Thieme

Neuro-Behcet: The Value of Transcranial Doppler

Neuro-Behcet: Der Wert des transkraniellen Dopplers

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ABSTRACT

Abstract Neurological involvement in Behcet disease (BD) is one of the most serious causes of long term morbidity and mortality and can be found in up to 49 % of cases. There are 2 main types of CNS involvement, parenchymal and non-parenchymal. Transcranial Doppler (TCD) ultrasonography provides a relatively inexpensive, noninvasive, evaluation of the haemodynamics within intracranial arteries.

Material and Methods Case control study of 15 patients with NBD all of them fulfilled the criteria of the International Study Group for Behcet's disease and fifteen apparently healthy volunteers age and sex matched. All patients and healthy controls were examined by TCD. Cranial Magnitic Resonance Imaging (MRI) examination was performed to the patients group.

Results Transcranial Doppler showed significant decline in the mean velocity (MV) of all the examined cerebral arteries in all NBD patients with the highest significant decrease in the vertebral artery (VA). On the other hand, a significant increase in the pulsatility index (PI) was detected only in the posterior cerebral artery (PCA). Regarding MRI examinations of our patients, 7 of 15 (46.7 %) patients had parenchymal lesions, 13 % had vascular lesions coexisting with parenchymal lesions (mixed). The parenchymal were located in the periventricular and superficial cerebral white matter, thalamus and brainstem followed by the cerebellum. Vascular lesions were dural and transverse sinus thrombosis.

Conclusion TCD provides a sensitive and accurate bed-side non-invasive imaging tool for the detection of flow pattern abnormalities in patients with NBD. MRI remains the gold standard for diagnosis.

ZUSAMMENFASSUNG

Hintergrund Die neurologische Beteiligung bei Morbus Behcet (BD) zählt zu den schwerwiegendsten Ursachen für langfristige Morbidität und Mortalität und betrifft bis zu 49 % der BD-Patienten. Es werden 2 Hauptarten der ZNS-Beteiligung unterschieden: die parenchymale und die nicht-parenchymale. Die transkranielle Doppler-Ultrasonographie (TCD) ermöglicht eine relativ kostengünstige, nicht-invasive Beurteilung der Hämodynamik innerhalb der intrakraniellen Arterien.

Material und Methoden Es wurde eine Fallkontrollstudie mit 15 Patienten durchgeführt, die alle an Morbus Behcet mit neurologischer Beteiligung (NBD) litten und die Kriterien der internationalen Studiengruppe für M. Behcet erfüllten. Zudem nahmen 15 gesunde Probanden mit entsprechender Alters- und Geschlechtsverteilung an der Studie teil. Alle Patienten und die gesunden Probanden wurden mittels TCD untersucht. Die Patientengruppe wurde zusätzlich einer kraniellen Magnetresonanztomographie (MRT) unterzogen.

Ergebnisse Die transkranielle Doppler-Sonographie zeigte bei allen NBD-Patienten in allen untersuchten Arterien eine signifikante Abnahme der mittleren Strömungsgeschwindigkeit (MV, „mean velocity"). Die höchste signifikante Abnahme fand sich in der A. vertebralis (VA). Eine signifikante Zunahme des Pulsatilitätsindexes (PI) wurde demgegenüber nur in der A. cerebralis posterior (PCA) festgestellt. Die MRT-Untersuchungen unserer Patienten ergaben bei 7 von 15 Patienten (46,7 %) parenchymale Läsionen. Bei 13 % der Patienten wurden koexistierende vaskuläre und parenchymale Läsionen (gemischt) festgestellt. Die parenchymalen Läsionen fanden sich in der periventrikulären und der oberflächlichen zerebralen weißen Substanz, im Thalamus, Hirnstamm und Kleinhirn. Bei den

vaskulären Läsionen handelte es sich um Thrombosen der Sinus durae matris und des Sinus transversus.

Schlussfolgerung Die TCD ist ein sensibles und präzises, nicht-invasives, direkt am Patientenbett durchführbares Bildgebungsverfahren zur Feststellung von Anomalien im Strömungsmuster bei Patienten mit NBD. Goldstandard in der Diagnostik ist nach wie vor die MRT.

Introduction

Behcet's disease is a chronic inflammatory vascular multisystem disease. Neuro-Behcet's disease occurs in up to 49 % of all cases [1, 2] and it is considered one of the most serious manifestations of BD with a high rate of morbidity and mortality [3, 4]. They are usually vascular-inflammatory in nature commonly presented with mild confusion with or without disturbance in consciousness, subacute brainstem syndrome, cerebellar findings and unilateral or bilateral corticospinal tract signs [5]. Patients commonly complain about fatigue, diplopia, nystagmus, loss of vision, cranial nerve palsies, dementia pseudobulbar palsy, cerebellar signs, pyramidal signs, sensory symptoms, speech disturbance, and isolated or recurrent aseptic meningitis [6]. It usually starts with an attack of headache, hemiparesis and/or gradual behavioural changes [7]. Early diagnosis of NBD is difficult, but important because appropriate treatment can be started as soon as possible [8]. MRI is by far the most helpful investigation for the diagnosis of NBD [9]. However, Chuang et al. 2013 [10] showed that brain perfusion single-photon emission computed tomography (SPECT) were more diagnostically sensitive in patients with NBD than either CT or MRI. Transcranial Doppler (TCD) allows monitoring of cerebral blood flow velocity and vessel pulsatility in the intracranial arteries.

Our aim was to evaluate haemodynamic patterns in patients with NBD by TCD and brain lesions by MRI.

Material and methods

Case control study carried out at the physical medicine, Rheumatology and Rehabilitation department and the Department of Neuropsychiatry of the Upper Egypt, Assiut University Hospitals, in the period between September 2015 and May 2016.

Members of this study had been divided into 2 groups fifteen patients with neuro-Behcet's disease (14 males and 1 female) all of them fulfilled the criteria of the International Study Group for Behcet's disease (ISGBD, 1990) and 15 apparently healthy volunteers age and sex matched. Any patient with vasculitic, neurologic, psychiatric or pharmacologic entity other than BD were excluded from the study. Patients with BD were subjected to full history taking and clinical examination (general and neurological). Neurological examination was done for patients with help of a qualified neurologist. Assessment of soft neurological signs was done according to soft neurological sign assessment [11] that includes assessment of coordination, involuntary movements, sensory function and visuospatial station. Patients with neurological findings suggestive of involvement of the nervous system by the disease were regarded as cases of NBD.

All patients and healthy controls were examined by TCD by ultrasonic insonation. The patient sat in a comfortable chair and intracranial arteries were insonated through windows of skull bone using probe after applying gel as a connecting material. Middle cerebral (MCA), anterior cerebral (ACA), posterior cerebral (PCA), vertebral (VA) and basilar (BA) arteries were examined. The MCA, ACA and PCA arteries were insonated through temporal window at depth 30–60, 60–80 and 60–70 respectively while VA and BA arteries were insonated through occipital window at depth 60–90 and 80–120 respectively. The waves of every artey were recorded for assessment of TCD parameters which include MV and PI. Cranial MRI examination was performed to the patients group (FLAIR, T1 and T2 sequences) using Philips, Achieva, 1.5 tesla MRI device. Evaluation of MRI to assess evidence of organic focal lesions and evaluate the site of involvement was done by the same radiologist.

Informed written consent was obtained from all participants before entering the study. This study was reviewed and approved by the ethics committee of Faculty of Medicine, Assiut University, Egypt.

Data collection and analysis

The data were coded and entered using the Statistical Package for Social Science programme (SPSS, Chicago USA, version 16). The values of each group of patients for each scale were analyzed separately by one-way analysis of variance (ANOVA) repeated measure analysis. Mann-Wittney U test and Fisher exact test were used for comparison between patients and control groups.

Results

This study included 15 patients with NBD their age ranged from 18 to 46 years with a mean age of 30.2 ± 8.3 years with male predominance [14 males and 1 female] and mean disease duration of 4.7 ± 3.2 years. 100 % presented with recurrent oral and genital ulceration. Eye lesions, skin lesions and positive pathergy test were 73.3, 60 and 40 % respectively. Neurological manifestations in the form of headache (100 %), dizziness (93.3 %), peripheral neuropathy (73.3 %), loss of consciousness (60 %). Soft neurological signs were positive in 46.6 % mainly for incoordination and involuntary movements. Manifestations of increased intracranial pressure were 40 % with muscle weakness in 33.3 %and transient ischemic attacks in 26.6 %. Cranial nerve palsies, hemiplegia, ataxia, epileptic seizures and sphincteric dysfunctions were 20, 13.3, 13.3, 6.6, 6.6 % respectively.

▶ **Table 1** showed TCD values for MCA, ACA, PCA, VA and BAin both patients and control groups. The results showed that the mean blood flow velocities in all examined arteries were significantly decreased in all patients of NBD compared with the normal control group, reaching high significant value ($p < 0.0001$) especially of the VA. We also found a significant increase in PI in the PCA ($P < 0.045$), however, it was marginally increased in the all other arteries when compared with the control, but this did not reach significance ($p > 0.05$).

▶ **Table 1** Transcranial Doppler (TCD) parameters in neuro-Behcet's disease patients and controls.

TCD parameters	Patients (N = 15)	Controls (N = 15)	P value
MCA			
MV	43.93 ± 13.85	59.6 ± 15.1	0.006 *
PI	0.83 ± 0.32	0.68 ± 0.13	0.104
ACA			
MV	33.4 ± 11.93	49.33 ± 14.84	0.003 *
PI	0.89 ± 0.41	0.69 ± 0.16	0.095
PCA			
MV	36.4 ± 10.5	48.8 ± 11.5	0.005 *
PI	0.79 ± 0.24	0.62 ± 0.16	0.045 *
VA			
MV	25.9 ± 8.8	41.7 ± 8.9	0.0001 * *
PI	0.80 ± 0.37	0.62 ± 0.11	0.068
BA			
MV	28.5 ± 8.1	43.3 ± 12.9	0.001 * *
PI	0.85 ± 0.40	0.63 ± 0.13	0.055 *

MCA: middle cerebral artery ACA: anterior cerebral artery; PCA: posterior cerebral artery VA: vertebral artery; BA: basilar artery; MV: the mean velocity PI: the pulsatility index; Values are mean ± SD (Mann Wittney test); * Statistically significant value (P < 0.05); * * Statistically highly significant value (P < 0.001)

MRI was normal in 8 patients and abnormal in 7 patients.

MRI lesions described were parenchymal lesions in 7 patients (46.7 %), and vascular lesions in 2 patients (13.3 %). Vascular lesions were existed together with parenchymal lesions (mixed lesion).

Parenchymal lesions were located in white matter (40 %), thalamus (26.7 %), brain stem (26.7 %) and cerebellum (20 %) (▶ **Table 2**).

According to anatomical site, MRI lesions were classified to lesions in hemispherical lobes, insula, thalamus, basal ganglia, internal capsule, cerebellum and brain stem (▶ **Table 3**).

There was significant positive correlation between disease duration and MV of ACA, while it was significant negative correlation with PI of VA and with MV and PI of BA (▶ **Fig. 1–4**).

There was no correlation found between disease duration and MRI lesions.

▶ **Table 2** Localization of MRI lesions in 15 patients with neuro-Behcet's disease.

MRI lesions	Number of patients (N = 15)	Percentage %
Parenchymal lesions	**7**	**46.7 %**
White matter	6	40 %
Basal ganglia & Internal capsule	0	0
Thalamus	4	26.7 %
Brain stem	4	26.7 %
Cerebellum	3	20 %
Spinal cord	0	0
Vascular lesions	**2**	**13.3 %**

▶ **Table 3** Anatomical sites of MRI lesions.

Anatomical site	Number of patients (N = 15)	Percentage %
Hemispherical lobes	4	26.7 %
Frontal lobe	3	20 %
Parietal lobe	4	26.7 %
Temporal lobe	1	6.6 %
Occipital lobe	1	6.6 %
Insula	1	6.6 %
Thalamus	4	26.7 %
Basal ganglia	0	0
Internal capsule	0	0
Cerebellum	3	20 %
Brain stem	4	26.7 %

MV: is the mean velocity; PI is the pulsatility index; Values are mean ± SD (Mann Wittney test); * Statistically significant correlation (p level < 0.05); * * Statistically highly significant correlation (p level < 0.01)

Discussion

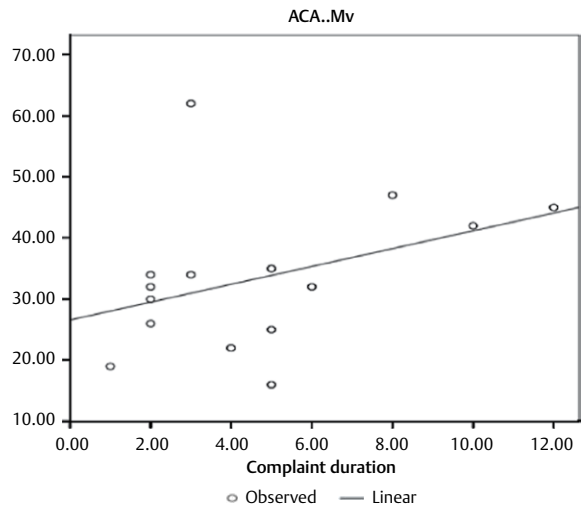
Behcet's disease is an inflammatory condition clinically characterized by recurrent oral aphthae, genital ulcers, skin lesions, and uveitis [12].

NBD is an inflammatory perivascular disease where acute meningoencephalitis is the most common neuropathologic findings. It consists mainly of infiltration of lymphocytes, eosinophils, macrophages, and neutrophils at the perivascular spaces and parenchyma. These infeltration lead to necrotizing and disseminated encephalitis of the diencephalon, cerebellum, brainstem and basal ganglia [13–15].

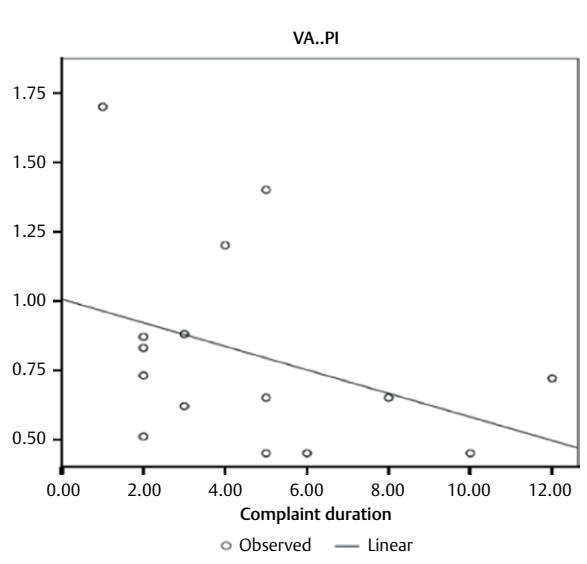
Concerning the neurological symptoms in our patients, headache was the most common neurological symptom. This coincides with the previous study of Mohammed et al. 2012 [16] in which headache was the commonest feature in patients with radiological evidences of cerebral vascular diseases.

On the other hand, Aykutlu et al. 2006 [17] and Borhani-Haghighi et al. 2008 [18] suggested that the headaches in NBD do not usually indicate any neurological involvement, but may be due to migraine or tension-type headache.

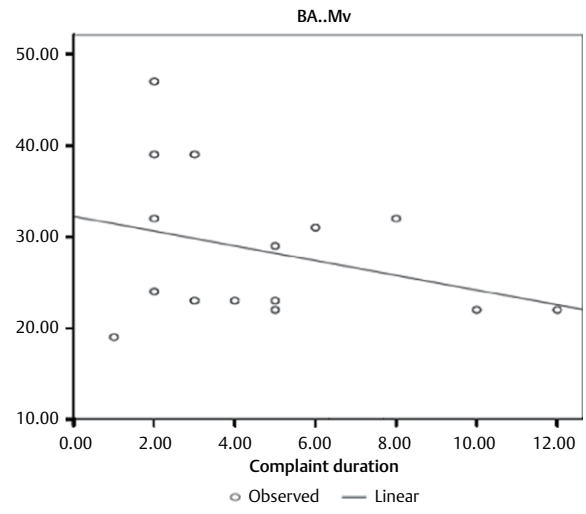
Transcranial Doppler ultrasonography allows insight into cerebrovascular function in many central nervous system disorders [19, 20]. It is a noninvasive, painless, safe, portable, lightweight, well tolerated, less costly diagnostic neuro-imaging technique, and robust to environmental/electrical artifact and has good temporal resolution. It requires a trained individual to be able to find the



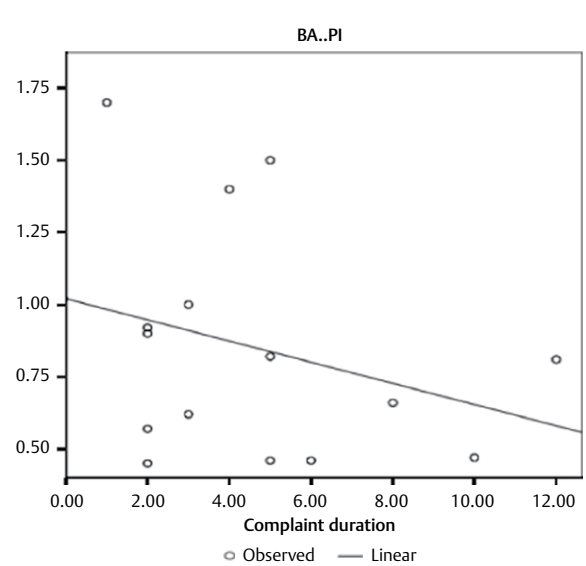
▶ **Fig. 1** Showed a positive significant correlation between mean velocity (MV) of anterior cerebral artery (ACA) and duration of illness (p = 0.008).



▶ **Fig. 2** Showed a negative significant correlation between pulsatility index (PI) of vertebral artery (VA) and duration of illness (p = 0.012).



▶ **Fig. 3** Showed a negative significant correlation between mean velocity (MV) of basilarartery (BA) and duration of illness (p = 0.03).



▶ **Fig. 4** Showed a negative significant correlation between pulsatility index (PI) of basilarartery (BA) and duration of illness (p = 0.05).

optimal signal [21, 22]. It does not measure actual blood flow, but flow velocity through the basal cranial arteries. Shigemori et al. 1992 [23] showed that changes in flow velocity in the MCA correlated well with changes in hemispherical cerebral blood flow measured by single-photon emission computed tomography (SPECT).

In the present study, TCD ultrasound abnormalities of the intracranial arteries were assessed in 15 patients with NBD by measuring their MV and PI [20, 24]. PI helps in diagnosing hyperdynamic flow states, vasospasm and increased cerebrovascular resistance [25].

TCD ultrasound demonstrated significant decline in the MV of all the examined cerebral arteries in all the 15 patients with NBD compared to the healthy controls ($P < 0.05$), with the high significance decrease in the MV of the VA ($P < 0.0001$). A decreased flow velocity can be due to low cereberal blood flow secondary to low cardiac output, to a larger diameter of the insonated vessel, to a high vascular bed resistance, or to combination of these factors [26]. Sharma et al. 2007 [27] reported that TCD enables the reliable evaluation of blood flow from the basal intracerebral vessels.

In our study, a significant increase in the PI was detected only in the PCA when compared with the controls ($P < 0.05$). This presum-

ably represents enhanced cerebrovascular bed resistance in the PCA due to cerebral vasculitis in NBD [25].

Similarly, Mohammed et al. 2012 [16], showed TCD abnormalities in all of the patients with NBD in the form of significant resistivity index and peak systolic velocity and were mainly reported in the vertebrobasilar tree and MCA.

However, Gad et al. 2007 [28] found significant increase in the PI of the MCA in only 5 (33.3 %) of the patients with NBD when compared with the controls ($P < 0.001$). Yilmaz and Akarsu 2006 [29], using color-coded duplex sonography in patients with BD, found ocular and cerebral haemodynamic changes of the MCA.

Neurologic lesions in BD are most frequently observed in the areas irrigated by the posterior system, as the neurologic involvement may originate from the vertebrobasilar system [30]. This could explain the highly significant decline in the MV of the VA in our patients.

Vertebral artery blood flow velocities are influenced by different factors, including systemic hypertension, diabetes mellitus, blood viscosity changes, smoking and immunosuppressive drugs [31]. Because our patients with these additional factors were excluded from the study, the high significant decline of the VA in our patients is thought to develop secondarily to vasculitic involvement associated with BD [32].

Taşolar et al. 2014 [33] suggested that identification of possible early changes in the VA on Doppler sonography might help in the diagnosis of NBD by a bedside noninvasive tool.

In the current study, 7 of the 15 (46.7 %) patients had MRI parenchymal lesions, of them 2 (13 %) patients had vascular lesions coexist with parenchymal lesions (mixed). The parenchymal lesions were multiple small foci of high intensity on T2/FLAIR weighted images. These lesions interest the periventricular and superficial cerebral white matter, thalamus and brainstem followed by the cerebellum with sparing of the basal ganglia, internal capsule and spinal cord. The 2 vascular lesions associated with parenchymal lesions detected in our series were dural sinus thrombosis in one patient and transverse sinus thrombosis in another.

These findings are inconsistent with results of some studies, although they are keeping with results of others. The ratios of parenchymal to non-parenchymal NBD were 162:38 [34], 49:9 [35] and 52:12 [9]. In the study of Farahangiz et al. 2012 [35], the parenchymal lesions were multiple small and medium-sized hyperintense in T2-weighted and FLAIR images with the most common sites were the superficial and periventricular white matter, midbrain and pons respectively with sparing of the red nucleus and cerebellum. Sparing of the basal ganglia and internal capsule were demonstrated by Kocer et al. 1999 [36] and lee et al. 2001 [37]. The brainstem and the white matter of hemisphere were the most commonly involved sites [9, 38].

Borhani-Haghighi et al. 2006 [1], found equal frequency of cerebral and brainstem lesions with spinal cord lesions and 5 (30 %) patients with vascular lesions. Of them, 4 patients had dural sinus thrombosis and cerebral artery occlusion in one patient.

Regarding the relation between TCD abnormalites and MRI lesions in our study, a significant reduction was demonstrated in the MV of MCA of patients with NBD. This suggests that the parietal lobes (the territory of the MCA) were frequently involved on MRI. Also, TCD showed decline in the MV of ACA, which supplies most of the parietal lobes and portions of frontal lobes may explain the majority of MRI parietal lesions followed by frontal lobes.

As the PCA supplies various deep structures including the thalamus, TCD showed haemodynamic abnormalities of PCA (decline in MV and increase of PI) were associated with the thalamus which was one of the most involved areas on MRI.

The vertebrobasilar system supplies blood to posterior part of the brain, cerebellum, brainstem and upper spinal cord. A high significant decline in the MV of VA ($P < 0.0001$) and a significant decline of BA ($P < 0.001$) can explain the majority of MRI lesions found in the brainstem than the cerebellum; and the high frequent symptom of dizziness (93 %) in this series.

So, TCD is more sensitive and of value in displaying evidence of NBD than MRI as TCD showed flow pattern abnormalities in 8 of 15 (53 %) of NBD without detectable lesions by MRI.

Our cohort was coincide with a TCD study [16] that showed TCD arterial flow abnormalities were detectable in nine cases (60 %) of 15 BD patients without clinical features of CNS involvement and without detectable lesions by MRI.

Inconsistent to our results, Gad et al. 2007 [28] found TCD arterial haemodynamic abnormalities in 5 of 15 (33 %) patients with NBD, while 12 of them (80 %) had brain lesions on MRI. The difference in the last study could be attributed to the highly operator dependency in performing TCD [25].

In conclusion, TCD should be routinely recommended as a sensitive non-invasive relatively inexpensive bed-side tool for the diagnosis of NBD.

Conflict of interest

Authors declare that there is no conflict of interest.

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