【 REVIEW ARTICLE 】

Neuro-Behçet Disease, Neuro-Sweet Disease, and Spectrum Disorders

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Abstract:

Behçet disease and its related disorder, Sweet disease, are multifactorial disorders whose susceptibility loci have been identified in the genes of various immunological factors aside from human leukocyte antigens. The neurological involvement of these diseases, including encephalitis, myelitis, and meningitis, referred to as neuro-Behçet disease (NBD) and neuro-Sweet disease (NSD) respectively, is sometimes difficult to diagnose, especially when the characteristic mucocutaneous symptoms do not precede neurological symptoms or when characteristics of both diseases are present in a single patient. NBD and NSD constitute a spectrum of diseases that are differentiated according to the combination of risk factors, including the genetic background. Encephalitis, myelitis, and meningitis similar to NBD or NSD can be diagnosed as spectrum disorders, even if the characteristic mucocutaneous symptoms fail to be detected. Understanding these conditions as a disease spectrum may help elucidate the disease pathogenesis and assist in the development of therapeutic agents.

Key words: neuro-Behçet disease, neuro-Sweet disease, spectrum disorder, neuro-neutrophilic disease, encephalitis, myelitis, meningitis

NBD and NSD

Behçet disease (1, 2) and its related disorder, Sweet disease (3-5), are multisystem inflammatory conditions characterized by mucocutaneous symptoms. When neuropsychiatric symptoms appear in Behçet disease, the condition is referred to as neuro-Behçet disease (NBD) (6). Sweet disease is also sometimes accompanied by neurological involvement, including corticosteroid-responsive encephalitis, myelitis, and meningitis; therefore, we proposed criteria for diagnosing neuro-Sweet disease (NSD) as well, named after NBD (7, 8).

Dermal infiltration with mature neutrophils in the absence of leukocytoclastic vasculitis in Sweet disease is different from dermal symptoms with vasculitis in Behçet disease; therefore, skin biopsies are necessary to diagnose Behçet disease and Sweet disease. Further complicating the matter is that some mucocutaneous symptoms and signs without vasculitis, including oral aphthae, benign genital ulcers, and pathergy reactions, are common to both diseases (1-5).

Pathological findings in the central nervous system (CNS) have been shown to differ between NBD and NSD. In NBD, vasculitis is seen in the CNS (6, 9) as well as in dermal lesions. However, vasculitis seems to be absent in CNS lesions as well as in typical eruptions in NSD (10). Therefore, the presence or absence of vasculitis in skin lesions appears to be important for differentiating between NBD and NSD. More severe inflammatory reactions involving the blood vessels likely result in the poorer prognosis associated with CNS lesions in NBD.

Multifactorial Disorders

The differences in clinical phenotypes between NBD and NSD are shown in Table 1 (6, 11). These differences in clinical manifestations may be due to differences in the genetic background (11).

There is a strong human leukocyte antigen (HLA) -B51 association in NBD (12), while there is a high frequency of HLA-Cw1 and/or HLA-B54 in NSD (8). These findings have been implicated in the differences in cytotoxic T cell

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Table 1.   Differentiation of Neuro-Behçet Disease and Neuro-Sweet Disease.

	Neuro-Behçet disease	Neuro-Sweet disease
Gender (male : female)	2.2-3.4 : 1	1.2-1.5 : 1
Age	Mainly 20-40 years old	30-70 years old
Common symptoms*	Fever, oral aphthae, benign genital ulcers, pathergy reaction	
Dermal symptoms	Erythema nodosum-like lesion (septal panniculitis, neutrophil infiltrates, followed by lymphocytes) Pseudofolliculitis subcutaneous thrombophlevitis	Raised erythematous plaque (dense dermal infiltrate of mature neutrophils, followed by lymphocytes, absence of vasculitis)
Neurological involvement*	Encephalitis, myelitis, meningitis	
Neurological symptoms	Headache, motor symptoms, pseudobulbar palsy	Headache, variable focal symptoms
CNS lesions	Brainstem, thalamus, basal ganglia	No site predilection
Pathology	Neuronal loss, parenchymal and perivascular intense inflammatory infiltration (neutrophils, eosinophils, lymphocytes, macrophages) Fibrinoid necrosis within small post-capillary venules	Mild neuronal loss, perivascular cuffing around particularly small veins (neutrophils, lymphocytes, macrophages) Absence of necrotic vasculitis
Ocular lesions	Uveitis	Episcleritis, conjunctivitis
Blood*	Neutrophilia, elevated ESR, CRP, and IL-6 level	
CSF*	Pleocytosis (neutrophilc, lymphocytic, or mixed), elevated protein, elevated IL-6 and other cytokines, absence of oligoclonal bands	
Genetic backgrounds		
HLA	B51	B54, Cw1
Familial Mediterranean fever gene	E148Q, G304R, P369S. R408Q	E84K, E148Q, R202Q
Prognosis	Poorer	More benign

*: common features, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IL: interleukin, HLA: human leukocyte antigen

responses elicited by non-professional antigen-presenting cells with HLA class I (11).

In addition to HLA, genome-wide association analyses in Behçet disease have identified new susceptibility loci in the genes of various immunological factors, such as interleukin (IL)-23 receptor (*IL23R*)/IL-12 receptor beta 2 (*IL12RB2*), IL-10 (*IL10*), endoplasmic reticulum aminopeptidase 1 (*ERAP1*), killer cell lectin-like receptor subfamily C, member 4 (*KLRC4*), chemokine c-c motif receptor 1 (*CCR1*), signal transducer and activator of transcription 4 (*STAT4*), Toll-like receptor 4 (*TLR4*), nucleotide-binding oligomerization domain containing 2 (*NOD2*), familial Mediterranean fever gene (*MEFV*), fucosyltransferase 2 (*FUT2*), IL12A (*IL12A*), *IL1A-IL1B*, receptor-interacting serine-threonine kinase 2 (*RIPK2*), 2-aminoethanethiol dioxygenase-early growth response 2 (*ADO-EGR2*), laccase domain-containing 1 (*LACC1*), interferon regulatory factor 8 (*IRF8*), and CCAAT/enhancer binding protein β-protein tyrosine phosphatase non-receptor type 1 (*CEBPB-PTPN1*) (13-20). Furthermore, *MEFV* mutations have also been shown to be associated with Sweet disease (21-23). These findings indicate that these diseases are caused by a combination of several immunological risk factors.

Other factors, such as preinfection with *Streptococcus* or certain viruses and smoking (12), have also been implicated as risk factors.

Cases without mucocutaneous symptoms

For the diagnosis of NBD, it is essential to meet the criteria for Behçet disease (1, 2, 6), including the presence of mucocutaneous symptoms. The criteria for diagnosing

"probable" NSD also include characteristic cutaneous symptoms of Sweet disease (8). However, mucocutaneous involvement does not necessarily precede neurological involvement. A skin biopsy cannot always be performed in a timely manner, resulting in the potential failure to demonstrate the typical pathological findings of Behçet disease and Sweet disease (24). Therefore, a tentative diagnosis other than NBD and "probable" NSD is necessary for cases without confirmation by a skin biopsy.

Cases presenting characteristics of both NBD and NSD

The differential diagnosis of NBD or NSD in some cases is not easy because the common clinical features of both diseases are present, as described above.

Sato et al. (25) described a patient presenting with skin lesions characteristic of Behçet disease and positive findings for HLA-B54 and HLA-Cw1, which are frequent in NSD.

Charlson et al. (26) reported a case of dense neutrophilic vasculitis based on a brain biopsy. In that case, HLA-B51, HLA-B54, and HLA-Cw1 were all negative. The patient had been diagnosed with Sweet syndrome months earlier because a skin biopsy of a painful nodular rash over her trunk and neck had demonstrated dense neutrophilic infiltration without evidence of vasculitis. NSD was therefore diagnosed in this patient.

Nofal et al. (5) proposed new diagnostic criteria for Sweet syndrome. They reported that blood vessels in skin lesions with a long duration were likely to develop vasculitis, which has been reported to be a variable feature of Sweet disease.

Mukai et al. (27) reported a case of corticosteroid-

Table 2. Clinical Manifestations Supportive for the Diagnosis of NBD/NSD Spectrum Disorders in Cases That Do Not Fulfill the Criteria for NBD and Probable NSD.

Clinical symptoms	• Episodes of mucocutaneous symptoms including oral aphthae, benign genital ulcers, and pathergy reactions, which were not enough to fulfill the criteria for NBD and probable NSD
	• Corticosteroid-responsive encephalitis, myelitis, or meningitis
	• No response to antibiotics and/or antiviral agents
	• Fever >38°C (for NSD)
Blood examinations	• Neutrophilia, elevated serum CRP level, elevated ESR, and a normal serum procalcitonin level
CSF examinations	• No findings of bacterial infection in cultures
	• No antibodies for meningitis or encephalitis/myelitis-causative viruses
	• Elevation in IL-6 and other related cytokine levels
	• Absence of oligoclonal bands
MRI	• High apparent diffusion coefficient in diffusion-weighted images of the brain indicating edematous lesion
Pathology in the CNS	• Neutrophil-dominant infiltration in brain biopsy
Genetic backgrounds	• HLA-B51, HLA-B54, and/or HLA-Cw1 positive
	• *MEFV* gene mutations

The possibility of other diseases with neurological involvement should be ruled out before the diagnosis of the spectrum disorder, although some immunological diseases could accompany other immunological diseases in the same patient. Differential diagnosis includes multiple sclerosis, neuromyelitis optica spectrum disorder, Hashimoto encephalopathy, bacterial and viral meningitis, antibody-mediated encephalitis/myelitis, neuropsychiatric systemic lupus erythematosus, Sjögren syndrome, neurosarcoidosis, Susac syndrome, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroid, and primary CNS lymphoma.

NBD: neuro-Behçet disease, NSD: neuro-Sweet disease, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, CSF: cerebrospinal fluid, IL: interleukin, HLA: human leukocyte antigen, *MEFV*: Mediterranean fever, MRI: magnetic resonance imaging, CNS: central nervous system

responsive encephalitis presenting with HLA-B54 and HLA-Cw1 without mucocutaneous lesions. The patient was diagnosed with "possible" NSD according to the criteria. In this case, atrophy of the cerebral cortex and brainstem progressed, and persecutory delusions, hyperactivity, incontinence of speech, behavior disorders, collectomania, aggravation, and cognitive disorders appeared gradually, resulting in the need for tube feeding. This course resembled that of chronic progressive NBD (28).

The above reports suggest that there might be other factors besides HLA influencing the prognosis of NBD and NSD.

Spectrum Disorder

In NBD and NSD, the dysregulation of cytokines following the onset of oral bacterial or viral infection may induce abnormal chemotaxis of neutrophils, causing ectopic encephalitis, myelitis, and meningitis (11).

Dermatologic diseases in which neutrophils play a core role in pathogenesis are called "neutrophilic dermatoses". "Neutrophilic disease" is also used as a name for such diseases involving multiple organs. Thus, these conditions with neurological involvement, such as NBD and NSD, have also been referred to as "neuro-neutrophilic disease" (24), and initial treatment targeting neutrophils has been proposed, at least in the early stages of these diseases.

In addition to neutrophils, lymphocytes, such as cytotoxic T cells, T helper 17 cells, and T helper 1 cells, have also been shown to play important roles in these diseases (11, 13). Therefore, the term "neuro-neutrophilic disease" may restrictively indicate only a part of their pathogenesis. Furthermore, the diagnosis of neuro-neutrophilic

disease may require a biopsy to confirm neutrophilic infiltration in the CNS (29, 30).

NBD and NSD seem to constitute part of a spectrum of disorders based on the combination of risk factors. The identity of Behçet disease and Sweet disease as multisystem disorders should be respected, and typical cases with neurological involvement of these diseases should be diagnosed as NBD and NSD, respectively. However, it may sometimes be inappropriate to diagnose cases without typical painful erythematous skin lesions in Sweet disease as "possible" NSD according to the criteria, even if it might be indeed "possible." It may instead be better to diagnose such cases as "spectrum disorders" rather than as "possible" NSD. Cases similar to NBD or NSD without mucocutaneous symptoms or cases presenting with characteristics of both NBD and NSD may thus be diagnosed as spectrum disorders of these diseases.

Clinical manifestations supportive for the diagnosis of NBD/NSD spectrum disorders in cases that do not meet the criteria for NBD and probable NSD are shown in Table 2 (31-33). The examination of polymorphisms in the various genes described above will help diagnose these spectrum disorders in the near future. The possibility of other diseases with neurological involvement should be ruled out before spectrum disorder is diagnosed, although some immunological diseases may accompany other immunological diseases in the same patient.

Understanding these conditions as a disease spectrum may help the elucidate disease pathogenesis and assist in the development of therapeutic agents in the future.

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