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Neuro-Behçet's Disease: A Review of Neurological Manifestations and Its Treatment

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Abstract

Behçet's disease (BD) is an inflammatory disorder characterized by recurrent oral and genital ulcers, ocular inflammation, arthritis and skin lesions. Neuro-Behçet's disease (NBD) is found in 5–30% of patients and is classified into parenchymal and non-parenchymal manifestations. Most common parenchymal NBD manifestation is brainstem meningoencephalitis and patients may also have cranial nerve palsies, myelitis, epilepsy and peripheral neuropathy. Non-parenchymal NBD manifestations are cerebral venous thrombosis and aseptic meningitis. NBD usually develop abruptly and generally clear completely within weeks, however a third of patients evolve with progressive course. Moreover, patients with BD without overt neurological manifestations may present silent neurological involvement, with abnormal findings on neuropsychological, neurophysiological and neuroimaging studies. NBD is an adverse prognostic factor. Herein we review NBD manifestations and its treatment.

Keywords: Behçet's disease; Neuro-Behçet's disease; Myelitis; Epilepsy; Peripheral neuropathy; Cerebral venous thrombosis; Vasculitis memory

Introduction

Behçet's Disease (BD) is a multi-systemic disease characterized by recurrent oral and genital ulcers, ocular inflammation, arthritis and skin lesions [1,2]. It most commonly affects male young patients, during the third decade of life [3–5]. Diagnosis is based on the clinical criteria of the International Study Group (ISG) and serological markers are usually absent [6,7]. Genetic and environmental factors are implicated in the pathogenesis of BD and its prevalence is significantly higher in the ancient Silk Route, which extends from Eastern Asia to Mediterranean countries [3,5]. HLA-B51 is a risk factor for BD and the disease is usually more severe in such patients [8].

Although it was initially thought that Th1 cells were the main cells mediating BD, the important role of Th17 cells in the pathogenesis of BD has emerged in recent years [9]. BD and auto inflammatory syndromes share common clinical characteristics, such as recurrent self-limited clinical manifestations, significant host predisposition and abnormally increased inflammatory response, with a robust innate component [10,11]. Genome-wide association studies have identified associations of BD and IL23R, IL10, STAT4, CCR1- CCR3, KLRC4, ERAP1, TNFAIP3, and FUT2 loci [12,13]. Deep resequencing of targeted genes identified additional associations with rare variants in MEFV and NOD2 genes, which are involved in monogenic auto inflammatory syndromes [12,13].

Oral ulcers are the initial symptom in the vast majority of the patients and usually predates other clinical manifestations [13].

However, approximately 5-23% of the cases patients with NBD present neurological manifestation as first symptom [14–17]. The CNS is involved in 5–30% of patients with BD most frequently in the form of recurrent meningoencephalitis, cerebral venous thrombosis (CVT), cranial nerve palsies, epilepsy, and episodes of diencephalic and brainstem dysfunction that resembles minor strokes [7,18–20]. The involvement of CNS is an adverse prognostic factor [14,21]. Type and frequency of neuro-Behçet's disease (NBD) manifestations are associated with ethnicity, and atypical and rare manifestations are more commonly seen in patients of caucasian and Japanese ancestry [14,16,17]. We review the clinical manifestations and treatment of NBD.

Clinical NBD Manifestations

Parenchymal and non-parenchymal NBD

NBD is classified into parenchymal and non-parenchymal manifestations. Parenchymal NBD is more frequently found and may occur with or without meningeal inflammation [15]. It classically affects the mesodiencephalic region, internal capsule and pons, determining important edema and occasionally small infarcts and petechial bleeding (Figure 1). Clinically patients may develop hemiparesis, impairment of consciousness as well as cranial nerve palsies. Spinal fluid analysis (CSF) may reveal increased cells and protein, and may also be predominantly neutrophilic [8,22]. Raised CSF IL-6 levels are usually associated with raised CSF cell count and protein, and these three parameters have been associated with disease activity and outcome over 3 years [22].

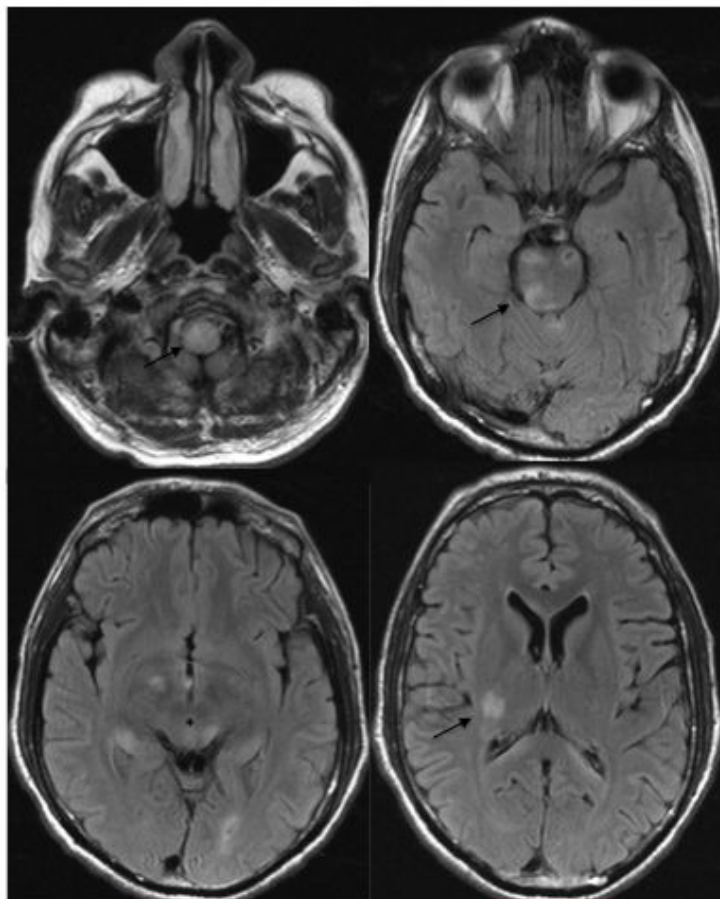


Figure 1: Parenchymal NBD. Asterix: Observe the involvement of the meso diencephalic region. Arrows: Involvement of medulla oblongata, pons and internal capsule.

The reversibility of lesions in parenchymal NBD supports the venous inflammatory pathophysiology and many patients evolve with brainstem atrophy after inflammation is resolved [23]. Some of them may present a pseudotumoral form of the disease, usually involving the capsule-thalamic region or cortex, with more severe clinical presentation at diagnosis but with good recovery [24] (Figure 2).

Neurological symptoms and signs seen in BD patients are not necessarily due to NBD, and other neurological conditions such as

stroke, migraine, neurotoxicity, malignancy and infections should be ruled out [22]. For that reason, the International Consensus Recommendation criteria for NBD diagnosis were established (Tables 1 and 2). Of note, NBD criteria include as probable NBD those patients with typical NBD manifestations that failed to fulfill ISG criteria (patient with recurrent bipolar ulcers and typical neurological manifestation, for example).

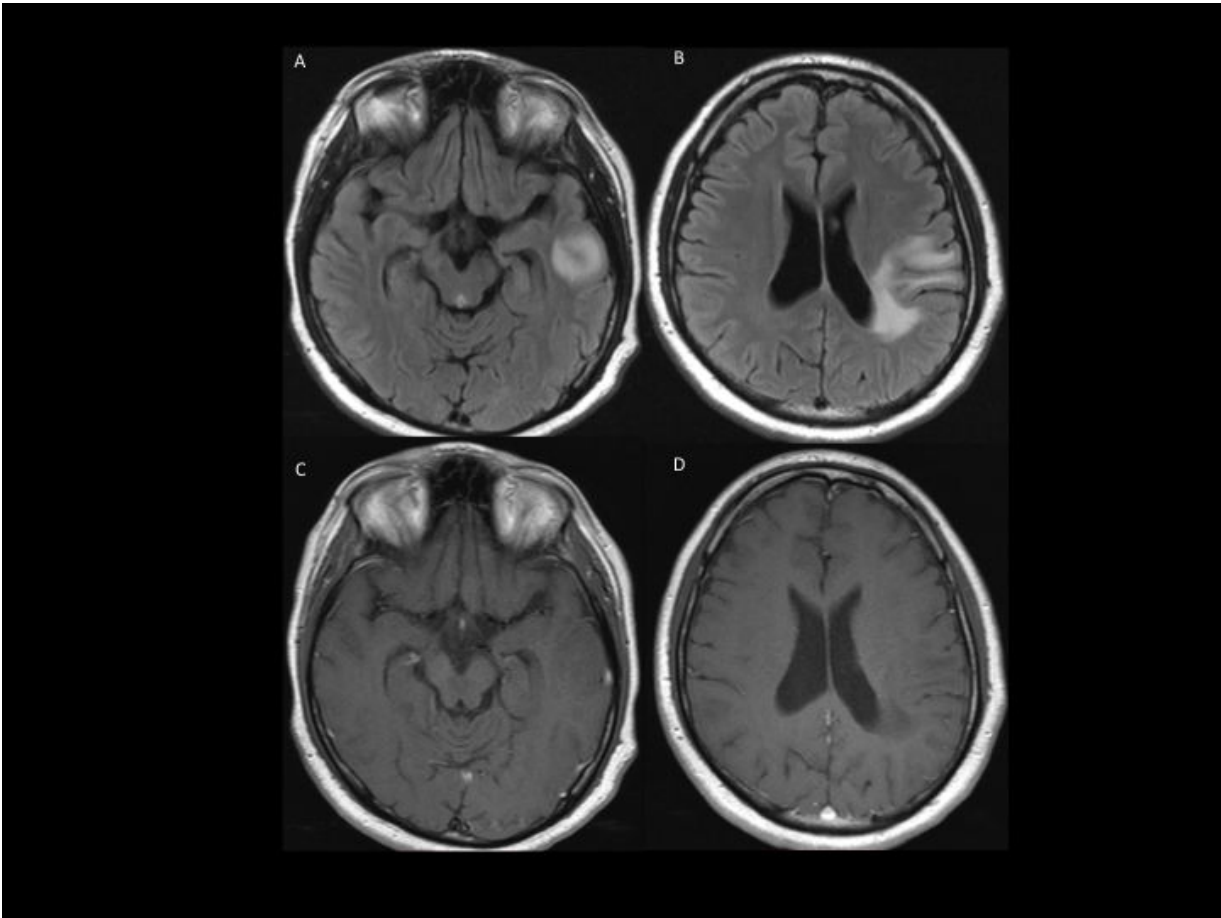


Figure 2: Pseudotumoral NBD. A, B: Flair weighted sequence. Observe pseudotumoral lesion with cortical involvement with proeminent vasogenic edema. C, D: T1 weighted sequence showing no contrast enhancement.

Definite NBD (all of the following three criteria):
1. Satisfy the ISG criteria for BD
2. Neurological syndrome (with objective neurological signs) recognized to be caused by BD and supported by neuroimaging or CSF
3. No better explanation for the neurological findings
Probable NBD (one of the following two criteria in the absence of a better explanation for the neurological findings):
1. Neurological syndrome as in definite NBD, with systemic BD features but not satisfying the ISG criteria

Table 1: International Consensus Recommendation criteria for NBD diagnosis [19]

Atypical parenchymal NBD such as optic neuritis, seizures, peripheral neuropathy, myelitis and demyelinating syndrome are rarely found in Turkish patients. However, in patients of Caucasian origin or mixed ethnicity such manifestations are more frequently found and present additional difficulties to the diagnosis, considering the low threshold for BD diagnosis in those countries [15,17].

Parenchymal syndrome (one or more of the following presentations at first/subsequent attack(s) or progression)
• Brainstem: symptoms and signs of brainstem involvement including ophthalmoparesis, cranial neuropathy, cerebellar or pyramidal dysfunction.
• Multifocal (diffuse): variable combination of brainstem signs and symptoms, cerebral or spinal cord involvement
• Myelopathy
• Cerebral: symptoms and signs suggestive of cerebral hemispheric involvement including encephalopathy, hemiparesis, hemisensory loss, seizures and dysphasia, and mental changes including cognitive dysfunction and psychosis
• Optic neuropathy
Non-parenchymal syndromes
Cerebral venous thrombosis
Intracranial hypertension syndrome (pseudotumour cerebri)
Acute meningeal syndrome

Table 2: Recognized neurological syndromes in NBD [19]

Headache is the most common neurologic symptom in BD and most likely to migraine or tension-type headache, and neuroimaging is warrant for the same red flags signs and symptoms as in general population [8,25]. However headache is common before and during the attack and 10–15 % of headaches reported in BD can be attributed to an ill-defined entity known as “non-structural headache of BD”, when criteria for either NBD or a primary headache disorder are not met [8,26]. For that reason, all BD patients with a recurring headache syndrome, regardless of apparent stability of headache character, require routine neurological examinations to identify “silent neurological involvement” predictive of future onset of NBD, and non-localizing pyramidal signs are the typical exam findings [20,25].

Epilepsy frequency varies from 4–27%, according to the population [16,17,20]. Seizure can be generalized or focal, and occur during an acute neurologic manifestation of the disease, quiescent phase or progressive form of NBD [23,27–29]. Although previous studies showed that seizures are more commonly secondary to medications and other provoking factors, some patients with NBD and epilepsy may present frontal or hippocampal involvement that justify the occurrence of seizures [23]. The occurrence of seizures is associated with a high mortality rate [29].

NBD may also present with a recurrent clinical course of subacute neurological symptoms suggesting demyelinating syndrome. Brain MRI may show small lesions scattered through the white-matter, and some of them may involve the brainstem [30]. This MRI pattern is different from those found in the classical brainstem encephalitis and may resemble Neuromyelitis optica and Multiple Sclerosis. Thus NBD should be considered in the differential diagnosis of those disorders when there are atypical features and associated systemic symptoms are found [22,31].

Optic neuropathy (ON) is rare, could be uni or bilateral and generally occurs in association with other parenchymal manifestations, however there are reports of isolated ON [8,14,18]. It could also be recurrent and patients may be left severely disabled.

Myelitis usually occurs in the setting of systemic activity and in the presence of other lesions involving the basal ganglia, brainstem or cortex [22]. It may be extensive or focal and requires vigorous treatment, because it presents worse prognosis when compared to other neurological manifestations [32–34].

Peripheral neuropathy is rare, and patients may present Guillain-Barré syndrome, sensorimotor neuropathy, mononeuritis multiplex, and autonomic neuropathy [21–23], with variable response to treatment [8,14,35,36].

Non-parenchymal NBD manifestations are CVT and aseptic meningitis [14]. Contrary do parenchymal NBD that relapses in 30–50% of cases, non-parenchymal NBD present good prognosis and rarely recur [14,18,20]. Aseptic meningitis is rare and in such cases, care should be taken to exclude infection, particularly in patients who are on immunosuppressant agents [8]. There have been few reports describing hypertrophic pachymeningitis in patients with NBD [37].

Middle West and Turkish series present more cases of CVT and rare cases of aseptic meningitis when compared to other populations [14,16,17]. A systematic review on CVT in NBD showed that intracranial hypertension syndrome was the most frequent presentation, being superior sagittal and transverse sinus the most commonly involved [38]. It is believed that CVT in NBD is secondary to an inflammatory process for that reason, although anticoagulation is

the standard treatment, in some centers patients are also managed with steroids [22,39]. It is advisable to rule out systemic aneurism before anticoagulation is initiated [22].

Systemic inflammatory disorders such as uveo-meningeal syndromes, sarcoidosis, systemic lupus erythematosus, neuro-Sweet syndrome and Sjogren's syndrome are important differentials diagnosis [22]. Autoinflammatory syndromes such as PFAPA that presents periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis should also be considered because it shares similar clinical manifestations [40].

NBD may present an acute or chronic course. Most patient present an acute course and approximately 30–50% relapse, depending on the population evaluated [14,41]. Moderate or severe neurological disability was found in 45 % NBD patients at 10-year follow-up [42]. It was found that patients with HLA-B51 relapse more often [41]. Other adverse prognostic factor in NBD are brainstem or spinal cord presentation, frequent relapses, early disease progression, residual neurological impairments in remission and high CSF pleiocytosis [8,18,20,22]. Factors such as gender, presence of other systemic manifestations of BD and age at onset did not have any influence on prognosis [14,42].

Silent Neurological Involvement

It has been described that patients with BD without overt neurological manifestation might have abnormal findings on neuropsychological, neurophysiological and neuroimaging studies, which represent silent neurological involvement [20,35,43,44]. Silent neurological involvement (SNI) is a milder neurological manifestation of NBD with reported rates between 20 and 40% [1,4,5]. The significance of this manifestation is unclear, however there are reports that patients with SNI may develop overt NBD with less severe clinical course [22].

Cognitive dysfunction occurs independently of neurological manifestation in 40–46% BD patients, with involvement of various cognitive domains such as visual and working memory, executive function, attention and language [44,45]. Risk factors for cognitive dysfunction are low educational level, anxiety, use of prednisone and systemic disease activity [45,46], although association with disease exacerbations is unclear [43]. Patients may also present pseudobulbar affect and personality disorders [36].

Progressive NBD

NBD usually develop abruptly and generally clear completely within weeks. However a third of patients evolve with progressive course characterized by dementia, ataxia and dysarthria, with persistently elevated CSF IL-6 levels [8,44]. It usually occurs in the late stage of the disease when other neurological manifestations are stable and without clinical exacerbation of other BD symptoms [43]. Unfavorable clinical outcome in chronic progressive type is associated with brainstem atrophy [8,40].

Treatment

There are no randomized trials on NBD treatment [49]. Acute presentations are managed with daily 1 g IV methylprednisolone infusions, followed by a slowly tapering course of oral steroids. At our center, patients with parenchymal NBD are usually managed with steroids and azathioprine or cyclophosphamide [11,42]. Other centers

treat parenchymal NBD with steroids alone, using immunosuppressant agents in the presence of variables associated with poor prognosis, especially in relapsing cases, although there is not enough data to support that immunosuppressant agents prevent relapses [11,19,43]. Mycophenolate mofetil and methotrexate can be used in NBD treatment and cyclosporin should be used with caution due to neurotoxicity [19,42].

Because non-parenchymal NBD have a more favorable prognosis, those manifestations are managed with steroids alone. CVTs are usually managed with anticoagulation and steroids in most centers [19,42,43]. Infliximab is an option for refractory patients with continued benefit in follow-up studies over 4-year period [44,45,47-51]. Adalimumab and tocilizumab have been reported as an alternative to infliximab [52,53]. For progressive NBD, evidence from one center suggests that administering weekly methotrexate will help slow down the progressive neurological disease in association with a reduction in CSF interleukin-6 concentration [54].

Conclusion

NBD is a rare disease that presents variable neurological manifestations, including progressive form and silent neurological involvement. Patients that with parenchymal NBD present relapse more often when compared to non-parenchymal NBD. Biological agents are a treatment option for refractory cases.

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