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# Diagnosing neuro-Behçet's disease

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## ABSTRACT

Behçet's disease is a rare systemic vasculitis characterized by uveitis, recurrent oral and genital ulcers, firstly described by the turkish dermatologist Hulusi Behçet.

The etiology is unknown, although autoimmune mechanisms are described. There is no specific test for the diagnosis of Behçet's disease. The International Criteria for Behçet's Disease (ICBD) proposed a new set of diagnostic criteria including oral and genital aphthosis, skin, ocular and vascular manifestations, CNS involvement and positive pathergy test. The neurologic involvement could be classified in parenchymal neuro-Behçet's and non-parenchymal neuro-Behçet's disease.

We report a case of a woman with a very impressive personal history. Over time, she had many specific neurological complications compatible with neuro-Behçet's disease (NBD). The other general symptoms also suggested Behçet's disease, according to ICBD.

**Keywords:** Behçet's disease, central nervous system (CNS), neuro-Behçet's disease (NBD), The International Criteria for Behçet's Disease (ICBD)

## INTRODUCTION

Behçet's disease is a rare systemic vasculitis characterized by uveitis and recurrent oral and genital ulcers. It was first described in 1937 by Hulusi Behçet from Istanbul who reported two patients with this triple-symptom complex [1]. It has an unknown etiology and can involve ophthalmologic and dermathologic lesions, gastrointestinal and renal manifestations, arthritis, vasculopathy and neurologic manifestations.

The highest incidence of Behçet's disease is along the ancient Silk Road, including places from the Middle East, the Far East and the Mediterranean basin [2]. It was recently proved that there is a strong association with HLA-B51 [3] for these places comparing with others.

Vascular injuries, hyperfunction of neutrophils, and autoimmune responses are characteristic for Behçet's disease. Large vessels are affected by a vasculitis of the vasa vasorum. The vascular injuries are superimposed on the hypercoagulability which is also characteristic of Behçet's disease and that may be due, in part, to activated endothelial cells and activated platelets [4]. Lymphocyte function is abnormal in patients with Behçet's disease [4, 5, 6]. In patients with active Behçet's disease there is clonal expansion of autoreactive T cells specific for the peptide derived from heat shock protein 60 [7].

In 2006, in an effort to achieve improved clinical sensitivity in the diagnosis of BD, a new set of diagnostic criteria were proposed by an international team of Behçet's experts, The International Criteria for Behçet's Disease (ICBD) [8,9]. In 2010, neurologic signs and pathergy test were included given its high specificity [10]. These criteria for Behçet's disease are written in the table below (table 1).

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**TABLE 1.** Point score system: scoring ≥ 4 indicates Behçet's disease diagnosis. Pathergy testing is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted, one extra point may be assigned for a positive result [9]

| Sign/symptom | Score |
|---|---|
| Oral aphthosis | 2 |
| Genital aphthosis | 2 |
| Ocular manifestations | 2 |
| Skin manifestations | 1 |
| Vascular manifestations | 1 |
| Central nervous system involvement | 1 |
| Positive pathergy test | 1 |

The frequencies of the clinical manifestations of Behçet's syndrome are summarized in the table below (table 2).

**TABLE 2.** The frequency of the clinical manifestations of Behçet's syndrome [11]

| Manifestation | Frequency (%) |
|---|---|
| Oral ulcers | 97-99 |
| Genital ulcers | ~85 |
| Papulopustular lesions | ~85 |
| Erythema nodosum | ~50 |
| Pathergy reaction | ~60 (Mediterranean countries and Japan) |
| Uveitis | ~50 |
| Arthritis | ~50 |
| Subcutaneous thrombophlebitis | 25 |
| Deep vein thrombosis | ~10 |
| Arterial oclusion/aneurysm | ~4 |
| CNS involvement | 10 |
| Epidymitis | ~10 |
| Gastrointestinal lesions | 1-30 (more prevalent in Japan) |

The CNS involvement of Behçet's disease has been reported in 5% of patients with Behçet's syndrome in a prospective study from Turkey. The prevalence could be higher in European and American patients [12,13].

The neurologic involvement could be classified in parenchymal neuro-Behçet's (table 3) and non-parenchymal neuro-Behçet's disease (table 4).

In the case of parenchymal neuro-Behçet's, Pallis and Fudge (1956) and Wadia and Williams (1957) described the clinical syndromes and classified them into three types: first, brainstem disturbance associated with systemic symptoms such as fever, arthralgia and skin eruption. Headache with meningism was commonly cited, and CSF pleocytosis was observed; second, meningomyelitis, including a meningitis with varying neurological signs; third, a confusional syndrome, in which meningoencephalitis without focal neurological signs arose, which was in some instances chronic and progressive [14].

**TABLE 3.** Parenchimal neuro-Behçet's disease [14]

| | |
|---|---|
| Brainstem disturbance with subacute evolution | Cranial neuropathies |
| | Ocular motor dysfunction |
| | Nystagmus |
| | Gaze palsies |
| | Dysarthria and ataxia |
| | Bulbar muscle weakness |
| Meningomyelitis | Meningitis with neurological signs |
| | Spinal cord signs |
| | Hemisphere signs |
| Confusional syndrome | Meningoencephalitis without focal neurological signs |
| | Parkinsonism |
| | Pseudobulbar palsy |
| | Quadriparesis |

In the second case, non-parenchymal neuro-Behçet's disease is represented especially by deep vein thrombosis. Superficial thrombophlebitis occurs more frequently in patients with major vessel disease. The affectation of the dural venous sinuses [15] and isolated intracranial hypertension [16] may occur. Stroke-like symptoms such as confusion, weakness, dizziness and headache could be present. Arterial thrombosis is rare and intracranial aneurisms may be found [17].

**TABLE 4.** Non-parenchymal neuro-Behçet's disease [18]

| | |
|---|---|
| Venous sinus thrombosis | Dural venous sinus thrombosis |
| | Superficial thrombophlebitis |
| Isolated intracranial hypertension | |
| Arterial thrombosis | rare |
| Intracranial aneurisms | |

## CASE PRESENTATION

A 68 years old female came into the neurology department for a persisting pulsatile headache, generalized myalgia, polyarthralgia and alteration of general state.

She confessed that the symptomatology was aggravated in the last year and her problems started 35 years ago when she had an episode of brainstem meningoencephalitis with the involvement of pons and midbrain. At that time, she followed corticotherapy for 3 months, but she remained with neurologic sequelae: visual field abnormalities with sparing of macular vision.

A musculo-cutaneous biopsy was performed 32 years ago and a limphocitary vasculitis diagnosis was given. The histological examination showed blood vessels surrounded by oedema and mononuclear cells into papillary region of dermis. The fragment of muscle had rare small vessels with mononuclear inflammatory infiltrate.

In time, repeated episodes of thrombosis with different localization occurred: thrombosis/superficial thrombophlebitis of lower limbs (2002), internal jugular artery thrombosis (2003) seen on computer tomography with intravenous contrast, pulmonary embolism (2004) confirmed by pulmonary scintigraphy.

Beginning with 2012, the patient declared the presence of vesicles on her upper body, lower limbs, anogenitals and in the oral cavity.

An anticoagulant treatment with Acenocoumarol was started in 2004. In 2012, due to the significant fluctuations in INR level, it was decided to replace it with dabigatran etexilat 150 mg X 2/day.

Over time, the patient had recurrent stroke-like symptoms such as headache, weakness and dizziness with spontaneous remission.

In present, the clinical examination revealed: BP = 130/70 mmHg; HR = 80/min; PMI = 5th ics; venectasias of the lower limbs, telangiectasias of the cheeks; impalpable superficial lymph nodes; oral and anogenital vesicular lesions/ulcerations which were extremely painful; generalized joint pain.

The neurologic examination showed a midbrain syndrome with bilateral ophtalmoparesis: important limitation of abduction/adduction and vertical gaze palsy without any complete movement of the eyes (figure 1); normal pupillary and consensual pupillary light reflex.

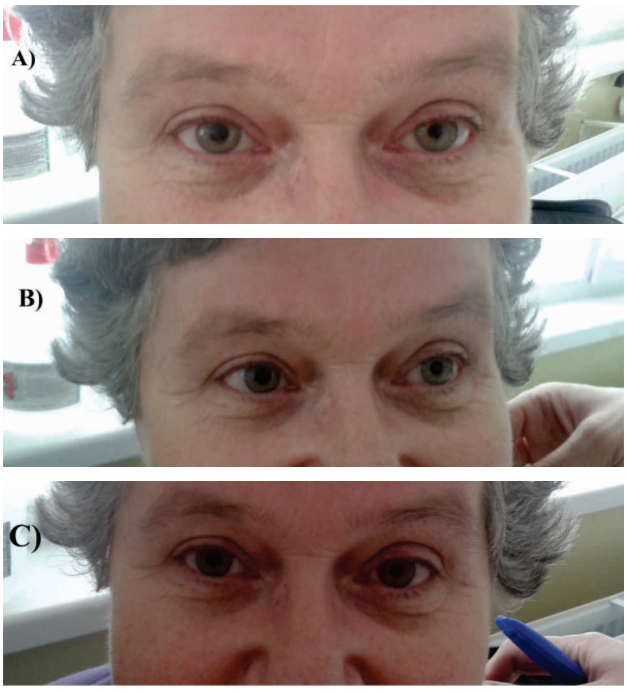


**FIGURE 1.** A) Primary position of the eye; B) Incomplete horizontal gaze palsy on left (accompanied by the movement of the head); C) Incomplete horizontal gaze palsy on right (accompanied by the movement of the head)

The cerebral MRI 0.4 T detected some small vascular demyelinating lesions (3-4 mm) localized frontal periventricular white matter bilaterally and minimal dilation of Virchoff spaces in both thalami.

The Doppler exam of the cervical vessels showed the thrombosis of the left internal jugular vein and bilateral atheromatosis.

The ophtalmologic examination revealed bilateral optic atrophy and visual field abnormalities (figure 2), chorioretinitis sequelae (compatible with posterior uveitis) and important affectation of extrinsic muscles of both eyes.

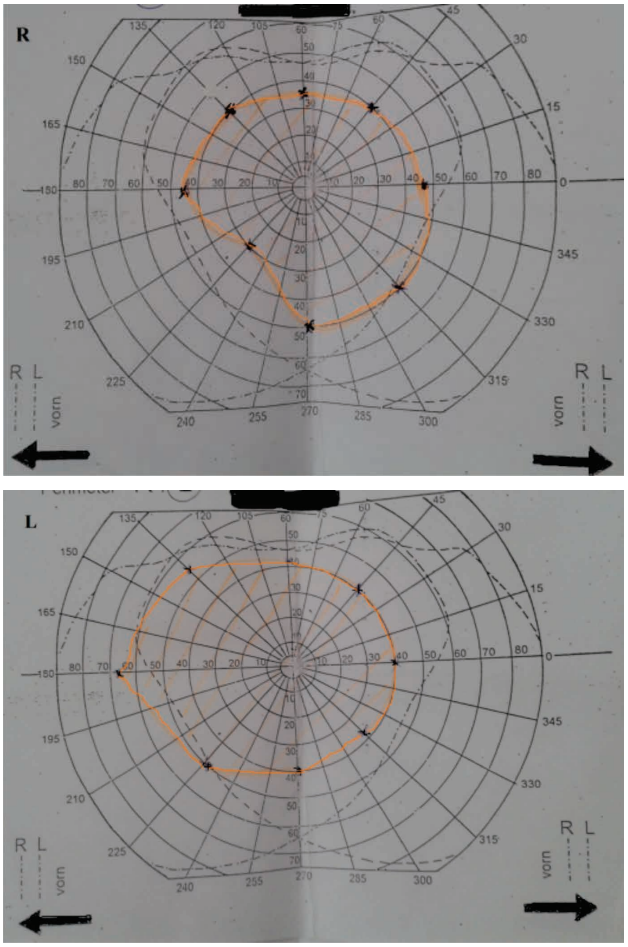


**FIGURE 2.** Visual field abnormalities seen on Kugel perimeter

The immunological parameters were in normal range: the myositis-specific antibody profile was negative, negative c-ANCA and p-ANCA antibodies, negative anti-cardiolipin and anti-CCP antibodies and normal range of antinuclear antibodies (the titer was on superior limit 1/100).

On the basis of the investigations and clinical findings we considered Behçet's disease a very likely candidate for our patient. The onset of the neurological symptoms through meningoencephalitis, the history of venous thrombosis in different territories, recurrent oral and anogenital vesicular/ulcerative lesions, the ophthalmologic sequelae of secondary corioretinitis compatible with posterior uveitis, skin lesions and dermographism and the immuno-

logical findings which excluded other rheumathological disorders represented major arguments for Behçet's disease.

The patient was discharged with an evaluation in the dermatology clinic recommendation (for pathergy test) together with a periodic evaluation and treatment in the rheumatology department.

## DISCUSSIONS

The diagnosis of Behçet's disease represents a challenge for clinicians because there isn't any specific paraclinical parameter and the proposed criteria by the international criteria for Behçet's disease are based on clinical findings. Hence, for diagnosing Behçet's disease it's very important to have an accurate clinical examination, a detailed personal history and a very careful differential diagnosis.

The differential diagnosis must be done with isolated recurrent oral and genital ulcerations, sarcoidosis, Reiter's syndrome, Steven-Johnson's syndrome, inflammatory bowel disease, multiple sclerosis, the Vogt-Koyanagy-Harada syndrome, PEAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) [19].

Nowadays, the authors sustain the idea of considering neuro-Behçet's disease as a probable diagnosis in a neurological patient who has recurrent oral and genital ulcers, uveitis or other systemic features of Behçet's disease. Neuro-Behçet's disease has characteristic clinical presentation pattern.

In conclusion, it makes sense to remember Behçet's disease in the differential diagnosis and to ask specifically about the systemic features of Behçet's disease, even if patients do not volunteer these symptoms [20].

Same authors summarized some recommendations regarding the role of investigations in the diagnosis of neuro-Behçet's disease (table 5).

**TABLE 5.** Recommendations regarding the role of investigations in diagnosing neuro-Behçet's disease (NBD) [20]

| |
|---|
| 1. ESR, CRP and inflammatory cytokines which are non-specific markers of inflammation are limited in the differential diagnosis of NBD. |
| 2. MRI study including contrast and Magnetic Resonance Venography (MRV) which can confirm cerebral venous thrombosis. The distinct MRI findings are helpful in the differentiation from the other CNS inflammatory disorders. |
| 3. CSF examination has a supportive role in the diagnosis, in addition to looking for mimics and especially CNS infections. Parenchymal NBD is usually associated with CSF and/or raised protein. Oligoclonal bands are frequently absent. A completely normal CSF does not exclude parenchymal NBD. Non-parenchymal NBD is associated with elevated CSF pressure only. The role of CSF abnormalities in prognosis and monitoring of the disease needs further research. |
| 4. Raised CSF IL-6 is an indicator of ongoing disease activity in NBD, usually in association with raised CSF constituents. It is recommended to consider CSF IL-6 for disease monitoring, especially in the absence of other raised inflammatory CSF constituents; its use in monitoring therapeutic response needs further research. |
| 5. The pathergy test is simple and has a well-established role in BD diagnosis. A positive pathergy test, in addition to other systemic BD features, would contribute significantly towards the NBD diagnosis. A negative test, however, will not exclude NBD. |
| 6. BD is associated with the HLA-B5 allele and, more specifically, with HLA-B51. It is not clear if HLA-B51/B5 testing has a role in the diagnosis or prognosis of BD or NBD. |
| 7. Neurophysiologic tests are not routinely recommended for NBD. These may be useful if peripheral nervous system or optic nerve involvement is suspected. The diagnosis of NBD should be avoided when solely based on asymptomatic neurophysiological findings. |
| 8. Nervous tissue biopsy can occasionally be useful in the diagnosis of NBD. It is usually not recommended as a part of the diagnostic process. As it is an invasive procedure, it is recommended especially for tumor-like presentation. |

Regarding the treatment of parenchymal NBD, there aren't any controlled or comparative trials on the treatment of any aspect of NBD [21].

In many neurology departments a relapse or an acute presentation of NBD is treated with daily 1g IV methylprednisolone infusions, followed by slowly tapering course steroids [20]. The dose and the duration of the intravenous treatment and the subsequent oral therapy vary between centers [21].

Azathioprine is usually used as a first DMT (disease modifying therapy) in many centers for the serious manifestations of BD, including NBD. There are other publications reporting success with alternative DMT for NBD, including mycophenolate mofetil, methotrexate, chlorambucil and cyclophosphamide [20].

Infliximab and other anti-TNF agents are used in the treatment of refractory ocular and NBD and in achieving favorable outcome [22,23].

The reason for using anticoagulants in the case of cerebral venous thrombosis after excluding systemic aneurysms is to reduce the risk of further extension of the clot in the cerebral venous system [20]. The duration is usually around 3-6 months [24]. The duration will be probably for life if clear evidence for an underlying pro-thrombotic status is found [20].

Behçet's disease has unpredictable exacerbations and remissions with a frequency and severity diminished in time [25].

Poor prognostic features of NBD include brainstem or myelopathy presentation, frequent relapses, early disease progression, and presence of CSF pleocytosis in parenchymal NBD [20].

## CONCLUSIONS

It makes sense to remember neuro-Behçet's disease in the differential diagnosis of neurologic manifestations accompanied by specific systemic symptoms for Behçet's disease like recurrent oral and genital ulcers, uveitis or other systemic features.

Although there isn't any specific paraclinical examination to be done, there are some examinations and investigations if there is a big suspicion of Behçet's disease. Neuro-Behçet's disease has some characteristic clinical features and an accurate clinical examination helps to diagnose it.

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