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ORIGINAL ARTICLE

What is the role of diffusion tensor imaging (DTI) in detecting subclinical pyramidal tract dysfunction in Behçet's and neuro-Behçet's cases?

Seyma Ciftci Aykac[1] · Figen Gökcay[1] · Cem Calli[2]

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Abstract

The aim of this study is to investigate the pyramidal tract integrity with DTI in Behçet's and neuro-Behçet's cases. We performed this technique in two subgroups of neuro-Behçet's patients (parenchymal and vascular), and Behçet's cases without neurological involvement and control group. Totally, 28 patients were investigated. The control group was composed of 14 healthy people. Cranial MR and DTI were performed in three patient groups and the control group. At DTI, circular regions of interest (ROI) were symmetrically drawn on axial slices on the left and right sides along the pyramidal tract pathway at two levels: middle one third of the cerebral peduncle and posterior limb of the internal capsule. Fractional anisotropy (FA) values for each ROI were obtained by averaging all voxels within the ROI. Calculated FA values on both sides (left and right) of the posterior limb of the internal capsule and cerebral peduncle are significantly lower in all three patient groups when compared to the control group. But there is no any difference of FA values in the selected brain regions of three patient groups. FA values on the posterior limb of the internal capsule and cerebral peduncle do not show a statistically significant difference in parenchymal neuro-Behçet's cases. Our study demonstrates that DTI can detect subclinical pyramidal tract dysfunction in neuro-Behçet's and Behçet's patients. Detection of subclinical nervous system involvement is crucial for morbidity in Behçet's disease. For this reason, studies based on DTI, which include a large number of patients and explore different brain regions, are needed to guide clinicians.

Keywords Neuro-Behçet's disease · DTI · Pyramidal tract

Introduction

Behçet's disease is a chronic, relapsing remitting, systemic vasculitic disorder which affects multiple organs. Typical clinical presentation of Behçet's disease is recurrent oral, genital ulcers and uveitis [1]. Central nervous system is affected primarily in neurological involvement and this form is called as neuro-Behçet's disease. In neuro-Behçet's disease, pathological findings are mainly seen in parenchymal and vascular structures in the central nervous system and parenchymal form constitutes 75–80% of neuro-Behçet's cases [1]. In the parenchymal form, clinical findings point out a pyramidal tract and brainstem dysfunction. In the vascular form, cerebral venous thromboses are commonly seen, but dissections, aneurysms are other vascular pathologies [2]. Parenchymal and vascular forms are usually observed separately, but in some studies, it is stated they have also seen together in the same case.

Diffusion tensor imaging (DTI) is a distinct imaging technique that gives information about microstructural organization, orientation and integrity of white matter tracts. It shows white matter tracts in the brain, which could not be demonstrated by other magnetic resonance imaging sequences. Nowadays, it is extensively used for detecting major brain areas which are affected in neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, and dementia.

In the study, we aimed to investigate the pyramidal tract integrity with DTI in Behçet's and neuro-Behçet's cases. We

✉ Seyma Ciftci Aykac
symciftci@hotmail.com

Figen Gökcay
gokcayf@gmail.com

Cem Calli
cemcalli@gmail.com

[1] Neurology Department, Ege University Faculty of Medicine, Izmir, Turkey

[2] Radiology Department, Ege University Faculty of Medicine, Izmir, Turkey

performed this technique in two groups of neural-Behçet's patients (parenchymal and vascular) and Behçet's cases without neurological involvement. We compare our findings in three groups and also with control group to try to find any difference which can point out motor dysfunction.

Material and method

Our study includes neuro-Behçet's cases composed of parenchymal or vascular subgroup and Behçet's cases without neurological involvement. All neuro-Behçet's cases are in the chronic stage. In the vascular group, sinus vein thrombosis is the main vascular pathology. Neuro-Behçet's cases who have spinal lesions, patients who are not diagnosed properly as neuro-Behçet's disease, neuro-Behçet's cases who are in acute attacks, and patients whom MRI (magnetic resonance imaging) contraindicated (who have metallic heart valve etc.) are excluded. Age, gender, duration of the disease, patient subgroups, number of neurological attacks, and clinical progression of the patients were determined from patient records. With patient group, neurological examination was performed and findings of pyramidal dysfunction (Paresis, spastisity, hyperreflexia, Hoffman-Babinski positivity) were defined as follows.

- EDSS-p 0: There is no deficit; neurological examination is normal.
- EDSS-p 1–2: There is a minor deficit, but not paresis, pyramidal tract findings in only neurological examination.
- EDSS-p $\geq$ 3: There is major deficit; pyramidal tract findings in neurological examination with paresis.

Cranial MRI and DTI were performed on three patient groups (parenchymal and vascular neuro-Behçet's patients, Behçet's patients without neurologic involvement) and also the control group. Imaging was performed with a 3 T MR machine (Magnetom Verio, Siemens). Firstly, the brain was scanned with conventional MR sequences as axial T2-weighted fast spin-echo (repetition time (TR)/echo time (TE), 2320/117) and sagittal T1-weighted MPR (multi planar reconstructed) (TR/TE, 1800/2.21). Then, DTI was performed. The properties of DTI sequences were single-shot spin echoplanar; voxel size $2 \times 2 \times 2$ mm; FOV (field of view) 100 mm; matrix 320×320; TR/TE, 9600/95 MSN; b, 0–1000 s/mm^2; and number of directions, 64.

DTI data were transferred to a workstation (Multi-Modality Work Place, Siemens Healthcare) for processing. Circular regions of interest (ROI) were symmetrically drawn on axial slices on the left and right sides along the pyramidal tract pathway at two levels: middle 1/3 of cerebral peduncle and posterior limb of the internal capsule. To include only the pyramidal tract region, the ROI size was set between 30 and 35 mm^2 boxes. FA values for each ROI were obtained by averaging all voxels within the ROI. Figure 1 is a sample of FA map which shows ROI.

Statistically, mean, standard deviation, median, the lowest and highest values, ratio, and frequency are used for descriptive analysis. Distribution of variables is controlled by Kolmogorv-Simirmov test. Quantitative data are analyzed with ANOVA (Tukey's test) and independent sample t test. Chi-square and Fisher's tests are performed for quantitative analysis. In repeated measurement, analysis, repeated measurement of variance

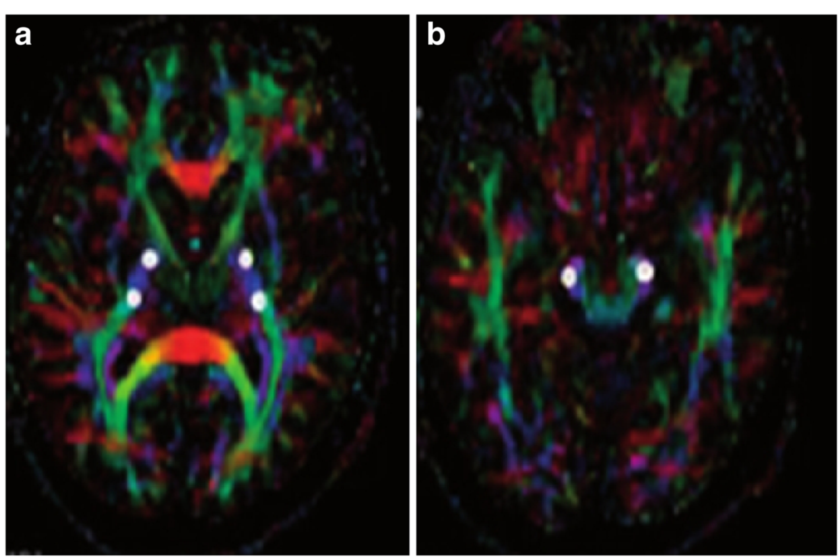

Fig. 1 Colored FA maps at the level of the internal capsule and cerebral penduncle. Colors indicate director of fiber tract (*red* transverse, *blue* craniocaudal, *green* anterior-posterior). White dots show ROI as posterior limb of the internal capsule on **a** and middle 1/3 of cerebral penduncle on **b**

analysis, and matched sample t test are used (all analysis are performed in the SPSS 22.0 program).

Results

The total number of patients in our study is 28. Nineteen of them are neuro-Behçet's cases (10 patients in the parenchymal, 9 patients in the vascular group), 9 of them are Behçet's patients without neurological involvement, and 14 of them are healthy people. In parenchymal neuro-Behçet's group, 4 patients are women and 6 patients are men. The vascular group is composed of 5 women and 4 men. Six women and 3 men are in Behçet's patients without neurologic involvement group. In the control group, there are 14 women. Mean age is 48.50 ± 11.58 years (min 33 years old, max 64 years old) in parenchymal neuro-Behçet's group, 40.56 ± 9.19 years (min 23 years old, max 54 years old) in vascular neuro-Behçet's group and 42.11 ± 6.35 years (min 35 years old, max 51 years old) in Behçet's patients without neurological involvement. The control group's mean age is 42.93 ± 5.28 years (min 35 years old, max 55 years old). Demographic data are summarized in Table 1.

Mean duration of Behçet's disease (BD) and mean duration of neurological involvement and the number of attacks in neuro-Behçet's subgroups are shown in Table 2.

In the vascular group, only one attack is seen as sinus vein thrombosis. On the other hand, in the parenchymal group, 5 patients have one attack, 2 patients have 2 attacks, and 1 patient has three attacks. Apart from clinical attack, in the parenchymal group, 1 patient has progressive clinical worsening. Duration of neuro-Behçet's disease and the number of clinical attacks are significantly higher in the parenchymal group than in the vascular group.

When the EDSS-p score was examined, it is higher in the parenchymal group than vascular and in the Behçet's without neurological involvement group ($p < 0.05$). The score does not show any significant difference between the vascular neuro-Behçet's and Behçet's without neurological involvement group ($p > 0.05$) (Table 3).

In the parenchymal group, EDSS-p score of 6 cases (EDSS-p score 1–2) indicates a minor motor deficit. However, 2 cases have a major motor deficit (EDSS-p ≥ 3). Duration of neuro-Behçet's disease is 25 years, and progressive paraparesis is the main clinical finding in one of them. The other patients have two clinical attacks. EDSS-p score of one patient in the vascular group is defined as 1 and accepted as minor defect. This patient has only bilateral Babinski positivity on neurological examination. Neurological examination is normal in the Behçet's disease without neurological involvement group and EDSS-p score is 0 in this group.

On routine T2 MRI sequence performed before DTI, 3 patients in the parenchymal group have brain lesions. These are pontine and subcortical hyperintense lesions in 2 patients and diffuse brainstem atrophy in 1 patient. There is no any lesion on MRI in the other two groups.

Calculated FA values on both sides (left and right) of the posterior limb of the internal capsule and cerebral peduncle are significantly lower in all three patient groups when compared to control group. When FA values of the same brain areas are compared between the three patient groups, no any difference has been detected (Table 4).

FA values on the posterior limb of the internal capsule and cerebral peduncle do not show a statistically significant difference in the parenchymal neuro-Behçet's cases (FA value average in internal capsule is 0.59 on the right side and 0.60 on the left side. In the cerebral peduncle, FA value average is 0.57 on the right side and 0.58 on the left side).

If we re-examine cases one by one, the patient in the parenchymal group who has diffuse brainstem atrophy has lower FA values on both sides of the defined brain areas, comparing to mean FA values in this group (right internal capsule FA 0.53, mean FA 0.57; left internal capsule FA 0.443, mean FA 0.60; right cerebral peduncle FA 0.44, mean FA 0.59; left cerebral peduncle FA 0.49, mean FA 0.56). Another patient with major motor deficits in the parenchymal group has also lower FA value on the right cerebral peduncle than the mean

Table 1 Demographic data

	Woman		Man			Age	
	N (number)	% (percentile)	*N*	%	Total *N*	Mean ± s.d	Median (min–max)
Parenchymal neuro-Behçet's patients	4	40	6	60	10	48.50 ± 11.58	52 (33–64)
Vascular neuro-Behçet's patients	5	55.6	4	44.4	9	40.56 ± 9.19	43 (23–54)
Behçet's patients without neurological involvement	6	66.7	3	33.3	9	42.11 ± 6.35	40 (35–51)
Total number of patients					28		
Control group	14	100	0	0	14	42.93 ± 5.28	42 (35–55)

s.d, standard deviation, *min–max* minimum–maximum

Table 2 Duration of Behçet's disease and neuro-Behçet's disease, and number of attacks

		Mean ± standard deviation (s.d)	Median	Min–max	*p*
Duration of BD	Parenchymal	14.20 ± 6.86	13	5–30	
	Vascular	8.02 ± 6.05	7	0–20	0.023
	Behçet's disease	6.44 ± 5.08*	4	1–17	
Duration of Neuro-BD	Parenchymal	10.50 ± 6.45	10	2–25	
	Vascular	4.83 ± 3.18	4	1–11	0.029
Number of attacks	Parenchymal	1.67 ± 0.87	1	1–3	
	Vascular	1.00 ± 0.00	1	1–1	0.029

ANOVA (Tukey's test), Independent sample t test/. *Difference from the parenchymal group $p < 0.05$

FA value of this group (right internal capsule FA 0.41, mean FA 0.59).

Discussion

In this study, we want to evaluate the pyramidal tract integrity in neuro-Behçet's patients because motor dysfunction could be a major morbidity. Clinicians usually suspect neurological involvement in Behçet's disease if they detect any clinical findings or pathology on routine MRI sequences. For this reason, we also search pyramidal tract integrity in the patients with the Behçet disease without neurologic involvement if we see any pathological changes on DTI.

DTI is a distinct imaging technique based on diffusion of water molecules which depends on the orientation of tracts, myelin density, integrity of the membrane, and fiber integrity of tracts. This technique demonstrates intracerebral tracts in vivo [3]. FA is main measurable value in DTI. It is an index for the amount of diffusion asymmetry of water molecule within a voxel. Its value varies between 0 and 1. For perfect isotropic diffusion, FA value is 0, but with progressive diffusion anisotropy, the FA value is 1. If we think about brain structure, FA value is detected high where white matter tracts are dense but its value is low on less organized white matter tract regions (like gray matter) [4]. Behçet's disease is a systemic vasculitic process which causes pathologic changes in central nervous system venules. Due to the anatomical location of intra-axial venous structures, the most affected brain areas are the upper brainstem, mesencephalo-diencephalic junction [5, 6]. We defined ROI as middle one third of the cerebral peduncle and posterior limb of the internal capsule because these brain regions could be more affected areas and pyramidal tract fibers are dense in these regions so they could be defined easily on DTI. In the study, our patients are in the chronic stage of the disease because we thought that acute attack can cause tissue edema on affected brain regions and this can lead to misjudgment.

Table 3 EDSS-p score of patients

	EDSS-p 0		EDSS-p 1–2		EDSS-p ≥ 3		
	n	%	*n*	%	*p*	*n*	%
Parenchymal	2	20%	6	60%		2	20
Vascular	8	88.9%*	1	11.1%	0.000	0	0
Behçet's	9	100%*	0	0.0%		0	0

Chi-square test. *Difference from the parenchymal group $p < 0.05$

There are different studies in the literature related to pyramidal tract mapping by DTI in various disease processes such as multiple sclerosis, ischemic infarcts, and tumoral lesions. Our study is the first DTI-based study performed in patients with Behçet's disease. We found that, when compared to the control group, FA values on both sides (left and right) of the posterior limb of the internal capsule and cerebral peduncle are significantly lower in two groups of neural-Behçet's cases and patients with the Behçet disease without neurological involvement. This is the most important result that shows subclinical pyramidal tract involvement in neurologically asymptomatic Behçet's patients. Furthermore, our study also supports that, apart from major cerebral veins, tiny parenchymal veins could be affected in the vascular subgroup and this cause subclinical parenchymal involvement in a vascular subgroup of neuro-Behçet's patients. Subclinical cerebral parenchymal involvement in Behçet's disease is also supported by other studies in the literature. These studies are mostly performed by diffusion-weighted imaging, perfusion MR and MR spectroscopy. Basel et al. conducted a study which was performed with diffusion MRI in the chronic stage of patients with Behçet's disease. They stated that patients with or without neurological complaints had diffusion increment on bilateral frontal, temporal, and occipital white matter, although conventional MRI did not detect any pathologies [7]. The same researchers conducted another study with MR spectroscopy in

Table 4 Left and right cerebral FA values of patients and control group

		Mean ± standard deviation (s.d)	Median (min-max)	*p*
Left internal capsule FA 1	Parenchymal	0.60 ± 0.08*	0.59 (0.44–0.75)	
	Vascular	0.63 ± 0.06*	0.62 (0.53–0.72)	0.000
	Behçet's disease	0.56 ± 0.05*	0.53 (0.50–0.63)	
	Control	0.77 ± 0.04	0.76 (0.7 1-0.83)	
Left cerebral peduncle FA2	Parenchymal	0.58 ± 0.08*	0.56 (0.49–0.72)	
	Vascular	0.65 ± 0.06*	0.63 (0.53–0.73)	0.000
	Behçet's disease	0.60 ± 0.07*	0.60 (0.52–0.72)	
	Control	0.85 ± 0.06	0.85 (0.77–0.97)	
Right internal capsule FA 1	Parenchymal	0.59 ± 0.06*	0.57 (0.54–0.72)	
	Vascular	0.59 ± 0.06*	0.58 (0.50–0.69)	0.000
	Behçet's disease	0.54 ± 0.04*	0.52 (0.50–0.61)	
	Control	0.76 ± 0.04	0.76 (0.68–0.83)	
Right cerebral peduncle FA 2	Parenchymal	0.57 ± 0.09*	0.59 (0.41–0.67)	
	Vascular	0.65 ± 0.08*	0.67 (0.41–0.71)	0.000
	Behçet's disease	0.58 ± 0.07*	0.55 (0.50–0.70)	
	Control	0.80 ± 0.06	0.78 (0.74–0.95)	

ANOVA (Tukey's test). *Difference from the control group $p < 0.05$

chronic Behçet's patients without neurological symptoms. They found increased choline/creatine ratio in periventricular white matter. They also implied that this finding could result from demyelination secondary to microangiopathy [8]. Consequently, the subclinical cerebral parenchymal involvement can be seen during the Behçet disease as it causes systemic vasculitis of venules.

Due to mainly parenchymal involvement, it was expected that FA values in selected brain regions should be lower in the parenchymal neuro-Behçet's group than in the vascular neuro-Behçet's and Behçet's disease without neurological involvement. In contrast to this idea, we did not find any significant difference between FA values of patients. We thought that the relation between EDSS-p score and FA values has an important role in this finding because an EDSS- p score showed mostly minor deficit in the neuro-Behçet's patient group. Only 2 patients in the parenchymal neuro-Behçet's subgroup had a major motor defect, and these patients had the lowest FA values. Therefore, the high number of patients with minor deficit in the parenchymal neuro-Behçet's group did not make any difference between FA values of neuro-Behçet's and Behçet's disease groups. In addition to that, we did not find a specific affected brain region in terms of pyramidal tract dysfunction in the selected brain areas because FA values on the posterior limb of the internal capsule and cerebral peduncle did not show a statistically significant difference in parenchymal neuro-Behçet's cases.

As a result, our study demonstrates that DTI can detect subclinical corticospinal tract dysfunction in Behçet's patients. Moreover, pathologic process of Behçet's disease mainly affects vascular structures but also parenchymal subclinical involvement can be seen in vascular neuro-Behçet's disease subtype. To the best of our knowledge, this is the first study that used DTI technique in pyramidal tract dysfunctions in Behçet's patients. The number of patients in our study was not enough to find a statistically significant difference in terms of pyramidal tract dysfunction between patient groups. Behçet's disease is a chronic process, and its effect on the central nervous system can be destructive, so detection of subclinical nervous system involvement is crucial for morbidity. For this reason, studies based on DTI, which include a large number of patients and explore different brain regions, are needed to guide clinicians.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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