assessed or monitored. Even more important, patients with infectious disease tend to have fragile vessel walls, which makes catheter placement risky and limits the application of this technique.

In contrast, TCD is a safe and efficient way of assessing the hemodynamic status of each vessel and, equally importantly, it provides necessary information about the collateral circulation [11]. As a result, in cases where a major vessel is occluded TCD may enable the examiner to predict the likelihood of infarction based on the state of the collateral blood flow.

Several studies in the literature discuss the hemodynamic consequences of vasculopathy in purulent bacterial meningitis. Using duplex Doppler and noninvasive fontanel tonometry, McMenamin and Volpe [12] demonstrated an inverse relationship between intracranial pressure and cerebral blood flow (CBF) in neonates and young children with bacterial meningitis. Paulsen [14] examined CBF responses using $^{133}Xe$ in 15 adult patients with encephalitis or meningitis. He found that blood pressure autoregulation was impaired in a significant number of individuals, but that $CO_2$ vasoreactivity was preserved in all cases. In a more recent study on children with meningitis, Ashwal [2] found that CBF was markedly decreased in 30% of the cases. The utility of TCD ultrasonography in acute cerebral infection was demonstrated by Bode [4], who examined the degree of vascular compromise in a small series of children with bacterial meningitis; however, the current literature contains no prospective systematic study on the value of TCD in TBCM-related vasculopathy.

In our study, TCD of the MCA in phase I patients (cases clinically characterized by TIA-like focal neurological symptoms) revealed signs of segmental narrowing of the vessel lumen. The increased Vm and normal to moderately decreased PI at this stage of the disease resembled the findings in the early phase of acute vasospasm due to aneurysmal subarachnoidal hemorrhage [9]. It is important that these features be recognized, because brain ischemia is reversible in this phase. In our study, the 8 patients whose disease did not progress to phase II had no neurological deficits when they were discharged from hospital.

Once the inflammatory process involves the proximal vessel segments that precede MCA, such as the distal internal carotid artery, TCD scanning reveals decreased Vm in the MCA. As noted in a study conducted by our group, a similar picture is seen in cases of progressive vasospasm after subarachnoid hemorrhage [9]. In TBCM-related vasculopathy, although the drop in Vm distinguishes phase I from phase II, PI (which is a calculated mathematical value) remains low (similar to phase I) as the disease advances to the second stage. Since audible turbulence is generated by anatomical irregularities of the vessel walls, this is still present in phase II.

As already mentioned, this reduction in Vm from the velocity seen in phase I should alert the physician to the fact that the pathologic process of occlusive endarteritis is progressing and the proximal internal carotid artery is involved. The next step should always be to examine the contralateral vessels and assess collateral support; however, our investigation showed bilateral involvement in each case, with one side manifesting neurological symptoms before the other. Radiological studies with contrast injection showed signs of inflammation surrounding the basal arteries, but infarcts at this stage were usually limited to a small area of brain tissue, as a result of occlusion of a perforating arteriole. Seven of 12 phase II patients did not progress to phase III, and 5 of these 7 were discharged from hospital with permanent focal neurological deficits.

Five patients in our series progressed to phase III and lost consciousness. In each case, blood flow in the examined MCA was almost completely blocked and the TCD readings were negligible. Radiological examination revealed brain infarcts in all cases. The finding of negligi-

ble blood flow on TCD is an ominous sign. Four of the 5 patients who advanced to this stage died in hospital, and the other was left severely debilitated.

To our knowledge, this is the first prospective study to systematically demonstrate the value of TCD not only as a diagnostic tool in TBCM-related vasculopathy, but also as an important potential aid for decision-making in these cases. Also, our TCD-based system for staging the condition may help clinicians identify the step-wise hemodynamic changes that occur as this disease progresses, and it is geared toward standardizing the approach to diagnosis and treatment. We feel that the latter is particularly important, especially since these cases need multidisciplinary collaboration.

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