Behçet's disease patients with multiple sclerosis-like features: discriminative value of Barkhof criteria

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ABSTRACT

Objective. *Behçet's disease (BD) is a systemic auto-inflammatory disorder of unknown cause, which may affect the central nervous system in around 5% of the patients [neuro-BD (NBD)], usually causing large lesions encompassing brainstem, diencephalon and basal ganglia regions. Occasionally NBD patients present with white matter lesions necessitating differential diagnosis from multiple sclerosis (MS). In this study, the efficacy of Barkhof criteria was tested in diagnostic differentiation of NBD and MS.*

Methods. *Charts and MRIs of 84 NBD patients were retrospectively evaluated. Clinical and radiological features of NBD patients fulfilling (Barkhof+) and not fulfilling Barkhof criteria (Barkhof-) were compared.*

Results. *While the Barkhof- patients (n=73) mostly displayed typical large lesions covering brainstem, diencephalon and basal ganglia regions and neurological findings consistent with brainstem involvement, all Barkhof+ (n=11) patients demonstrated MS-like white matter lesions, fulfilled McDonald's criteria and showed reduced frequency of brainstem symptoms and increased frequency of hemiparesis, hemihypesthesia and spinal cord symptoms. Moreover, the Barkhof+ group had more female patients, increased number of attacks, higher rate of oligoclonal band positivity and less patients with cerebrospinal fluid pleocytosis.*

Conclusion. *A subgroup of BD patients with neurological complaints displays MS-like lesions, fulfills the clinical and radiological criteria of MS and presents with clinical and laboratory features resembling those of MS rather than NBD. These results suggest that Barkhof+ patients are either an overlapping group between NBD and MS, or they represent MS patients with concomitant systemic findings of BD, rather than NBD. Barkhof criteria appear to be effective in discriminating these patients.*

Introduction

Behçet's disease (BD) is a systemic inflammatory disorder of unknown cause. It usually causes the tri-symptom complex including recurrent oral aphtae, genital ulcerations, and uveitis (1, 2). BD is prevalent in the Mediterranean basin, Middle East and Far East and affects young adult males more commonly than females. Among other tissues such as the vascular endothelium, gastrointestinal tract and joints, BD may affect the central nervous system (CNS) in around 5% of the patients [neuro-BD (NBD)] (3). Around 80% of the cases with NBD present with a typical brainstem-diencephalon-basal ganglia involvement (parenchymal NBD), while less commonly BD may cause dural sinus thrombosis leading to symptoms of raised intracranial pressure. Most patients with parenchymal NBD present with cerebrospinal fluid (CSF) pleocytosis, positive pathergy test, and no CSF oligoclonal bands (4-8).

In the differential diagnosis of NBD many disorders should be considered including, CNS infections, other vasculitides, lymphoma and sarcoidosis. Multiple sclerosis (MS) should also be considered since both disorders affect young adults and may present similarly (9). Typical parenchymal NBD is not difficult to differentiate from MS due to distinctive brainstem-diencephalic involvement (10, 11). Also, in contrast with NBD, MS is characterised with female predominance, CSF oligoclonal band positivity and usually normal CSF cell counts (12). However, BD patients might occasionally present with periventricular and subcortical white matter lesions or transverse myelitis

prompting differential diagnosis from MS (13-16). Whether MS-like white matter lesions represent an unusual and distinct subtype of parenchymal NBD or simply indicate coincidental presence of MS and BD is a matter of controversy. Since MS and NBD are treated differently, it is imperative to discriminate an MS patient from an actual NBD patient presenting with MS-like white matter lesions.

Barkhof criteria has long been used to accurately diagnose MS (17). In an attempt to test the efficacy of Barkhof criteria in discrimination of NBD patients from MS patients, we applied these criteria to a cohort of BD patients with white matter lesions and compared the clinical and radiological characteristics of BD patients that fulfill and do not fulfill Barkhof criteria.

Patients and methods

Between 1990 and 2014, the files of the NBD outpatient clinic were retrospectively evaluated. All the cases fulfilling the criteria of International Study Group for BD (18) and having at least one available cranial MRI scan in our files were included in the study. BD presenting with pathological neurological examination findings (*e.g.* hemiparesis, vision loss, ataxia) were defined as NBD. BD patients presenting with primary headache disorders without any abnormal neurological examination findings and thus not having NBD were excluded. The requirement for informed consent was waived because of the nature of this retrospective chart review study. Also, due to the retrospective nature of the study, MRIs had been performed on various scanners with a minimum field strength of 1.5 Tesla. Slice thickness of scans ranged from 3 mm to 5 mm. All patients received gadolinium. Brain and spinal MRI scans were performed on sagittal, axial and coronal planes. Enhancing lesions were recorded from post-contrast T1-weighted sequences. Based on location and appearance, brain lesions were classified as typical NBD lesions, MS-like white matter lesions and non-specific white matter lesions. Typical NBD lesions were defined as large extensive lesions covering one or more of brainstem, diencephalon and basal ganglia regions, as shown previously (19-21). White matter lesions with a diameter of ≥5 mm, an ovoid shape and perpendicular to the corpus callosum and ventricles were described as MS-like lesions. Lesions that did not fulfill these criteria were accepted as non-specific lesions (Fig. 1). All MRIs were evaluated masked to the clinical status of the patients. Barkhof criteria for the MRI diagnosis of MS (17) were applied to the scans. Clinical, demographic and laboratory features during the last MRI examination were recorded. Increased CSF cell count was accepted as presence of more than 5 cells/mm^3 in CSF. The isoelectric focusing of CSF produce one of five internationally standardised distinct patterns (22). Pattern 1 indicates that CSF and serum do not contain oligoclonal bands. Pattern 2 shows the presence of oligoclonal bands only in CSF, which indicates the production of intrathecal IgG. Identical bands in serum and CSF with additional bands in CSF, known as pattern 3, is interpreted as the passage of oligoclonal bands into sera from CSF, also compatible with intrathecal IgG production. Mirror pattern, named as pattern 4, represents the results of identical bands found in serum and CSF indicating especially systemic immune activation. Pattern 5, in which monoclonal bands are seen, is characterised with systemic paraproteinemia. Since pattern 2 and 3 CSF oligoclonal bands are typical for MS, these patterns were accepted as positive whereas patterns 1, 4 and 5 were accepted as negative.

Clinical, demographic, laboratory and MRI characteristics of the patients satisfying Barkhof criteria (Barkhof+) were compared with those that do not fulfill Barkhof criteria (Barkhof-). Pathergy test, HLA-B51 genotyping and CSF analysis had only been done in 69, 37 and 63 patients, respectively and therefore could not be compared among all patients.

For statistical analysis, age, disease duration and number of neurological episodes were compared with Student's *t*-test. Gender, incidences of BD symptoms, positive pathergy test, HLA-B51 genotype positivity, neurological syndromes, CSF findings and MRI lesion types were compared with Fisher's exact test. A p-value <0.05 was considered as statistically significant.

Results

Clinical and MRI characteristics of the patients

There were a total of 164 cases fulfilling the criteria of International Study Group for BD with at least one cranial MRI scan. There was more than one MRI evaluation in 72 patients' files and the last MRI was taken into consideration in patients with multiple neuroimaging studies. Only 24 of the patients also had spinal MRI scans. Among 164 cases, 63 (38.4%) had typical NBD lesions, 43 (26.2%) had white matter lesions, 21 (12.8%) had dural sinus thrombosis, 37 (22.6%) had normal cranial MRI examination and 22 (13.4%) had normal neurological examination and had been diagnosed as primary headache disorder (15 migraine, 7 tension-type headache). Since the major goal of this study was to investigate the differences and test the diagnostic significance of Barkhof criteria between NBD and MS, the patients with dural sinus thrombosis, with normal MRIs and with no abnormal neurological examination findings were excluded and 84 patients were included in the study.

The average age of the included patients (55 men, 29 women) was 34.8±9.9 years (mean±standard deviation). They had an average disease duration of 5.9±4.0 years and had undergone an average of 2.3±1.3 attacks during their follow-up. Pathergy test was positive in 52 of 69 (75.4%) tested patients, and HLA-B51 genotype was positive in 15 of 37 (40.5%) tested patients. Neurological examination had revealed brainstem findings, hemisyndrome (hemiparesis and/or hemihypesthesia without brainstem-cerebellar findings), spinal cord syndromes (paraparesis or quadriparesis, sensory deficit with a dermatomal level and sphincter disturbance) or optic neuritis during the MRI examination in 71 (84.5%), 13 (15.5%), 8 (9.5%) and 2 (2.4%) patients, respectively. CSF examination had been performed in 63 patients and had revealed increased cell count (more than 5 lym-

phocytes/mm^3) in 34 (53.9%) and oligoclonal band positivity in 14 (22.2%) patients.

Comparison of Barkhof+ and Barkhof- patients

MRI findings of 11 out of 84 NBD patients fulfilled the Barkhof criteria. Notably, none of the Barkhof+ patients displayed typical NBD lesions and all had periventricular and/or subcortical MS-like MRI lesions. By contrast, Barkhof- patients (n=73) predominantly displayed typical neuro-BD lesions (63/73, 86.3%) and 10/73 (13.7%) patients showed white matter lesions (p<0.001 for both lesion types). MS-like lesions were present only in 5 of 73 (6.85%) Barkhof- patients (p<0.001) and 5 (6.85%) patients had non-specific white matter lesions. Eight of 10 Barkhof- patients with non-NBD lesions had brainstem (n=4) or spinal cord (n=4) symptoms and 2 patients had optic neuritis. None of the patients with brainstem symptoms had MRI lesions in brainstem or diencephalon and only one patient with spinal symptoms had cervical and dorsal spinal cord lesions, suggesting that most of these patients' findings were sequelae of previous attacks. Two optic neuritis patients had only non-specific white matter lesions in their MRIs. When serial MRIs were examined, it was found out that in an average follow-up period of 7.6±2.3 years (4–12 years), all Barkhof+ patients had fulfilled revised McDonald's criteria for MS (by developing objective evidence of dissemination in time and space of lesions) and developed multiple MS-like lesions with or without contrast enhancement (23), while none of the patients with MS-like lesions in Barkhof- group had fulfilled McDonald's criteria. All Barkhof+ patients and Barkhof- patients had abnormal neurological examination findings. Barkhof+ patients were inclined to display higher incidences of spinal cord (p=0.066) and hemisyndrome symptoms (p=0.062) and they had a significantly lower incidence of brainstem symptoms (p<0.001) (Table I).

There were no statistical differences by means of age, duration of BD, incidence of major BD symptoms and positive pathergy reaction between Barkhof+ and Barkhof- patients. Barkhof- patients had significantly higher HLA-B51 genotype positivity than Barkhof+ patients (p=0.012). The Barkhof+ group had significantly higher female to male ratio (p=0.001), higher number of neurological episodes (p=0.011), more patients with CSF oligoclonal bands (p<0.001) and significantly less patients with increased CSF lymphocyte counts (p=0.001) (Table I).

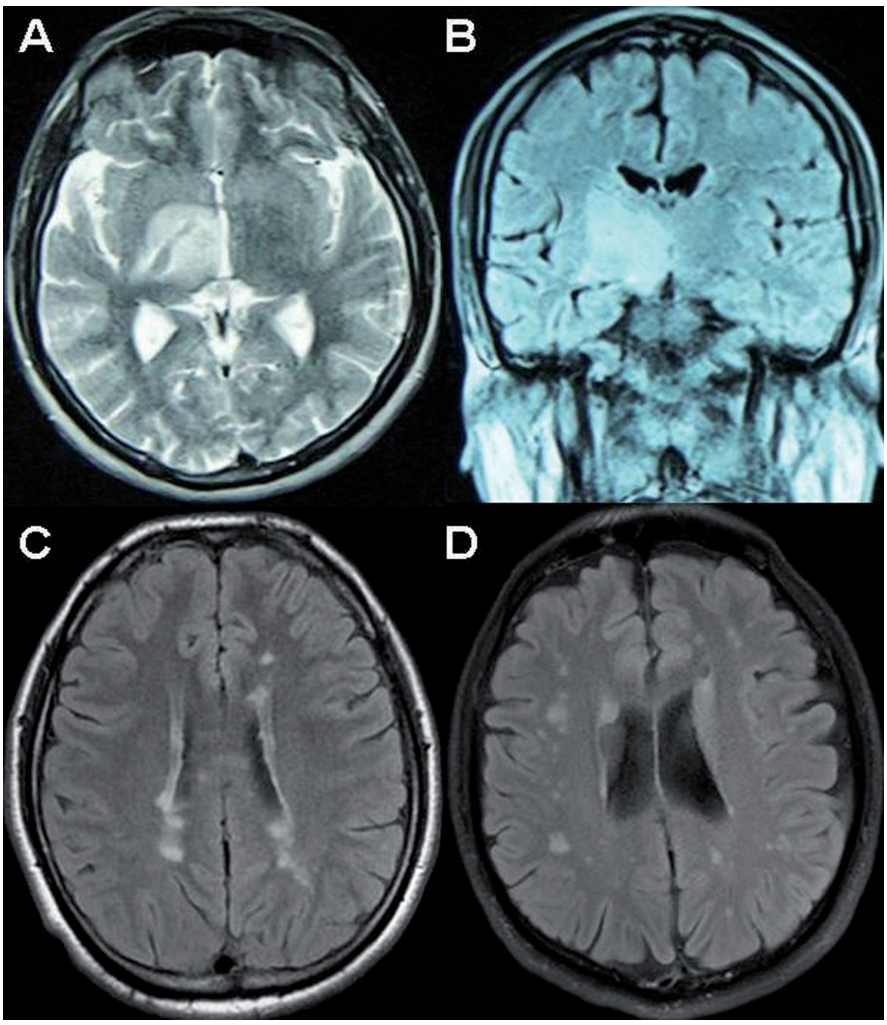

Fig. 1. MRI sections of BD patients with abnormal neurological examination findings showing a typical parenchymal neuro-Behçet's disease lesion extending from diencephalon to basal ganglia (**A**, **B**), MS-like lesions (**C**) and non-specific lesions in the white matter (**D**).

Since this is a retrospective analysis, a systemic evaluation of treatment effects are beyond the scope of this manuscript. As an observational note, all patients with abnormal neurological examination findings received steroids at the acute setting and azathioprine as long term treatment. However due to incomplete response to azathioprine (more than one attack/year) and since the patients also fulfilled McDonald's criteria, interferon-beta (7 cases) or glatiramer acetate (1 case) was added to azathioprine treatment in 8 of 11 Barkhof+ patients. The patients responded well to these treatments, there were no further attacks in 6 patients and attacks were reduced in 2 patients. On the other hand in the Barkhof- group 66 of the patients responded well to azathioprine treatment (without any further attacks) and only 7 patients required additional immunosuppressive treatment due to further attacks.

Discussion

Cerebral white matter lesions have always attracted attention in NBD patients (10, 13, 19). Such cases are more commonly reported from European or

Table I. Clinical and demographic features of Behçet's disease (BD) patients satisfying (Barkhof+) and not satisfying (Barkhof-) Barkhof criteria.

	Barkhof+ (n=11)	Barkhof- (n=73)	*p*-value for Barkhof+ *vs.* -
Age (±SD), range	38.8±11.3, (26-65)	34.2±9.7, (17-60)	0.176
Gender (M/F)	2/9	53/20	0.001
Disease duration (years±SD), range	4.9±3.7 (1-13)	6.1±5.5 (0-22)	0.770
Number of attacks (±SD), range	3.3±1.4 (1-5)	2.1±1.2 (1-7)	0.011
BD symptoms			
Oral aphthous ulcers	11/11 (100%)	73/73 (100%)	NA
Genital ulcers	10/11 (90.9%)	62/73 (84.9%)	0.509
Ocular inflammation*	6/11 (54.5%)	54/73 (73.9%)	0.165
Skin lesions**	8/11 (72.7%)	34/73 (46.6%)	0.097
Positive pathergy reaction	7/11 (63.6%)	45/58 (77.6%)	0.264
Positive HLA-B51 genotype	1/11 (9.1%)	14/26 (53.8%)	0.012
Neurological examination findings			
Brainstem	4/11 (36.3%)	67/73 (91.8%)	<0.001
Hemisyndrome***	4/11 (36.3%)	9/73 (12.3%)	0.062
Spinal	3/11 (27.3%)	5/73 (6.8%)	0.066
Optic neuritis	0/11 (0%)	2/73 (2.7%)	0.754
Cerebrospinal fluid (CSF) findings			
Increased cell count†	0/8 (0%)	34/55 (61.8%)	0.001
Oligoclonal band positivity	7/8 (87.5%)	7/55 (12.7%)	<0.001
Lesion type in cranial MRI			
Typical neuro-BD lesions††	0/11 (0%)	63/73 (86.3%)	<0.001
White matter lesions	11/11 (100%)	10/73 (13.7%)	<0.001
MS-like lesions†††	11/11 (100%)	5/73 (6.8%)	<0.001

SD: standard deviation; M: male; F: female; NA: not applicable.
*Ocular inflammatory diseases associated with BD (iritis, uveitis, retinal vasculitis), **Inflammatory skin lesions suggestive of BD such as folliculitis and erythema nodosum, ***Include patients with hemiparesis and/or hemihypoesthesia without brainstem and/or cerebellar findings, †More than 5 lymphocytes/mm^3, ††Large extensive lesions covering one or more of brainstem, diencephalon and basal ganglia regions, †††Lesions ≥5 mm with an ovoid shape and perpendicular to the corpus callosum and ventricles. Note that pathergy test, HLA-B51 genotype and CSF analysis were done in 69, 37 and 63 patients, respectively and some patients displayed more than one clinical syndrome (*e.g.* brainstem and spinal).

North American NBD series (20, 21). In fact, female cases and cases with predominantly white matter lesions comprise the majority of some Western NBD series (21). In a previous study where we had examined one single case with MS-like features, we had concluded that coincidence of both disorders is quite unlikely (24). However, it is not definitely known if such patients represent a form of parenchymal NBD, an overlapping syndrome between NBD and MS, or concomitant MS. A definite answer to this question requires histopathological evaluation, which is usually very difficult to obtain. Even post-mortem analyses would pose some difficulties since death usually occurs many years after the active disease has started, during which time pathological features are expected to be transformed.

Our study has shown that using Barkhof criteria, BD patients with neurological findings are clearly divided in two distinct groups. Although Barkhof+ and Barkhof- patients show identical BD symptoms, Barkhof+ patients fulfill McDonald's criteria, tend to be of the female gender, develop more attacks, have normal CSF cell counts and display CSF oligoclonal bands with the same frequency as MS patients (80-90%) (22). Also, in contrast with typical NBD patients, Barkhof+ patients are less likely to develop brainstem symptoms and usually present with hemiparesis, hemihypesthesia or spinal cord symptoms. All of these characteristics are reminiscent of MS rather than NBD suggesting that BD patients without typical NBD lesions and with lesions satisfying the Barkhof criteria are probably MS patients with coincidental concomitant BD.

One of the requirements for MS diagnosis is that there should not be any other disease that could explain the symptoms (23). This, therefore, should theoretically exclude the possibility of co-morbidity of BD and MS. However, the clinical characteristics of some NBD patients resemble MS, to a certain degree, suggesting that these patients might represent some overlap cases, with features more like MS. For this reason, we had added MS treatments to azathioprine in those cases when response was not optimal. Since this study was not intended to evaluate the treatment responses of NBD patients, we have not methodically compared the clinical courses of patients under different treatments. However, we have got the impression that our MS-like BD patients under azathioprine and interferon beta or glatiramer acetate treatment tended to have a better course than those under only azathioprine treatment supporting the view that Barkhof+ BD patients are not genuinely NBD patients.

In the Barkhof- group, there were 5 patients who had MS-like MRI lesions but did not satisfy McDonald's criteria. These patients probably represent actual NBD patients with coincidental clinically silent MS lesions. In line with this suggestion, none of these 6 patients displayed clinical findings suggestive of periventricular white matter involvement and presented with brainstem or spinal cord symptoms which were probably sequelae of previous NBD episodes. Nevertheless, these patients must probably be followed closely for development of MS and treated like typical NBD patients until they satisfy Barkhof's and McDonald's criteria.

Although Barkhof+ patients' clinical features resemble those of MS, the gender ratio was somewhat different in this group than what would be expected in MS. In usual MS series there is a female to male ratio of around 2:1 (22, 23). However in our group of "MS-like" BD patients, the ratio was around 4:1 more similar to antibody-mediated autoimmune disorders (25, 26). Also, HLA-B51 genotype positivity in the Barkhof+ group was far less than expected in a typical BD cohort, although these patients did not differ from typical BD patients by means of BD symptoms and signs. BD patients with a certain small ubiquitin-like

modifier 4 (SUMO4) gene variant have been shown to be consistently lacking the HLA-B51 genotype (27). Likewise, Barkhof+ BD patients might represent a peculiar subgroup with specific genetic features rendering susceptibility to the coexistence of MS and BD. However, this needs to be further elucidated, since we did not check this in our study.

In conclusion, a subgroup of BD patients with neurological complaints show white matter lesions resembling MS and satisfy Barkhof and McDonald's criteria. Although the diagnostic criteria for MS require that all other possible diagnoses should be ruled out, patients with BD and MS-like white matter lesions tend to behave like MS, rather than NBD. Therefore, BD patients presenting with neurological findings and MS-like white matter lesions that satisfy Barkhof criteria might conceivably be treated as an MS patient, especially if not responding to conventional BD treatments. This view should be supported with prospective trials comparing patient groups receiving azathioprine only and azathioprine in combination with a disease modifying drug.

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