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Focus on neuro-Behçet's disease: A review

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Abstract:

Behçet's disease (BD) is a multisystemic vasculitis disorder of almost unknown etiology, which involves small and large vessels and affects both veins and arteries. BD is characterized by recurrent oral aphthae (the main and most recurrent symptoms), genital ulcers, variable skin lesions, arthritis, uveitis, and thrombophlebitis. Other reported symptoms concern the involvement of the gastrointestinal and the central nervous system. Neuro-Behçet's disease (NBD) is one of the main causes of long-term morbidity and mortality, making its prompt recognition and treatment fundamental to attaining a better outcome. As pointed out by Kalra *et al.*, there are definite consensus statements for BD, but less data are available for NBD. A multidisciplinary team of rheumatologists, dermatologists, ophthalmologists, neurologists, cardiovascular surgeons, and gastroenterologists, often led by rheumatologists, participate in the management of patients with BD and NBD.

Key Words:

Differential diagnosis of NDB, neurological involvement in BD, treatment

Key Message:

Behcet's disease causes a widespread vasculitis of arteries or venules of any size which can involve nearly every system and organ. Its neurological manifestations may be due to the occurrence of primary neuro-Behcet's disease, due to the coexistent neurological associations of systemic Behcet's disease (for example, migraine), or due to the side-effects of its immunosuppressive therapy (for example, the development of infections and central nervous system malignancies).

Behçet's disease (BD) is a multisystemic vasculitis disorder of almost unknown etiology, which involves small and large vessels, affects both veins and arteries and is characterized by a non-specific inflammatory process of blood vessels.[1,2] The classical syndrome is characterized by recurrent oral aphthae (the main and the most recurrent symptoms), genital ulcers, variable skin lesions, arthritis, uveitis, and thrombophlebitis. Other reported symptoms concern the involvement of the gastrointestinal and the central nervous system (CNS). Neurological involvement, which is generally labelled as neuro-Behçet's disease (NBD), is one of the main causes of long-term morbidity and mortality in Behçet's syndrome;[3] although it is quite rare, it seems fundamental to recognize NBD and to consider it in the differential diagnoses of inflammatory, infective, and demyelinating CNS diseases.[4]

As pointed out by Kalra *et al.*,[5] there are definite consensus statements for BD.[6,7] There are limited studies concerning NBD, and therefore, there is a strong need for a well-defined criteria. This prompted Kalra and his group to apply the Delphi method, including repeated rounds of communications among a wide expert panel, to report conclusive data on NBD in 2014. Thus, our report is one of the first reports focusing on studying the neurological manifestations of BD,[8,9] that may be co-existent with BD as a primary event *per se* (for example, migraine); may owe its existence to the treatment of BD (i.e., the infectious manifestation of CNS because of immunosuppressive therapies or the development of secondary malignancy in the brain); and, NBD, which is a different entity. This review aims to define NBD and its clinical and pharmacological aspects.

Behçet's disease

The exact pathogenesis of BD is still unclear, but the main histopathological feature is a widespread vasculitis of arteries or venules of any size which can involve nearly every system and organ, such as the gastrointestinal tract, large vessels (veins and/or arteries), heart, and rarely, kidney.

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The frequency of BD and its different clinical manifestations vary significantly from country to country, and several studies are published every year on the topic.

It has been found that the pathology has a distinct geographical distribution along the so-called "Silk Route", from the Mediterranean areas to the Far East, and is more prevalent in Turkey, Iraq, and Israel than in other parts of the globe (UK, Spain, France, and USA). Moreover, even some clinical manifestations show regional differences (for example, gastrointestinal involvement was more frequently described in the Far East, but it is relatively infrequent in Turkey). The prevalence of BD is also known to decrease from South to North.[10-13] The syndrome is usually more frequent in the third decade, whereas the onset is rare in the childhood and over 50 years of age. The disease course is more severe in young patients with involvement of major organs often being seen.[14] Men and women are almost equally affected,[15] even if different male-to-female ratio has been reported from some countries; the disease course, severity, and types of organ involvement vary substantially among patients, depending on their age and sex; the time of onset of BD is associated with a significant morbidity and mortality, particularly in male patients who often have a precocious onset of the disease.[16-18]

A genetic contribution has been found; human leucocytic antigen (HLA)-B5 allele, and, more specifically, HLA-B51, was found to be the most strong genetic factor related to the onset of BD (even if it accounts for less than 20% of cases and other genetic factors remain to be discovered).[19] The prevalence of HLA-B51/B5 varies across the world; data from literature showed that HLA B5 genotype is seen in 40%–65% of patients with BD and in 10%–20% of healthy ethnically matched controls.[20,21] As far as etiopathogenesis is concerned, the etiologic factors of BD remain largely unknown. Several other genes are of potential interest for enhancing the susceptibility for BD: CCR1, KLRC4, IL12A-ASN1, STAT4, MICA-A6, SOCS1, IL10 and IL23R-IL12RB2, IFI16, and AIM2, in addition to miRNA polymorphisms.[22-28]

Regarding neurological involvement, the prevalence of HLA-B51/B5 among patients with NBD is not dissimilar to that found in patients with BD and without neurological signs.

In summary, the epidemiologic findings suggest that the autoimmune process is triggered by an infectious or environmental agent specific for the geographic region. Herpes viruses have also been thought to play a pivotal role in pathogenesis.[29,30] Moreover, there is still no information supporting the hypothetical role of a single microorganism as a specific cause of autoimmune dysregulation.[31]

The main clinical symptoms include firstly the mucocutaneous lesions, particularly oral aphthae that are described in 98% of cases. Painful oral ulcers have been found, either singular or multiple, in the tongue, pharynx, buccal, and labial mucosal membranes. In 60%–65% of cases, genital aphthae are recognized mostly on the scrotum, less frequently on the penis or in the urethra in man, or on the vulva and vagina in women.[32,33] Ocular involvement represents the second most frequent symptom, generally severe, often bilateral. Anterior uveitis, cataract, glaucoma, posterior segment involvement with vasculitis, vitritis, retinitis, panuveitis, retinal edema, cystoid macular degeneration, venous or arterial occlusion, disc edema, and retinal detachment have all been detected.[34,35] Skin involvement affects 38%–99% of patients with BD, and papulo-pustular and acne-like lesions are common.[36,37]

The incidence of cardiovascular features ranges from 7% to 49%; superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, and aneurysms are common and might be included in the diagnostic criteria of BS.[38,39] Cardiac involvement includes pericarditis, myocarditis, endocarditis, mitral valve prolapse, valve lesions, intracardiac thrombosis, endomyocardial fibrosis, myocardiopathy, and coronary artery lesions.[40]

Gastrointestinal symptoms have been described; the whole gastrointestinal tract might be involved but usually ulcers are most common in the terminal ileum. The main symptoms include abdominal pain, vomiting, diarrhea, bloating, or bleeding.[41] Renal involvement is usually transient and less frequent.[42]

Neurological Involvement

NBD is defined by the Consensus Status Agreement[5] as the neurological predominant symptoms of a patient who has suffered or is suffering from all the other systemic symptoms of BD; the neurological symptoms can affect the CNS, the peripheral nervous system, and, be in the form of mixed parenchymal and non-parenchymal disease. NBD occurs in 5%–10% of patients; it usually appears within 5 years after the onset of the disease and is more frequent in men,[43,44] and usually the CNS is more affected than the peripheral nervous system.[9,45]

One of the most intriguing parts of the diagnosis of NBD relies on the strict differentiation of secondary neurological involvement due to BD (as defined in the introduction, meaning therefore, that stroke, cephalgia or cranial pain, or polyneuropathy could be secondary to infections or malignancy induced by BD therapies) from NBD by itself. There are two main phenotypes of NBD: the parenchymal and the non-parenchymal.[10] In CNS involvement, the onset is usually abrupt, and CNS manifestations appear as an attack rather than having a mild progressive course.

The parenchymal involvement is more common (around 80% of cases) and it mainly affects the brainstem and basal ganglia, but spinal cord lesions and hemispheric lesions have also been described. The parenchymal forms of NBD are heterogeneous and manifest clinically by a variety of symptoms and signs that reflect the focal or multifocal involvement of the disease. Headaches, multiple cranial nerve involvement, cerebellar dysfunction, tumor-like lesions, white matter disease, encephalopathies, and myelopathies are frequent clinical manifestations of this form of the disease. Many patients with parenchymal forms of NBD are young and show supratentorial white matter and cortical involvement that may mimic white matter disease, or have ischemic lesions that may lead to the misdiagnoses of multiple sclerosis (MS) or stroke. The most common presentation is related to an inflammatory meningo-encephalitic process, related to an acute-subacute onset, with a mild progressive course. Usually,

parenchymal syndrome comprises the four most affected sites of damage: the brainstem, most frequently, with brainstem signs of neurological involvement, such as ophthalmoparesis, dysphagia, cerebellar, and pyramidal involvement; the diffuse or multifocal presentation, with a worse prognosis, with variable combination of signs and symptoms, determined by territorial involvement (pyramidal, cerebellar, brainstem, or spinal signs could coexist in a single patient); the myelopathic features, determined by an acute myelitis; the cerebral form, which involves a vast part of the hemispheric regions, with consequent neurological signs (i.e., hemiparesis, aphasia, cortical visual loss, or agnosia); psychiatric symptoms including personality changes;[46,47] and, finally, a possible optic neuropathy (thus, the entity has to be differentiated from MS and other central nervous inflammatory diseases). Parenchymal NBD usually maintains a recurrent clinical pattern of presentation, with relapse and remittent phases, even if the progressive course is accepted by clinicians.

Non-parenchymal NBD occurs as a secondary manifestation of vascular lesions. It should be emphasized that non-parenchymal NBD is principally related to the presence of dural sinus thrombosis, intracranial and extracranial aneurysm formation, and arterial vasculitis. Usually, veins are more affected than arteries. Even a stroke has been described in NBD, as expressed by the Consensus Statement. When found, the stroke is pathologically related to atherosclerosis and not to vasculitis. In non-parenchymal NBD, headache and bilateral visual impairment, due to intracranial hypertension, are the more common symptoms. Confusion, weakness, dizziness, and epileptic seizures may also occur.[7] Vertebral artery dissection and middle cerebral artery occlusion have been described.[8] Non-parenchymal involvement is usually monophasic, even if recurrent presentations have been described (but these recurrent manifestations do not occur frequently). These forms are less frequent than the parenchymal forms and occur in 13%–23% of patients with NBD. The venous vascular thrombosis form has a frequent subacute manifestation; it is strongly associated with systemic major vessel disease and appears to manifest earlier in the course of the disease.

Data on pediatric patients with NBD confirmed the well-known geographical distribution of the disease, with a high prevalence being seen in Western Asia and Southern Europe; a prevalence of male cases was seen with a peak incidence of neurological manifestations around puberty. Increased intracranial pressure, headache, papilledema, and possibly diplopia owing to the involvement of intracranial portion of the sixth nerve represent the prevalent clinical presentations of the vascular form of NBD. However, the parenchymal and non-parenchymal forms have been reported almost equally.[48]

Diagnostic Tools for Neuro-Behçet's Disease

The diagnosis of NBD is usually challenging and relies on the rigid exclusion of other neurological conditions that may also present with a similar clinical presentation (such as CNS infections, brain tumors, and neurological involvement due to the administration of immunosuppressive therapies used as a treatment for BD). Moreover, the diagnosis usually relies on supportive criteria, which is based upon on neuroimaging [magnetic resonance imaging (MRI) in particular, but also MR angiography and venography and computed tomography (CT)], cerebrospinal fluid (CSF) findings, serum profiles, pathergy test, HLA determination, neurophysiological examination, and eventually, nervous tissue biopsy.

There are several differential diagnoses. MS may have several neurological manifestations. However, sensory presentation, optic neuritis, internuclear ophthalmoplegia, limb ataxia, and cerebellar dysarthria are more common in MS, rather than headaches, motor symptoms, pseudobulbar speech, and cognitive–behavioral changes that are usually found in NBD. In addition, cerebrovascular diseases, brain tumors, and compressive myelopathy should be considered in the differential diagnosis of NBD.

Magnetic resonance being is the gold standard radiological examination for establishing the diagnosis of NBD. The consensus characteristics of MRI findings of lesions that are characteristic of NBD are different in the parenchymal and non-parenchymal forms. When considering the parenchymal NBD, MRI gives information concerning the nature of the lesions and their time of occurrence, the location, and the dissemination of the lesions. As far as the nature of the lesions is concerned, MRI can distinguish between acute, subcute or chronic brain alterations. In the first case, the lesions are hypo-intense to iso-intense on T1-weighted images, hyper-intense on T2W and FLAIR images, and hyper-intense on diffusion-weighted images with or without a defined restricted apparent diffusion coefficient (ADC); when present, the restricted ADC might represent the vasogenic edema and vasculitic process; when absent or decreased, it is usually related to diffuse to cytotoxic edema, mainly seen in subacute NBD.[5,49-53] In the chronic state of NBD, widespread lesions can be detected, whose size is smaller than those seen in the acute phases. These lesions are non-enhancing and and are relatively non-specific. Quite often, signs of brainstem atrophy may be visible. In the non-parenchymal form of NBD, the MR or CT venography usually confirms the presence of a cerebral sinus or vein thrombosis, or meningeal enhancement; on the other hand, if the non-parenchymal NBD presents with an intracranial hypertension syndrome, the neuro-imaging might be normal.[49,54,55] Clinical findings report that brain perfusion MRI could be a very sensitive method to detect brain involvement in patients with parenchymal NBD, providing direct information related to regional hypoperfusion, in which small vasculitic lesions may be seen.[41,56] Localization of the lesions is the second fundamental diagnostic parameter, which may be visible on neuro-imaging; the brainstem is the favored site of the lesions that is usually seen in NBD; the pons, the midbrain, and the diencephalon may be involved. Cerebral involvement does not give a specific pattern of presentation, but the location is quite characteristic; the lesions are different from that seen in MS as the lesions in NBD are not peri-ventricular. Isolated lesions have been described in the basal ganglia, cerebral hemispheres, and spinal cord, although the involvement of the latter is less common in NBD. Diffusion-weighted imaging may help in the cases presenting with stroke-like episodes, revealing an increase in diffusion coefficient in NBD lesions. The clinical similarity between successive attacks may also be helpful in diagnosing NBD.[5]

In summary, the parenchymal distribution of lesions in NBD appears to support the hypothesis of small-vessel

vasculitis. This pattern of lesion distribution might help to differentiate NBS from other vasculitides and from the inflammatory-demyelinating diseases of the CNS.

For establishing the correct diagnosis of NBD, a lumbar puncture may be helpful. The cerebrospinal fluid constituents may be seen to be altered in around 70%–80% of patients with parenchymal NBD; however, the CSF examination could be normal in the case of non-parenchymal NBD, especially when the pattern of presentation is cranial hypertension or venous thrombosis. The only marker in that case, would be a higher opening pressure seen on lumbar puncture.

In parenchymal NBD, the CSF examination shows a higher level of protein levels, whereas the oligoclonal bands are absent;[7,57,58] pleocytosis (both lymphocytosis and mixed cellularity) is very frequent; and, glucose levels are normal. Increased interleukin (IL)-6 has been described in parenchymal NBD. Some studies tried to detect the possible existence of a triad of parameters: increased IL-6, increased cell count, and elevated protein, as parameters that signify a graver prognosis and an enhanced disease activity.[59-62] The results, however, are often quite contradictory and ambiguous. Therefore, at the present moment, IL-6 is not considered as a reliable marker for establishing the diagnosis or for monitoring the disease activity.

A genetic contribution has been found in BD. The HLA-B5 (HLA-B5-101) was found to be the most strongly associated genetic factor responsible for the development of BD (even this factor accounts for less than 20% of cases and other genetic factors remain to be discovered).[19,20] The prevalence of HLA-B51/B5 among subjects with NBD is often similar to that found in patients with BD without neurological signs. Therefore, its testing does not seem to be charcteristically indicating the diagnosis of NBD.

The presence of pathergy (that is, an exaggerated skin injury occurring after minor trauma such as a bump, bruise, needle stick injury) is one of the most important criteria that is supportive of the presence of BD. If the sign is negative, however, it does not preclude the diagnosis of NBD.

Changes in neurophysiological tests may be indicative of CNS involvement and may also be present as a part of peripheral NBD manifestations. CNS involvement may be studied by electroencephalography that may help in distinguishing NBD from other viral encephalitis; evoked potentials may be helpful in determining optic nerve, brainstem, or spinal cord involvement. For determining the presence of peripheral nervous system involvement, nerve conduction studies and electromyography could be important; however, there are no specific patterns of dysregulation in NBD.[63,64]

Finally, nervous tissue biopsy is not mandatory; in case it is done, the following findings may be found: vasculitis lesions and perivascular infiltration with lymphocytes and neutrophils; and in the tardive stages, axonal loss and gliosis may be found.[65]

Neuro-Behçet's Disease: Differential Diagnosis

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 men.[50] Some symptoms are present in both the conditions, but the frequency of their presentation varies in the two forms, that is, 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 precocious cognitive–behavioral changes are more common in NBD. Brainstem atrophy seen on MRI is very important for establishing the correct diagnosis of NBD, in particular, when its manifestations are precocious and isolated.[49] Lesions of the brainstem that commonly extend to the basal ganglia and diencephalic structures can strongly support the diagnosis of NBD, whereas MS lesions preferentially involve periventricular areas and the corpus callosum. The brainstem lesions in MS are usually very small. There is lack of brainstem and cerebellar atrophy and there is no cerebral loss in MS, which as has already been previously stated, is a typical finding in NBD.[66,67]

Spinal cord involvement is more common in MS and usually involves a few vertebral segments, whereas the lesions are more extensive in NBD.[49,68] The CSF findings might be useful in excluding the presence of MS: unmatched oligoclonal bands are present in a majority of MS patients, but are uncommon in NBD; moreover, cells and neutrophils predominate in NBD, whereas cells are usually scarce in MS and lymphocytes preponderate.[69]

Optic neuropathy is a characteristic manifestation in NBD. This may occur as an isolated symptom representing a systemic manifestation of BD. Optic neuropathy can affect both the optic nerves and may present as a recurrent event for many years. Naturally, the exclusion of other optic neuropathies is relevant: most commonly, those which occur due to the common demyelinating inflammation of the optic nerve associated with MS; or, the rare form of optic nerve demyelination occurring in neuromyelitis optica (NMO, also defined as Devic's disease).

Optic neuritis may be the initial manifestation of MS and typically affects female patients (in contrast to NBS, where male patients are more significantly affected) with the peak age of manifestation being between 30 and 40 years (as also seen in NBS).[70] MRI must be performed to search for other CNS lesions, and CSF must be analysed to distinguish the two diseases. Optic neuritis in MS is generally unilateral, and although it may be recurrent, it is not as periodic as may occur in NBD.

NMO is a severe necrotizing demyelinating disease predominantly affecting the optic nerves and the spinal cord. It is characterized by severe and abrupt vision loss, often bilateral (either simultaneous or sequential). The optic nerve involvement is associated with an extensive spinal gadolinium enhancement on MRI, equal to or greater than three spinal segments; Devic's disease is also characterized by very limited lesions in the brain and has a strong association with other autoimmune/connective tissue diseases; spinal involvement is not a common feature in NBD; the evidence of NMO-IgG antibodies is an exclusive feature of NMO and not of NBD.[71-74]

The second differential diagnosis is related to CNS infections. The easiest to differentiate are the infectious encephalitis, either

isolated to the brain (encephalitis), or, also involving the spinal cord (encephalomyelitis) or the meninges (meningoencephalitis). Headache, an altered mental status, seizures, focal cerebral signs, behavioral changes, and spinal signs can be common manifestations of both the infectious condition and NBD. Continuously monitoring the patient's temperature might help, as the fever is usually high in the presence of infectious diseases, while temperature may be normal or of moderate degree in NBD. The CSF analysis is very useful in distinguishing the two entitites. In infective encephalitis, it shows an increased opening pressure, a decreased (<40 mg/dL in bacterial infections) or normal-to-mildly decreased (viral) CSF glucose level, an elevated (>45 mg/dL, often 100–500 mg/dL in bacterial infections) or mildly elevated CSF protein, 1000–10000 white blood cells/mm^3 (in bacterial infections) or 10–500 white blood cells/mm^3 (in viral infections), with predominantly polymorphonuclear cells (in bacterial infections) or lymphocytes (in viral infections). The CSF may be turbid in bacterial infections or may be clear in viral infections. Specific blood tests may be performed to establish the identity of specific pathogens.

The approach with mycobacterium infections can be very different. *Mycobacteriun tuberculosis* (MBT) can resemble NBD in many ways. Both share the systemic and CNS signs of involvement. The typical pulmonary involvement of MBT is not common in BD, and on the contrary, the mucocutaneous lesions of BD are not typical of MBT. The two principal CNS components of MBT involvement are the meningeal involvement and the presence of intracranial tuberculomas. Neuroimaging helps in both the conditions. MRI shows the typical signs of meningeal enhancement with gadolinium-T1 weighted image revealing basal enhancement with enhancing exudates, and the normal non-contrast scans, showing T1 and T2 shortening after disease progression (indicating the presence of leptomeningitis); in the case of pachymeningitis, hypo-intense, thick plaque-like dura mater lesions can be seen on T1 and T2 weighted images, whereas an intense homogeneous enhancement of the thickened meninges can be seen on gadolinium enhanced -T1 weighted images. Intracranial tuberculomas appear as ring-like lesions, isointense with grey matter and with central hyper-intensity on T1weighted images, isointense with grey matter and with central hypo-intensity on T2 weighted images, with a ring-enhancement pattern on gadolinium-T1 weighted images, with a surrounding area of vasogenic edema. The appearance of tuberculous abscesses are very similar to that of pyogenic abscesses, with abundant surrounding edema. One aspect that might somehow distinguish the MBT abscess is the presence of the characteristic ring, which is slightly thicker than that seen in pyogenic abscesses, surrounding the necrotic center of the lesions. Another characteristic aspect of brain involvement by the MBT is brainstem encephalitis, presenting as multiple confluent tuberculomas of the brainstem and cerebellum. Widespread tuberculous encephalitis usually develops in children and infants, manifesting as lethargy, anxiety, aggressiveness, seizures, and generalised rapid worsening of clinical status: on radiology, it is characterized by diffuse cerebral edema, with features similar to those of acute disseminated encephalomyelitis. Microscopic and pathological examination of the body fluids and tissue specimens, as well as culture and polymerase chain reaction analysis are useful to identify the presence of tuberculous affliction of the brain.[49,75-77]

The other granulomatous (non-caseating) condition which is often considered in the differential diagnosis of NBD is neuro-sarcoidosis (NS). NBD and NS share some common features: the systemic involvement, a possible CNS affliction, and widespread range of signs and symptoms. NS most often affects female patients in the third to fourth decade; it can be the isolated primary form of a systemic sarcoidosis (1%–17% of cases) not previously diagnosed; or, the CNS involvement in the diagnosed case of systemic sarcoidosis may occur.[78-81] The diffuse and widespread granulomas may involve the meninges, pituitary gland, and brain parenchyma, and very rarely, the spinal cord. The most common features of NS are isolated cranial nerve neuropathies, mostly affecting the seventh cranial nerve, chronic meningitis, hypothalamic involvement (primarily diabetes insipidus), and hydrocephalus as a consequence of chronic meningitis.[82] MRI findings are quite characteristic and likely to distinguish between the two entities: although NS may involve meninges and optic and facial nerve just like NBD, it generally causes affliction of the pituitary gland and the hypothalamic region as well as the periventricular area, with the presence of significant T2 white matter lesions and enhancing nodules.

When other systemic features are present, the diagnosis becomes easier: the presentation of uveitis and arthritis in NS may be very similar to that seen in BD but the absence of oral and genital aphthae, and the presence of peripheral lymphadenopathy and bilateral hilar lymph nodes on chest X ray, as well as pathological examination of the non-caseating granulomatous lesions clearly differentiates sarcoidosis from BD. The higher angiotensin converting enzyme (ACE) levels, and increased calcium in blood samples in NS will also help in establishing the differential diagnosis.

The third differential diagnostic of NBD is the autoimmune disease causing primary or secondary CNS vasculitis. Patients with primary vasculitis does not have systemic signs, which are always present in NBD; on the other hand, both NBD and secondary CNS vasculitis have systemic signs.[83,84]

The most frequently encountered diagnostic differential diagnoses that needs to be considered with NBD are Cogan's syndrome, Susac's syndrome, neuro-Sweet syndrome, and less frequently, Eale's syndrome and Vogt–Harada syndrome. Cerebral angiography has been reported to be abnormal in up to 90% of CNS vasculitides, and MRI has usually shown multiple infarcts that have mostly involved the cortical areas as well;[85] the angiographic findings are usually normal in NBD.

Cogan's syndrome is quite similar with NBD with regard to the widespread dissemination of its manifestations within the body, but it is characterized by interstitial keratitis and uveitis and inner ear inflammation.[86,87]

Susac's syndrome, which can present with neurological manifestations, is an autoimmune endotheliopathy that causes small infarcts in the retina, cochlea, and brain, thus resulting in the clinical triad of retinopathy, hearing loss, and encephalopathy.[88,89]

Neuro-Sweet syndrome has the rare CNS involvement; Sweet's syndrome is an idiopathic multisystem inflammatory disorder characterized by tender, red, well-demarcated papules and plaques that show dense infiltrates by neutrophil granulocytes on histologic examination; fever, and elevated white blood cell count may also be present. The ocular signs are episcleritis and conjunctivitis, in contrast to panuveitis that is present in NBD. An association of HLA-CW1 and B54 has been reported in Sweet's syndrome in comparison with a high frequency association of HLA-B51 in NBD.

Eale's disease is a syndrome characterized by retinal perivasculitis and recurrent intraocular hemorrhages, which is infrequently associated with neurologic abnormalities but must be considered in the differential diagnosis of those cases with BD with an ocular involvement.[90-92]

The Vogt–Koyanagi–Harada's syndrome is a rare granulomatous inflammatory disease that affects pigmented structures, such as the eye, inner ear, meninges, skin, and hair. The acute uveitic stage is characterized by a diffuse choroiditis with serous retinal detachment and optic disc hyperemia and edema; all these ocular symptoms can become chronic, and the symptom complex can extend to meningeal irritation and occasional encephalopathy with cerebrospinal fluid (CSF) pleocytosis.[93]

Other systemic inflammatory conditions, such as the uveo-meningitic syndromes including lupus erythematosus and Sjogren's syndrome, which share some common aspects with BD, may also be considered in the differential diagnosis. Occasionally, primary CNS lymphoma can present with uveal alteration and diencephalic involvement.[94] The MRI findings, CSF analysis, and the eventual steroid response may help in distinguishing the conditions.

Interestingly, the peripheral nervous system is more often involved in primary and secondary vasculitis than in NBD.[5]

Finally, it is relevant to express this statement: acute parenchymal form of NBD can simulate acute stroke-like manifestation. Patients with BD may also exhibit a higher risk of vascular stroke, the etiology of which remains debatable.[95] Rarely, non-parenchymal NBD can manifest as acute ischemic stroke, as a consequence of arterial dissection or aneurysm formation. 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 infarction.[96,97]

Diagnostic Criteria

There are no definite diagnostic criteria for NBD. Only the International Consensus Recommendation criteria (ICR) have been developed for establishing the diagnosis of NBD.[5] The ICR suggested two forms of clinical NBD: the definite and the probable.

For the diagnosis of definite NBD, the patient should satisfy the three International Study Group (ISG) criteria: they should present with neurological signs and symptoms (parenchymal and non-parenchymal) caused by BD; these manifestations should not better explained in any other way; and, the clinical presentation should be supported by neuroimaging and laboratory examinations.

The diagnosis of probable NBD rests on the presence of one of the two following criteria: the presence of a neurological syndrome with systemic BD features, not completely satisfying the ISG criteria; or, on the other hand, the evidence of a non-characteristic neurological syndrome, but inside a definite BD diagnosis, supported by complete fulfillment of the ISG criteria.

Due to the immense importance of correctly identifying the presence of NBD, we report a brief mention of the ISG criteria, whose fulfillment is a pre-requisite for establishing its correct diagnosis.

Usually, the diagnosis of BD is only supported by clinical criteria that require the exclusion of other diagnoses based on clinical presentation. The most important and popular diagnostic criteria were created in 1990 by the ISG.[72]

The ISG criteria comprise five items, two of which are mucous membrane manifestations; following these criteria, diagnosis could be made on the presence of oral aphthous ulcerations, and two of the other clinical manifestations, including recurrent genital ulcerations, skin lesions, such as erythema nodosum-like lesions, papulopustular lesions, ocular involvement, and positive pathergy test. The ISG criteria were based on the most common presenting symptoms of the disease, namely, the mucocutaneous features (recurrent oral aphthous ulcerations and genital ulcerations being the most common). The sensitivity of the ISG criteria, however, in the detection of the BD is low.

After the ISG, other classification systems have been investigated, and in 2006, the new International Criteria for Behçet's Disease (ICBD) was established.[98]

Following the introduction of the new classification, the ISG criteria were improved upon with the introduction of the vascular manifestations. The vascular impairment was defined as superficial phlebitis, deep vein/arterial thrombosis, large vein thrombosis, and aneurysm formation. Similar to the ISG criteria, in the ICBD criteria, different values were attributed to different disease manifestations (for example, genital aphthous lesions and eye lesions were scored as 2, whereas the oral aphthous lesions, skin lesions, vascular manifestations and pathergy phenomenon were scored as 1 each, respectively. The diagnosis of BD was made when a score of ≥ 3 was present.

Data from literature revealed that the ICBD criteria exhibited a higher sensitivity, specificity, and accuracy than the ISG criteria. Moreover, according to the new criteria, oral aphthae are no longer considered as a mandatory diagnostic clinical manifestation of BD.

In 2014, the International Team for the Revision of the International Criteria for BD proposed new classification based on the analysis of more than 2500 BD patients. From the revision, it emerged that ocular lesions, oral aphthae,

and genital aphthae are each assigned 2 points, whereas skin lesions, CNS involvement, and vascular manifestations are assigned 1 point each. The pathergy test, when used, was assigned 1 point. The score ≥4 points represents BD.[99]

Treatment

At the onset, it must be stated that there have been no controlled trials that have determined the optimum therapeutic management of NBD.[5,100]

The main goal of any therapy in patients with NBD is to control symptoms and to improve the patients' quality of life. The choice of treatment is generally based on the clinical presentation and the site affected. The treatment of acute NBD includes high-dose intravenous methylprednisolone pulses for 7–10 days, followed by the gradual tapering of the oral doses over 3–6 months, depending on the severity of the relapse. Good results have been reported with this treatment in brainstem lesions and in the parenchymal form of NBD.[9]

A long-term anti-inflammatory treatment has been administered with traditional immunosuppressive agents, such as azathioprine, salazopyrine, and other 5-aminosalicylic acid derivatives,[101] as well as with cyclosporine, for treating the ocular manifestations of BD.

Biological therapy and monoclonal antibody therapy have been extensively studied; among these treatments, the tumor necrosis factor α inhibitors such as infliximab, etanercept, and adalimumab have shown beneficial effects. Infliximab has been particularly used in the management of refractory uveoretinitis, entero-Behçet's disease, neuro-Behçet's disease, vascular BD, and arthritis. The main effect of the drug is to induce prompt suppression of ocular inflammation, reducing the attacks of uveitis and allowing the moderate use of corticosteroid therapy. The usually dose is 5 mg/kg every 6–8 weeks. The combination of infliximab with other agents such azathioprine or cyclosporine A (CsA) or methotrexate (MTX) appears to be superior to infliximab alone. The side effects include pyomyositis, perianal abscess, and non-Hodgkin's lymphoma. Positive results have been reported in entero- Behçet treatment and arthritis associated with BD.[102,103]

In NBD, infliximab was especially used for the treatment of parenchymal forms of the disease, and the results have been favorable in terms of clinical remission and regression of parenchymal lesions on MRI; the dose most commonly used has been 3–5 mg/kg administered at 0, 2, and 6 weeks and then repeated every 6–8 weeks.

In the same way, adalimumab has been found to be effective in uveitis and to have a corticosteroid-sparing effect. Adalimumab has also been found to be beneficial in treating recalcitrant leg and genital ulcers, steroid-dependent ileocolitis, and cerebral vasculitis. Moreover, the drug has been effective in maintaining disease remission.

Treatment with two doses of rituximab 1 g/dose given 15 days apart, significantly improved ophthalmic vasculitis and visual acuity in 6 week's time with no relapse occurring after the steroid-tapering period. More data are needed to understand the efficacy of rituximab for the management of other BD symptoms.

Other biological factors, such as interleukin 1β (Il-1β) inhibition and IL-6 inhibition, have been tested for their response in the treatment of different manifestations of BD, but their routine use in clinical practice still needs more studies for confirmation. The efficacy of interferon alpha (IFNα) used in the treatment of mucocutaneous, articular, and ocular manifestations has also been mentioned . Treatment with IFNα significantly reduced the duration and pain of oral and genital ulcers. It also reduced the severity and rate of recurrence of attacks of the eye manifestations. Its beneficial role in parenchymal neurological involvement is still unclear.

Nonsteroidal anti-inflammatory drugs are mainly used to control pain.[85] For the treatment of mucocutaneous manifestations, Colchicine has been extensively studied. Colchicine improves arthralgia and erythema nodosum, and moreover, has been shown to reduce the recurrence of genital and oral ulcers.

Anti-tumor necrosis factor (TNF) and thalidomide may be beneficial in refractory cases. Immunosuppressive treatment, including azathioprine and infliximab, seems to be essential to avoid further relapses.

Recommendations

In Delphi Consensus, 10 recommendations have been proposed.[5]

Briefly, they may be summed up in the following way:

1. There are two main types of NBD, defined as parenchymal and non-parenchymal, with specific radiological, laboratory, and prognostic features
2. NBD should be taken into consideration as a differential diagnosis of MS, intracranial hypertension, meningo- or myelo-encephalitis, and stroke when young people are affected
3. Erythrocyte sedimentation rate, C-reactive protein, cytokines, and other inflammatory markers are not specific or sensitive enough for the diagnosis of NBD
4. There are specific sequences and neuroimaging findings, especially on MRI that define NBD well
5. The CSF examination might help in the diagnosis of NBD and can especially help in its differential diagnosis
6. CSF-interleukin (IL) 6, at the current moment, is not suggested as a diagnostic NBD marker; rather, it is regarded as an indicator for monitoring of the disease
7. Pathergy test is a valid supportive measure, not a marker that can exclude the presence of NBD (a negative pathergy test will not exclude the presence of NBD)
8. There is not a specific HLA haplotype directly involved in establishing the diagnosis of NBD; the presence of HLA-B5 or B51 serves as a supportive marker for the diagnosis of BD
9. Neurophysiology can help to differentiate or support the clinical findings; it should not be used as a diagnostic criteria for NBD
10. Nervous tissue biopsy could be considered, but it is not recommended for the diagnosis of NBD.

Conclusion

In summary, NBD occurs worldwide and may cause a high degree of morbidity and mortality. Prompt recognition and aggressive therapies are required especially in NBD; early diagnosis of NBD helps to initiate appropriate treatment, thereby modulating the course of the disease and in preventing complications.

A multidisciplinary patient care is essential for the diagnosis and management of multisystem diseases. It provides several benefits to clinicians and patients. A multidisciplinary team of rheumatologists, dermatologists, ophthalmologists, neurologists, cardiovascular surgeons, and gastroenterologists, often led by rheumatologists, takes part in the management of patients with BS and NBD.

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Conflicts of interest
There are no conflicts of interest.

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