Neuro-Behçet Disease and Autoinflammatory Disorders

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Abstract

Misregulation of innate immunity leads to autoinflammation. Behçet disease is an autoinflammatory condition involving recurrent attacks of inflammation in skin, eyes, joints, and even the nervous system. The etiology may involve vascular inflammation. Central nervous system involvement in neuro-Behçet disease (NBD) comes in the form of parenchymal NBD or nonparenchymal NBD. The parenchymal form has a predilection for the brainstem, diencephalon and cerebral hemispheres, and represents a meningoencephalitis thought to be related to small vessel vasculitis. Cerebral venous sinus thrombosis, arising from a vasculitic process of large veins, comprises the majority of vascular NBD cases. The rarer monogenetic autoinflammatory syndromes are characterized by periodic fever, and typically present in the pediatric population. Neurologic involvement in these syndromes typically presents in the form of an aseptic meningitis. Treatment of autoinflammatory disorders involves immune modulation with corticosteroids, disease-modifying antirheumatic medications, and increasingly antibodies targeting cytokines like tumor necrosis factor α and interleukin 1.

Keywords
► neuro-Behçet
► autoinflammatory syndromes
► neurologic disease
► cerebral venous thrombosis
► vasculitis

Behçet disease (BD) is an inflammatory condition with characteristic mucocutaneous lesions and a wide variety of systemic manifestations, including central nervous system (CNS) involvement. The pathogenesis remains unclear, but histopathologic studies have consistently shown evidence of vascular inflammation involving a wide range of vessels. The family of autoinflammatory disorders similarly involves disorders in immune regulation, which often presents as a periodic fever syndrome. Neurologic disease occurs within this class of disease as well, although less commonly than in Behçet disease. Understanding the neurologic features of Behçet and other autoinflammatory diseases is important because the neurologic deficits are a significant cause of morbidity. Further, NBD is an important consideration in the differential diagnosis of demyelinating and inflammatory central nervous system conditions.

General Clinical Features of Behçet Disease

Behçet disease is an inflammatory condition clinically characterized by recurrent oral and genital ulcers and involvement of other organ systems including eyes, skin, joints, and the gastrointestinal, nervous, and vascular systems. The specific diagnostic criteria created by the International Study Group for Behçet’s Disease in 1990 involves the presence of recurrent oral ulcers, plus two of either genital ulcers, eye involvement (uveitis or retinal vasculitis), skin lesions (typically erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform rash), or a positive pathergy test (√ Table 1).

The highest prevalence of BD patients is in the areas along the “Silk Road,” extending from Asia through the Middle East into European countries around the Mediterranean.
typical age of onset is between 20 to 40 years, and men and women have been reported to be affected with equal frequency. Interestingly, male patients often have more severe symptoms and have more frequent central nervous system involvement. The average disease course lasts approximately 20 years before going into remission.3

Proposed Pathogenesis
Behçet’s disease is commonly described as an inflammatory disorder; however, the cause of the inflammation remains incompletely understood. On the histopathologic level, BD is categorized as a vasculitis involving all sizes of vessels within the body and afflicting veins as well as arteries. Analysis of samples from BD patients has shown perivascular inflammation composed of T cells, B cells, and neutrophils.4

At times BD has been categorized with autoimmune disorders, and several serologic markers have been loosely linked, including heat shock proteins and annexins among others,5 yet these are detected in only a minority of BD patients and are not specific to the disease. In fact, no disease-specific autoantibodies have been found to date.6

Alternatively, BD has also been proposed to be a member of the autoinflammatory family of diseases, which are diseases of the innate immune system. Unlike the adaptive immune system, which involves antigen-specific recognition by T and B cells, the innate immune system is a phylogenetically older system that is antigen-independent. The effectors of the innate system involve neutrophils, macrophages, natural killer cells, and mast cells. Familial Mediterranean fever is the prototypical autoinflammatory disease; diseases of this family commonly involve periodic episodes of unprovoked inflammation and concurrent fevers. These diseases often involve rash, arthritis, and serositis. Increasing evidence is mounting to suggest that BD involves the misregulation of the innate immune system. Critics of this theory argue that unlike other autoinflammatory disorders, BD is not a pediatric disorder, is not linked to a clear genetic mutation, and is not as prototypically associated with attacks of fever and widespread inflammation.7,8 On the other hand, there are many similarities between BD and other autoinflammatory disorders.

Furthermore, this concept, proinflammatory cytokines, including tumor necrosis factor α (TNF-α), are upregulated in autoimmune diseases as well as BD,5 and research in BD pathogenesis has shown elevated levels can be detected in the serum.9 Recently a meta-analysis looked for an association between single nucleotide polymorphism (SNPs) in TNF-α and susceptibility to BD, with the idea that certain SNPs may affect the degree to which TNF-α is expressed. Looking at 17 studies involving 1,708 BD patients and 1,910 healthy matched controls, the authors found significant associations between four specific TNF polymorphisms and BD susceptibility.9

Altogether, the question of pathogenesis remains unanswered, but recent data heavily support the idea that certain genetic backgrounds that predispose to autoinflammation are more susceptible to the development of BD.

Neurologic Manifestations
The diagnosis of neuro-Behçet disease (NBD) involves the findings of systemic BD, as described above, in conjunction with the presence of neurologic symptoms that are not explained by another cause. Objective findings of neurologic involvement of the disease can include an abnormal neurologic exam, abnormal neuroimaging, or an abnormal CSF profile.

Review of the literature reveals that 5% to 50% of BD patients in various series exhibit neurologic involvement that typically presents several years into the disease course.10 Of note, however, neurologic manifestations were observed as the first sign of the disease in 6 of 200 patients in a Turkish study,11 6 of 36 patients in a Brazilian study,12 and 13 of 20 patients in a Spanish study.13 Further, at least one group has described a patient who experienced neurologic and ocular BD who never developed typical mucocutaneous lesions, even after long-term follow-up.14 As noted above, CNS involvement is much more prevalent in men than women in certain ethnic backgrounds (see reference 10 for more detailed discussion).

Neurologic involvement can be classified as one of two forms: parenchymal involvement and nonparenchymal-vascular involvement. Parenchymal NBD is the most commonly seen form of neurologic involvement in BD, comprising 60% to 75% of cases in several studies,11,13,15,16 and commonly affecting the brainstem, mesodiencephalic junction, cerebellar peduncles, and cerebral hemispheres. Both isolated and multifocal lesions have been described and are typically characterized by areas of T2 prolongation on brain magnetic

<table>
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<th>Table 1 International study group criteria for Behçet disease2</th>
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<td>Recurrent oral ulceration</td>
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<td>Plus two of the following:</td>
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<td>Recurrent genital ulceration</td>
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<td>Eye lesions</td>
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<td>Skin lesions</td>
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Involvement of cerebral hemispheres can lead to memory and dysarthria, may be apparent with brainstem lesions. 

Ventricular enlargement, intracranial pressure, including papilledema, nausea and vomiting, and dysarthria, may be apparent with brainstem lesions. Involvement of cerebral hemispheres can lead to memory disturbance, depression, aphasia, neglect, sensory deficits, and hemiplegia, depending again on the specific region involved. 

Seizures related to the lesions have also been described, but appear very rare, with a prevalence of approximately 2% in one case series. 

Optic neuropathy has been reported in several case studies, though this also appears to be quite rare among the larger population of patients affected by NBD. An isolated aseptic meningitis is also described in multiple studies, varying in frequency among populations studied from quite rare (< 1% of cases) to 16%,4,12,15 It has been speculated that many of the initial reports of isolated aseptic meningitis likely had parenchymal lesions that were not detected on neuroimaging. 

In a study of 200 patients followed in a NBD clinic in Turkey, brainstem involvement was most common, seen in approximately 50% of their cohort, followed by lesions of the cerebral hemispheres. A similar predilection for the brainstem was seen in a smaller group of Brazilian patients. Spinal cord lesions have also been described, often in association with lesions within other parts of the neuroaxis as well as a longitudinally extensive transverse myelitis.

The nonparenchymal form of NBD is less common than parenchymal cases and usually comes in the form of a cerebral venous sinus thrombosis (VST). In a systematic review of the literature, 15% of NBD involved VST. Headache is a common presenting symptom, as well as other signs of elevated intracranial pressure, including papilledema, nausea and vomiting, and cranial nerve VI palsies. The superior sagittal sinus and the transverse sinuses were the most frequently involved vessels. Venous thrombosis has been linked to a vasculitic-type process that has a propensity for the venous system. Vascular NBD often presents earlier in the disease course and is associated with systemic vascular disease. Although parenchymal NBD and vascular NBD were traditionally thought to not to coexist in the same patient, several case series have now reported mixed cases. This may be related to the expansion of imaging technology and the increasing ease of obtaining MRI.

A variety of other vascular issues, including ischemic stroke, arterial dissection, and intracranial aneurysms, have been noted in patients with BD. Their relative frequency, however, raises the question as to whether these are related to the pathogenesis of the disease, or unrelated events that would also be observed in the general population. We await further studies to clarify this point.

Supporting the idea that a vasculitic process is part of the pathogenesis of all forms of NBD, a small study of 40 patients utilized transcranial Doppler to investigate the integrity of cerebral vasculature and noted abnormal flow patterns in the carotid and vertebral arteries of all patients (15/15) with NBD. Further, transcranial Doppler studies were abnormal in five BD patients who did not have a clear neurologic syndrome or NBD diagnosis.

In considering the diagnosis of NBD in a patient with known BD, it is important to note that common neurologic issues like migraine and stroke can also be seen and may not have any relationship to the BD diagnosis.

**Differential Diagnosis**

The differential diagnosis for the parenchymal form of NBD includes infectious, autoimmune, inflammatory, and neoplastic entities. This differential is particularly important in patients without known systemic BD, as NBD can be the first manifestation of BD. The young age at presentation and predilection for the brainstem lead to multiple sclerosis being an important consideration, though imaging findings generally help to distinguish MS from NBD (discussed further below). Rheumatologic and inflammatory conditions to consider include systemic lupus erythematosus, Sjögren syndrome, and neurosarcoidosis. Possible infections from tuberculosis, neurosyphilis, viruses, or fungi may need to be excluded in the setting of meningitic presentation, as well as carcinomatosis and lymphomatosis. Other neoplastic processes, like CNS lymphoma or glioma, can manifest in a subacute manner, similar to NBD.

**Diagnostic Evaluation**

Unfortunately, there is at present no diagnostic test that is specific to NBD. Rather, evaluation for NBD involves a combination of clinical diagnosis with the addition of serum studies, MRI, and CSF analysis.

The goal of most serum studies in the diagnosis of NBD is primarily to exclude other relevant items on the differential diagnosis. This includes white blood count with differential to investigate for evidence of infection as well as relevant serologies and cultures to rule out infective entities of interest. Rheumatologic studies, including ANA, anti-Ro, and anti-La antibodies, can be helpful. Though erythrocyte sedimentation rate is nonspecific, it is frequently found to be elevated during disease attacks and therefore can be used as a marker of disease activity.

Human leukocyte antigen (HLA) typing is frequently performed, as patients with HLA-B51 allele have a significantly increased risk of developing BD. The pooled odds ratio based on a meta-analysis of 80 published studies involving 4,800 cases of BD was determined to be 5.78, though it was noted that there is some variability in the degree of increased risk.
among different ethnic groups. The prevalence of HLA-B51 is highest in Asian, Middle Eastern, and southern European populations compared with northern European and North American populations.

Magnetic resonance imaging is usually the next test in the investigation of new neurologic symptoms in a patient with BD and, at present, the gold standard for diagnosis. The MRI findings are dependent on the type of NBD. As described above, parenchymal lesions are hypo- or isointense on T1 and hyperintense on T2 sequences; lesions can be found throughout the brain but are characteristically located within the brainstem and diencephalon, as well as throughout the white matter of the cerebral hemispheres. An example of typical MRI findings is shown in Fig. 1. In contrast to lesions found in multiple sclerosis, cerebral white matter lesions do not have a clear preference for the periventricular area; NBD parenchymal lesions often enhance with contrast in an acute attack. A recent study looked at diffusion-weighted imaging in NBD and found that NBD lesions tended to have increased apparent diffusion coefficient (ADC) values. This is in contrast to cerebral infarctions, which acutely show restricted diffusion and low ADC values. These lesions can also show evidence of microhemorrhage, which is detected using susceptibility-weighted imaging (SWI), an MRI sequence that is quite sensitive for the detection of blood products. Further, decrease or resolution of MRI lesions frequently follows remission from an attack. Magnetic resonance venography or computed tomography venography are the tests of choice when there is suspicion for cerebral venous sinus thrombosis. Unlike cases of general venous sinus thrombosis, venous infarction or hemorrhage are very rarely encountered in NBD-associated VST.

Cerebrospinal fluid is also obtained by lumbar puncture when NBD is suspected. In cases of parenchymal NBD, the spinal fluid is typically characterized by elevated protein level as well as a neutrophilic pleocytosis which may later transition to a lymphocytic predominance, with white cell counts ranging from 0 to 400 cells per milliliter. The CSF glucose levels are normal. Oligoclonal bands are found in only a minority of patients. The CSF from vascular NBD is usually benign, though can at times be associated with an elevated opening pressure from elevated intracranial pressure related to VST.

On occasion, in the setting of no known systemic BD or atypical presentations, a tissue biopsy is obtained to help make the diagnosis of NBD. As described elsewhere in this article, on a histopathologic level NBD lesions are defined by a perivascular infiltrate composed of both neutrophils and lymphocytes, with gliosis apparent only in later, chronic stages of the disease.

An international panel convened in 2013 to develop a consensus regarding criteria to be used for the diagnosis of NBD. Definite NBD was defined as a case satisfying the standard study group criteria for BD, having a neurologic syndrome with typical characteristics of NBD that are supported by imaging or CSF studies and with no alternative or better explanation for the neurologic complaints.
Treatment

There is a wide variation in the types, dosages, and durations of treatment utilized in the treatment of NBD. The most in depth and current guidelines include a treatment algorithm proposed by an international panel 2013 as well as a comprehensive review by Akman-Demir, Saip, and Siva. Current treatment paradigms stand with treatment of acute attacks with high-dose steroids followed by a slow taper. Disease modifying therapies are then considered with relapses or continued symptoms despite immunsuppression. The general algorithm is shown in – Fig. 2.

Recommendations for treatment of the initial attack involve treatment with intravenous methylprednisolone 1 g daily for 5 to 10 days, followed by an oral steroid taper over several months. Treatment with steroids has not been shown to prevent relapses. Azathioprine is recommended as first line disease modifying therapy for patients who fail to respond to corticosteroids or have frequent relapses, typically administered to reach a target dose of 2 to 3 mg/kg/d. Multiple observational studies have reported that azathioprine may control disease activity. Of note, however, there was no significant difference in event-free survival in a study of 115 NBD patients in a French center when comparing treatment with the combination of corticosteroids and azathioprine to corticosteroids plus cyclophosphamide to corticosteroids alone. Alternatives to azathioprine include methotrexate, with target doses of 12.5 to 25 mg/wk, and intravenous cyclophosphamide, at 500 to 1000 mg/m². Although cyclophosphamide has been effective in the treatment of uveitis, there is evidence that it can cause or exacerbate NBD activity.

TNF-α blocking agents, including infliximab and etanercept, are alternatives to the traditional disease modifying therapies noted above. In light of the increasing evidence of elevated levels of proinflammatory cytokines, including TNF-α, in the pathogenesis of BD, these agents have become more popular as they may directly inhibit the development and evolution of the disease. Review of the current literature reveals numerous case reports describing successful use of infliximab in refractory and aggressive cases, maintenance of remission in chronic disease as well as in new-onset NBD, often used in combination with a disease-modifying therapy.

Nonparenchymal NBD in the form of venous sinus thrombosis is typically treated with corticosteroids as above, with or without anticoagulation. Though anticoagulation is the standard of care for non-NBD associated VST, the use of heparin or similar products is controversial in NBD patients, relating to the presumed inflammatory nature of the pathogenesis and concern that the thrombus is tightly adherent to the wall of the sinus, as well as concerns over increased bleeding risk in NBD patients related to potential increased prevalence of intracranial aneurysms. As an alternative to anticoagulation, daily aspirin therapy can be used.

Prognosis

Two-thirds of patients with NBD recover without notable neurologic deficits following steroid treatment for the initial attack; however, approximately half of those who recover go on to have at least one relapse. Approximately 30% of patients, across numerous ethnic populations, have progressive neurologic decline despite treatment with various modalities. At 10 years, 78% of patients have at least mild neurologic disability and 45% have severe neurologic disability in one longitudinal study.

In regard to factors that may be predictive of disease course, HLA-B51 carriers tend to have a worse prognosis, as illustrated in a recent study of 115 men with NBD. Forty-nine percent of the patients had the HLA-B51 allele; this was associated with a more aggressive course of disease leading to a relapse rate of approximately 51% over a 7-year follow-up period. Abnormal CSF studies, with elevated white cell counts or protein, involvement of the brainstem, more than two attacks or relapse during treatment with steroids are all factors that have been significantly associated with poor prognosis, defined as dependent functional status or death. Neuro-Behçet disease in the form of venous sinus thrombosis, on the other hand, tends to have a more benign course with rare relapses.
Autoinflammatory Disorders

Autoinflammatory disease is a broad term used to describe disorders of uncontrolled and unprovoked inflammation driven by the innate immune system. Behçet disease is a multifactorial disorder that falls into this category. More commonly, however, the designation of autoinflammatory disease is used to refer to the monogenetic periodic fever syndromes. These are a family of genetic diseases characterized by periodic fever and attacks of inflammation in the absence of an infectious insult. The prototypical disorder in the family is familial Mediterranean fever, an autosomal recessive disorder caused by mutation of MEFV gene that encodes the protein pyrin, which may aid in regulation of neutrophil-mediated inflammation. Another example is TNF-associated periodic syndrome (TRAPS), which has an autosomal dominant inheritance pattern of mutations in the TNF receptor that are suspected to lead to periods of uncontrolled inflammation. Other syndromes in this family include deficiency of the interleukin 1 (IL-1) receptor antagonist (DIRA), deficiency of the IL-36 receptor antagonist (DITRA generalized pustular psoriasis), familial cold autoinflammatory syndrome (FCAS), hyper IgD syndrome (HIDS), Muckle-Wells syndrome, nucleotide oligomerization domain-like receptor family, pyrin domain (NLRP), neonatal-onset multisystem inflammatory disorder (NOMID), and pyogenic sterile arthritis pyoderma gangrenosum acne syndrome (PAPA).

Clinically, these disorders present with various skin rashes, arthralgias, and arthritis, and in some circumstances, serositis, and aphthous ulcers, and most commonly manifest in the pediatric age range.

The identification of the genetic basis of these syndromes has advanced our understanding of the pathogenic mechanisms behind the development of autoinflammatory conditions. A common theme among mutated genes is their role in the antigen-independent or innate immunity pathway, leading to improper assembly of the inflammasome and overproduction of IL-1β. This has led to the hypothesis that autoinflammatory disease attacks are caused by deregulated immune signaling causing unprovoked and overwhelming inflammation in various organs in the body.

The attacks of inflammation affect many organ systems, and each syndrome tends to have its own pattern of affected systems. Central nervous system involvement has been reported for many of these syndromes but is rare. Most neurologic symptoms described in monogenetic autoinflammatory syndromes are nonspecific in the form of headache; however, focal neurologic deficits have been reported for TRAPS.

Further, patients with NOMID have signs of elevated intracranial pressure and evidence of chronic aseptic meningitis with neutrophil predominance on CSF analysis. Aseptic meningitis occurring with disease attacks has also been described in Muckle-Wells syndrome, familial Mediterranean fever, and TRAPS.

Similar to BD, corticosteroids are the first-line treatment of monogenetic autoinflammatory disorders, as well as nonsteroidal anti-inflammatories. Prophylactic colchicine is used to manage symptoms and disease progression in familial Mediterranean fever. Additional treatment involves modulation of cytokine signaling, particularly through IL-1 receptor antagonism with anakinra, canakinumab, or rilonacept. Clinical response to IL-1 targeting molecules has been demonstrated in familial Mediterranean fever, FCAS, Muckle-Wells syndrome, NOMID, and TRAPS. Alternatively, TNF blockade with etanercept has been shown to be beneficial in TRAPS, while infliximab can lead to paradoxical worsening of symptoms.

Summary

Neuro-Behçet disease and autoinflammatory syndromes are overall relatively rare, but important to consider when evaluating patients with neurologic deficits and serologic evidence of an inflammatory process. Increased understanding of the mechanism of innate immune system dysregulation within this class of disorders has led to further insight into disease pathogenesis and a move toward therapies that are more directly targeting the downstream effects of aberrant signaling through these pathways.

References
