

Neuro-Behcet's disease – case report and review

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ABSTRACT

Introduction: Behcet's disease (BD) is a multisystem autoimmune relapsing vasculitis with almost unknown etiology, which involves both large and small vessels. The involvement of the central nervous system (CNS) is rare, divided into two main sub-types: parenchymal and non-parenchymal. The peripheral nervous system is generally preserved or involved in very rare cases.

Case report: We present a rare case of neuro-Behcet's Disease (NBD) in a young 25-year-old female. The patient presented to our clinic with sudden onset complaints of general weakness, quadriparesis more prevalent for the right limbs, slurred speech, and swallowing disorders. Initially, a clinical diagnosis of cerebral infarction was made, but later the condition was defined as parenchymal Neuro-Behcet disease and the patient underwent corticosteroid and immunosuppressive treatment.

Discussion: NBD remains a difficult diagnosis to establish as other diseases may have a similar clinical presentation. The diagnosis is based on the clinical presentation and the typical lesions in brain magnetic resonance imaging (MRI). The development and disappearance of lesions at MRI in relation with disease-specific treatment may correlate with the course of clinical neurologic deficits.

Conclusions: Differential diagnosis of NBD should be considered in cerebrovascular disease, brain tumors, and demyelinating diseases.

Keywords: Neuro-Behcet's disease; Behcet's Disease; Cerebral Infarction; Stroke; Magnetic resonance; Neuroimaging; Imaging; Differential diagnosis.

INTRODUCTION

Behcet's disease (BD) is a disease with autoimmune etiopathogenesis characterized by recurrent genital and oral ulceration and uveitis¹. The neurological involvement called neuro-Behcet's disease (NBD) is rare and remains a difficult diagnosis to establish as other diseases and conditions may have similar presentation². It is crucial to early diagnose NBD and treat it properly because it is one of the main causes of long-term disability and mortality in BD³.

We present a case report of a female diagnosed with NBD and a review on clinical presentation, classification, and neuroimaging pattern of NBD.

CASE REPORT

We describe a case of a 25-year-old female hospitalized in November 2019 in the Second Clinic of Neurology of UMHAT "St. Marina", Varna, with sudden onset complaints of general weakness, which was more prevalent for the right limbs, slurred speech, and swallowing disorders. Two days prior she complained of pain when trying to move her lower limbs and during swallowing.

A review of her medical history revealed BD diagnosed in December 2018, when the patient complained of general fatigue, oral and genital aphthous ulceration. During this hospital stay uveitis was also diagnosed by ophthalmologist and a positive pathergy test was documented. Additional medical conditions were secondary adrenal insufficiency, and two previous episodes of aseptic meningitis.

On admission, she was in poor general condition with severe dysarthria. Inspection of the skin revealed stretch marks in the abdomen and both thighs and aphthae of the vaginal and oral mucosae. She was in a non-febrile state with a regular pulse at 108 beats per minute and blood pressure of 135/92 mm/Hg.

On neurological examination, the patient was conscious, with limited command response due to severe dysarthria. There were no signs of meningoradicular

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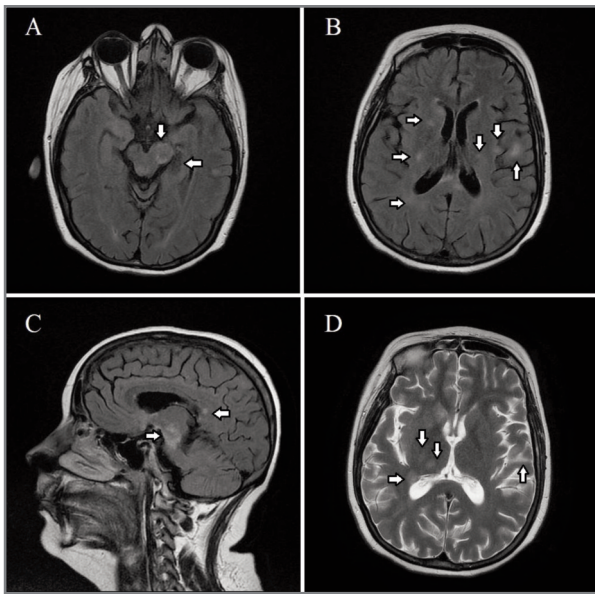


FIGURE 1. MRI imaging from March 2019. A: Axial T1 and C: Sagittal T1 - Hyperintense lesion at the left mesencephalon extending to crus cerebri and the posterior limb of capsula interna with mild mass-effect mimicking a mesencephalic tumor. B: Axial T1 – Hyperintense lesions with different shape at right basal ganglia and thalamus; bilateral periventricular lesions and insular cortex and right inferior frontal gyrus; D: Axial T2 – Hyperintense lesions at right basal ganglia and thalamus; bilateral periventricular lesions

irritation. The pupils were equal, with slow reaction to light, unaffected eye movements. There was a central lesion of the right facial nerve, dysphonia, and dysarthria. The motor activity examination revealed quadriplegia, the pattern being severe for the right limbs and mild on the left. Tendon reflexes were asymmetrical and diminished for the left side. Babinski's sign was absent bilaterally.

Initial laboratory tests showed elevated leucocyte count – 14.78×10^9 , high C-reactive protein (CRP) – 62.14mg/l, and increased total and LDL cholesterol levels – 7.50mmol/l and 5.54mmol/l, respectively. Immunologic panel for searching antibodies was also performed as the results for p-ANCA, c-ANCA and ENA antibodies were negative. The lab-report was positive only for RID-C3 - 2.00 g/L, RID-C4 – C4 and ANA IIF-Hep2. The patient was offered a lumbar puncture for further diagnostic clarification, which she refused.

Computed tomography (CT) scan of the head showed no pathological findings.

On magnetic resonance imaging (MRI), multifocal pathological signal intensity was found – hyperintense on

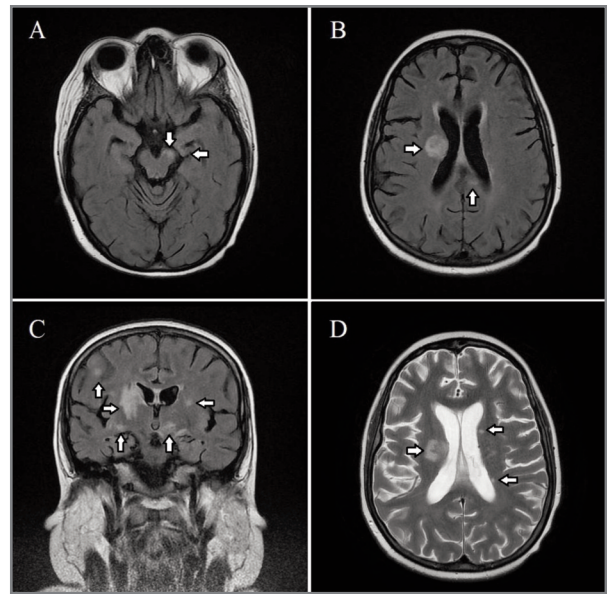


FIGURE 2. MRI imaging from November 2019 – Definite diagnosis of Parenchymal Neuro-Beçet Disease with migration (development and disappearance) of lesions. A: Axial T1 - Hyperintense lesion at the left mesencephalon extending to crus cerebri and the posterior limb of capsula interna, with reduced volume and reduced mass-effect in comparison with previous images. B: Axial T1 and D: Axial T2 – Newly formed hyperintense lesion in right basal ganglia with edema and mass-effect; C: Coronal T1 – Newly formed hyperintense lesion in right basal ganglia with edema and mass-effect; new smaller lesions in left thalamus and in the right cortical area

both T1 and T2 sequences. A comparison with previous MRI images revealed the development of new and disappearance of previously known lesions (Figures 1 and 2).

The largest new lesion was 18mm in diameter with perifocal edema and mass-effect in the periventricular basal ganglia on the right side. Another new lesion with 3.5mm was found in the left thalamus. Previously known lesions, visible in the left mesencephalon with mild mass-effect and the right pontine area near the cerebellar limb, were reduced in size. The disappearance of some of the known lesions was noticed – near the right lateral ventricle and in the right inferior frontal gyrus and the left insular cortex.

The patient fulfilled the International Study Group (ISG) criteria for the diagnosis of BD. There were typical skin and genital lesions represented by recurrent aphthous and herpetic ulceration. A previous anamnesis of uveitis diagnosed by ophthalmologist and a positive pathergy test during previous hospitalization in rheumatologic clinic for BD were also available criteria for BD. The neurological syndrome

supported by characteristic abnormalities on the MRI led to the diagnosis of parenchymal NBD.

We considered treatment with high-doses of corticosteroids, but due to previous history of gastro-intestinal bleeding we performed a therapeutic course with intravenous application of methylprednisolone (40 mg/daily) for 5 days combined with colchicine (0,5 mg/daily) and azathioprine (100 mg/daily) and nonsteroidal anti-inflammatory drugs to control the pain syndrome. During the hospital major improvement was observed regarding the dysphonia, dysphagia as the paresis showed only mild improvement – quadriparesis persisted as the pattern was moderate for the right limbs and mild on the left. Upon hospital discharge per oral methylprednisolone (8mg/daily), colchicine (0,5mg/daily) and azathioprine (100mg/daily) was prescribed.

DISCUSSION

NBD is one of the most serious manifestations of BD. Though NBD is relatively rare - occurs in 5%–10% of

patients²³. As there are different therapeutic options available for this disease, it should be considered in the differential diagnosis in different neurological conditions such as neuroinfection, multiple sclerosis and cerebral infarction⁴. It is fundamental to early recognize NBD and treat it properly because it is one of the main causes of long-term disability and mortality in BD⁵.

NBD is defined by the Consensus Status Agreement as a form of BD with predominant neurological symptoms. In such cases there might be symptoms from the peripheral and central nervous system in the form of parenchymal and non-parenchymal disease⁴.

The diagnostic criteria for BD are presented in Table I and the criteria for NBD are presented in Table II^{4,6}.

The neurological symptoms can be manifested by damage of both central and peripheral nervous system (PNS)⁴. The CNS is the usual target of NBD and there are two main categories of CNS involvement – parenchymal (P-NBD) and non-parenchymal (NP-NBD) involvement⁴.

P-NBD accounts for the majority of NBD – about

TABLE I. INTERNATIONAL STUDY GROUP (ISG) CRITERIA FOR THE DIAGNOSIS OF BEHCET'S DISEASE⁶

I. For diagnosis, patient must have had the following symptoms:

- Recurrent oral ulceration—minor or major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in a 12-month period

II. Plus two of the following:

- Recurrent genital ulceration – aphthae or scarring, observed by physician or patient
- Eye lesions—anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
- Skin lesions—erythema nodosum observed by physician or patient, pseudofolliculitis, papulo-pustular lesions; or acneiform nodules observed by physician in post-adolescent patients not on corticosteroids
- Positive pathergy test—read by physician at 24–48 h

TABLE II. INTERNATIONAL CONSENSUS RECOMMENDATION (ICR) CRITERIA FOR NBD DIAGNOSIS⁴

I. Definite diagnosis of NBD - must be meeting all of the following three criteria

1. Satisfy the ISG or any other accepted current or future criteria for BD (presented in Table 1)
2. Neurological syndrome (with objective neurological signs) recognized to be caused by BD and supported by characteristic abnormalities seen on either or both: Neuroimaging and CSF
3. No better explanation for the neurological findings

II. Probable diagnosis of NBD – must be meeting one of the following two criteria in the absence of a better explanation for the neurological findings:

1. Characteristic neurological syndrome as in definite NBD, with systemic BD features but not satisfying the ISG criteria
2. A non-characteristic neurological syndrome occurring in the context of systemic BD satisfying the ISG criteria

TABLE III. CONSENSUS CLASSIFICATION OF NEURO-BEHÇET'S DISEASE⁴

Central nervous system		Peripheral nervous system
Parenchymal (P-NBD)	Non-Parenchymal (NP-NBD)	
<ul style="list-style-type: none"> • Multifocal or diffuse • Brainstem • Spinal cord • Cerebral • Asymptomatic (silent) • Optic neuropathy 	<ul style="list-style-type: none"> • Cerebral venous thrombosis • Intracranial hypertension • Intracranial aneurysm • Cervical extracranial aneurysm/dissection 	<ul style="list-style-type: none"> • Peripheral neuropathy • Mononeuritis multiplex • Acute meningeal syndrome • Myopathy • Myositis
Mixed form of Parenchymal and Non-parenchymal NBD		

80-90% of the cases⁸. This form is featured by diffuse brainstem, cerebral, optic, and spinal cord symptoms. P-NBD commonly presents with an attack of hemiparesis, cognitive disturbances, pelvic-reservoir troubles and fever. Recent study in South Korea reports the frequency of these manifestations - pyramidal signs (52.0%), headache (45.9%), dysarthria (42.9%), and fever (31.6%)⁹. The symptoms may have sudden onset – acute attack. The last one may be followed by a relapsing or progressive course of the disease¹⁰.

A further division of P-NBD into an acute type and a chronic-progressive type is well-known¹¹. The first type is presented by acute and transient symptoms such as fever and hemiparesis accompanied by inflammatory features from the blood samples and in the cerebrospinal fluid (CSF). The chronic type is characterized by slowly progressive over time ataxia, dementia, incontinence, and brainstem atrophy⁸.

NP-NBD accounts for 20% of the cases and usually affects major intracranial vessels with frequent involvement of the venous sinuses, cerebral veins and less commonly the arteries¹². The most frequent vascular manifestation is venous sinus thrombosis, followed by thrombosis of the deep and the cortical cerebral veins¹³.

The major classification and forms of NBD are presented in Table III.

NEUROIMAGING IN NEURO-BEHÇET DISEASE

The diagnosis of NBD is challenging and relies on the exclusion of other neurological conditions with similar clinical picture such as CNS infections, brain tumors, demyelinating disorders and neurological involvement due to immunosuppressive therapies. There are additional criteria, which are based on neuroima-

ging, serum profiles and HLA determination¹⁴.

Magnetic Resonance Imaging (MRI) is crucial for the diagnosis and is the gold standard for neuroimaging examination to prove NBD⁴.

In patients with P-NBD there are focal or multifocal CNS abnormalities in the clinically affected areas. The lesions are located in the brainstem, thalamus and basal ganglia. Rarely, they can affect the cerebral hemispheres, cerebellum, and the spinal cord¹⁰.

Typical MRI findings are small foci of high signal intensity on T2-weighted images, which are iso- or hypointense compared to the normal brain parenchyma on T1-weighted images. Besides in some cases T1 lesions can be hyper-intense¹⁵. Lesions may be with different shape - circular, linear or irregular. The migration - development and disappearance of lesions on MRI correlates with the course of clinical neurologic deficits and is typical feature of NBD¹⁶. NBD lesions may diminish in size in response to steroid and immunosuppressive treatment¹⁷.

Parenchymal NBD lesions have predilection to the brainstem-thalamic-basal ganglia region. The meso-diencephalic junction is typically affected as this is commonly seen during acute attacks¹². The second most common location is the ponto-bulbar region as the pontine base is most affected and occasionally the lesion extends to brachium pontis. The white matter is more often involved, but lesions also might be seen within the grey matter structures, including brainstem nuclei¹⁸. In one-third of the cases the basal ganglia and internal capsule region is affected¹⁰. Diffusion-weighted imaging may help in the cases, presenting with stroke-like episodes, revealing an increase in the diffusion coefficient in NBD lesions. The clinical similarity between successive attacks may also be helpful in diagnosing NBD⁴.

Atypical presentation of P-NBD is seen as a space-occupying lesion mimicking a unilateral brain tumor. In such situations the diagnosis is difficult, especially if there is no exacerbation on the systemic Behçet's disease signs¹⁹.

In patients with NP-NBD the most common presentation is venous thrombosis. In more rare cases there might be an arterial aneurism, arterial occlusions or dissection and aseptic meningitis¹.

The most common MRI findings in NP-NBD are occlusion of the cerebral venous sinuses without or with venous infarcts⁴. MRI in conjunction with magnetic resonance venography (MRV) is highly sensitive in detecting such lesions²⁰. Neuroimaging features are similar to those in patients with central venous thrombosis due to other causes.

DIFFERENTIAL DIAGNOSIS OF NEURO-BEHÇET'S DISEASE

First, NBD should be primarily differentiated from MS. The age of onset of the two diseases is about the same (20–40 years), but MS is generally more common in women, whereas NBD is seen frequently in men²¹. Some symptoms are present in both the conditions, but the frequency of their presentation varies. Optic neuritis, sensory symptoms, cerebellar symptoms such as dysarthria or ataxia, and spinal cord involvement are common in MS and are quite rare in NBD. On the other hand, headache, pseudobulbar speech, and cognitive-behavioral changes are more common in NBD²². Lesions of the brainstem that commonly extend to the basal ganglia and diencephalic structures support the diagnosis of NBD, whereas MS lesions preferentially involve periventricular areas and the corpus callosum¹⁴. The migration of the lesions - development and disappearance of lesions are typical feature for NBD¹⁶.

The second DD is bacterial meningitis. It is essential as it is condition of medical emergency. Clinical presentation of headache, an altered mental status, seizures and focal cerebral signs can be common manifestations of both the infectious condition and NBD⁴. Anamnesis for toxic-infectious syndrome and continuous monitoring of the patient's temperature might help, as the fever is usually high in bacterial meningitis, while temperature may be normal or of moderate degree in NBD. The CSF analysis is very useful in distinguishing the two conditions. In infective encephalitis there is decrease of the CSF glucose levels, proteinorrhachia (pro-

tein levels above 0,45 g/l usually between 1-5 g/l) pleocytosis (up to 1000–10000 white blood cells/mm³). Specific blood tests may be performed to establish the identity of specific pathogens¹⁴.

The third DD of NBD is the autoimmune disease causing primary or secondary CNS vasculitis. Patients with primary vasculitis do not have systemic signs, which are always present in NBD²³.

Atypical NBD space-occupying lesions are mimicking primary or secondary brain tumors or even abscesses. A stereotactic biopsy would show perivascular infiltration of leukocytes and microglia, oligodendroglial degeneration and areas of necrosis in NBD. Steroid administration may be a diagnostic option in uncertain clinical cases as they can shrink in size the lesion¹⁹. In the context of Behçet's disease the typical clinical picture is more important than a brain biopsy²⁴.

Finally, acute P-NBD can simulate acute stroke-like manifestation. Patients with BD may also exhibit a higher risk of vascular stroke, the etiology of which is uncertain²³. Diffusion-weighted MRI is useful in differentiating the two conditions: whenever a stroke-like episode occurs in BD, an increase in the diffusion coefficient is seen, in contrast to the restriction in diffusion coefficient that is a typical manifestation of infarction²⁵.

CONCLUSION

In differential diagnosis of NBD should be considered cerebrovascular disease, brain tumors, and demyelinating processes. The MRI findings of NBD are distinct and they can prove the diagnosis even in cases without typical systemic manifestations. Stereotyped localization and migration over time of the lesions within the brain parenchyma are characteristic of NBD. Vascular NBD should be considered in cases with venous sinus thrombosis.

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