

Neuro-Behçet's disease, its mimickers and anti-TNF therapy: a case-based review

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ABSTRACT

When the central nervous system is the primary affected site in an initial attack of Behçet's disease (BD), the differential diagnosis is particularly challenging. Because the specificity of immunobiologic therapy is growing, the specific diagnosis may impact the chosen therapy. For instance, anti-tumour necrosis factor agents are efficacious in BD but may be harmful in multiple sclerosis or systemic lupus erythematosus. We present two cases with similar neurological features but different diagnosis (BD and systemic lupus erythematosus) as a starting point to review diagnostic and therapeutic approaches for neuro-BD and its differential diagnoses.

Introduction

This review begins with the report of two cases, which appeared at the same time at the internal medicine service of a university hospital.

Case 1. A 22-year-old woman with recurrent orogenital ulcerations and severe bilateral panuveitis received the diagnosis of Behçet's disease (BD) at the rheumatology outpatient clinic. Prednisone 30 mg/day and cyclosporine 3 mg/kg/day were started, but there were recurrent uveitis attacks and, a few months later, she developed severe bilateral pyramidal signs (spastic tetraparesis). Magnetic resonance imaging (MRI) revealed a T2 hyperintense lesion in brainstem. Cerebrospinal fluid (CSF) analysis revealed mild lymphomononuclear pleocytosis (16 cells/mm³) and microorganisms were not identified. Antinuclear and anti-aquaporin-4 antibodies were absent. Neuro-BD was diagnosed and monthly pulse cyclophosphamide was started along with prednisone 60 mg/day. Six months later, she had worsened neuro-

logical signs, with paraplegia and urinary incontinence. A new MRI revealed T2 hyperintense lesions in brainstem and spinal cord, with longitudinally extensive myelitis (Fig. 1). At this point, infliximab, an anti-TNF (tumour necrosis factor) agent, was started at 5 mg/kg each 8 weeks. After six months, she was able to walk without aid and recovered urinary sphincter function. Prednisone was tapered until 5 mg/day without relapse of disease.

Case 2. A 44-year-old woman presented to the emergency service with sudden spastic paraplegia and loss of control of urinary sphincter. MRI revealed a longitudinally extensive myelitis (Fig. 2) and CSF analysis revealed only mild lymphomononuclear pleocytosis (18 cells/mm³) and slightly raised protein levels (49 mg/dl). When specifically asked, she reported recurrent oral ulcers and painful leg lesions resembling erythema nodosum (not observed at the physical examination). Influenced by the recent experience of the case 1 (described above), the medical team suggested neuro-BD as a possible diagnosis and anti-TNF treatment was considered as a therapeutic option for this patient. However, the patient had positive antinuclear antibodies (1:1280 titer, cytoplasmic pattern) and mild lymphopenia (900 cells/mm³). Anti-aquaporin-4 antibodies were absent. Serologic and polymerase chain reaction tests for herpesviruses and HIV were negative. Therapy with intravenous methylprednisolone 1g/day during three days followed by prednisone 60 mg/day was started. Anti-TNF treatment was postponed, to be considered only if a refractory neuro-BD could be truly defined in the follow-up. Two weeks later, the neurological signs improved, but proteinuria appeared in urine examination, with progressive worsening to achieve 2.5 g/day, and antidiolipin

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antibodies were also observed. Systemic lupus erythematosus (SLE) was diagnosed and azathioprine was added to the treatment. The anti-TNF idea was completely discarded and, six months later, she had no neurological complaints and only mild proteinuria (400 mg/day) was present. After this experience, the medical team wondered if the inadvertent use of an anti-TNF agent in this neuro-SLE case would have been harmful and how to improve our diagnostic competence on neuro-BD and its mimickers. This preoccupation is justified in a moment when a trend for more intensive treatment is observed in the management of BD (1).

BD is a relapsing inflammatory disorder of unknown origin, and its diagnosis is solely based on clinical data due to the lack of specific diagnostic tests. The diagnostic criteria are defined by the presence of recurrent oral ulceration in combination with two of the following symptoms: genital ulceration, ocular lesions, typical skin lesions and a positive pathergy test (2). More severe cases potentially lead to vascular, gastrointestinal or neurological disease (neuro-BD). A diagnosis of neuro-BD can be made if there is central nervous system (CNS) involvement and BD diagnostic criteria are fulfilled. However, certain patients (particularly at disease onset) may present with prominent CNS involvement and few mucocutaneous features, hindering diagnosis. Alternatively, it is noteworthy that the prevalence of recurrent aphthous stomatitis (RAS) is 1.5% in adolescents and 0.85% in adults (3). Thus, oral ulcers alone are not a reliable marker of BD in patients with CNS involvement.

Hence, if the CNS is the primary affected site in BD onset, the differential diagnosis with other causes of CNS inflammation can be particularly challenging. Because the specificity of immunobiologic therapy has grown in recent years, the specific diagnosis may impact the chosen therapy. For instance, anti-tumour necrosis factor (anti-TNF) agents are clearly efficacious for neuro-Behçet's disease (4); however, these treatments may be harmful in multiple sclerosis (MS) (5), systemic lupus erythematosus (SLE) (6) or neu-

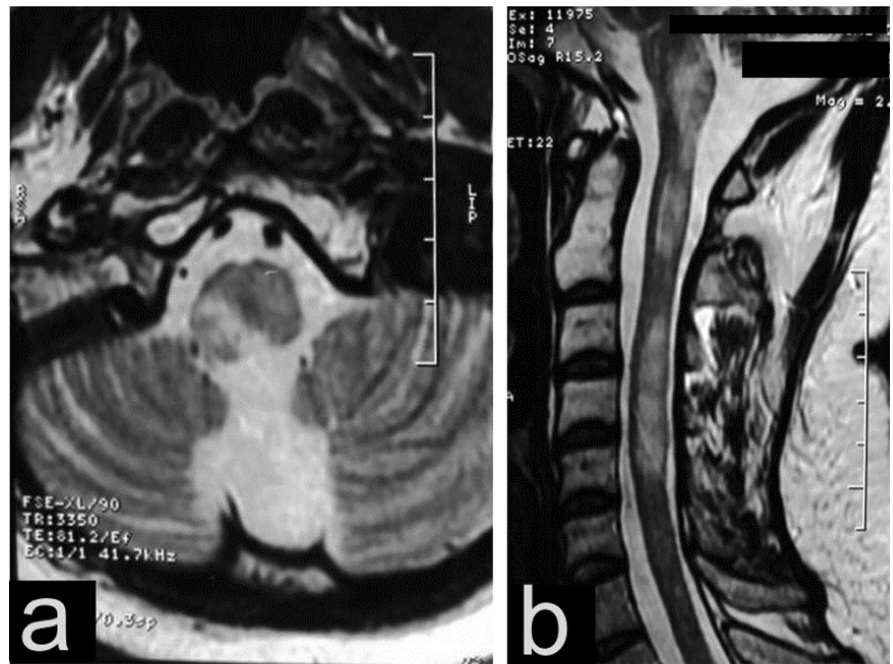


Fig. 1. a. Axial FLAIR MRI image of a 22-year-old female patient (case 1) with recurrent orogenital ulcerations, uveitis and severe bilateral pyramidal signs revealing hyperintense lesion involving brainstem (pons); b. sagittal T2 MRI image of the same patient revealing multiple hyperintense lesions in brainstem and cervical spinal cord. In this case neuro-Behçet's disease was clearly defined according to diagnostic criteria. Despite intensive immunosuppressive treatment with cyclophosphamide and glucocorticoids, there were recurrent attacks. Clinical improvement was finally obtained after 3 doses of infliximab 5 mg/kg.

rotuberculosis (7). Thus, the purpose of this manuscript is to review the diagnostic and therapeutic approaches for clinicians dealing with cases in which BD may be suspected, but in which CNS involvement prevails over other disease features.

Behçet's disease (BD)

The largest neuro-BD case series (n=200) was published in Turkey by Akman-Demir *et al.* in 1999 (8). Several smaller series of neuro-BD or BD cases have corroborated their findings (9-11). The mean age at the onset of neurologic disease was 31 years (5 years following the observed onset of mucocutaneous features). Apparently, only a minority of patients exhibited neurological features without evident systemic disease: fifteen cases (8%) exhibited a neurological onset concomitant with BD onset, and 6 cases (3%) exhibited neurological disease prior to the occurrence of other BD features. However, these numbers may be higher: the authors reported that more cases of neuro-BD may have occurred but were not considered, because cases

that did not fulfill the diagnostic criteria were not included in their series (8).

Neuro-BD primarily affects the brainstem (51% of cases). In the typical case, the mesodiencephalic junction is the origin of the lesion, which may extend anteriorly to the basal ganglia or posteriorly to the mesencephalon and pons. The mesodiencephalic junction is particularly vulnerable because BD is a vasculitis with a predilection for the venous system, and the venous drainage in this region is less efficient than in the cerebral hemispheres (12). Hemispheric and spinal involvements are observed in 16% and 14% of cases, respectively. In many cases, multiple CNS regions are affected (*e.g.* brainstem plus hemispherical, 30% of cases; brainstem plus spinal cord, 8% of cases). Pathologically, perivenular meningoencephalitis is observed, consisting of low-grade neutrophilic and lymphocytic infiltration with multifocal necrotic foci. Magnetic resonance imaging (MRI) is the method of choice for the assessment of parenchymal disease (8).

Patients with neuro-BD frequently present acutely (within 2 or 3 days of on-



Fig. 2. Sagittal T2 MRI of a 44-year-old female patient presenting longitudinally extensive myelitis (case 2). She had recurrent oral ulcers, thus neuro-BD and anti-TNF treatment was suggested. However, she had positive ANA and persistent lymphopenia. A few weeks later, despite methylprednisolone intravenous therapy 1g/day during three days followed by prednisone 60 mg/day, she developed proteinuria and anticardiolipin antibodies were also observed, defining systemic lupus erythematosus. There was improvement of neurologic findings with corticosteroid therapy alone, but azathioprine was needed due to renal disease. These imaging findings can be very similar to neuro-Behçet's disease (Fig. 1).

set) with symptoms that are related to brainstem dysfunction such as ophthalmoplegia, bilateral pyramidal symptoms and subcortical symptoms (behavioural changes). Headache is common, fever is reported in 19% of cases and meningeal signs are observed in 8% of cases. Cortical signs such as seizures or aphasia are rare. Nearly 40% of patients exhibit progressive disease with recurrent attacks. Disability occurs in 25% of patients, and the three-year mortality is near 20% (8).

The most typical imaging result in neuro-BD is a large single lesion involving the diencephalon and the brainstem (Fig. 3). A subset of patients exhibits multiple scattered lesions in this same location. The cerebrospinal fluid in neuro-BD is normal in 40% of cases. In cases where changes are observed

in the CSF, mild pleocytosis (median neutrophil count of 10 cells per mm^3 ; median lymphocyte count of 30 per mm^3) and mildly elevated protein levels (median 60 mg/dl) are observed. Oligoclonal bands are observed in 16% of cases (8).

The diagnosis of neuro-BD must be hypothesised when typical brainstem-diencephalic lesions (also known as rhombencephalitis) are observed (Fig. 3), even when systemic disease is not evident. If infections or neoplastic causes are ruled out (see below), immunosuppressive treatment (including anti-TNF agents in cases of refractory disease) may be considered, even if the diagnostic criteria for BD are not fulfilled (of note, in Brazil, 36% of BD patients presented no ocular involvement, and the pathergy test was

positive only in 24% of BD patients) (13), because rhombencephalitis is not a typical feature of other autoimmune diseases in which anti-TNF may be harmful, as MS or SLE.

In contrast, 15% of neuro-BD patients exhibit hemispheric involvement, with scattered small white matter lesions, some of which are periventricular (MS-like). Moreover, 14% of neuro-BD cases present with pure spinal cord involvement (8). Hemispheric and spinal cord lesions in neuro-BD may be quite similar to those observed in MS and SLE. In these cases, if the BD diagnostic criteria are not fulfilled, anti-TNF agents are not a safe therapeutic option, because they may exacerbate the symptoms of MS and SLE.

In the following sections, we discuss the differential diagnosis of “typical” (mesodiencephalic region and brainstem) and “atypical” neuro-BD (hemispheric and spinal cord disease) and the appropriate therapeutic options.

Causes of mesodiencephalic lesions and rhombencephalitis other than neuro-BD: an important role for empiric antimicrobial therapies and possibly biopsy procedures before aggressive immunosuppressive treatment

Listeriosis

Listeria monocytogenes is a common cause of CNS infection and listerial rhombencephalitis is more frequently observed in previously healthy young adults (14). Following a prodromic phase of approximately four days, with headache, fever, nausea and vomiting, there is an abrupt onset of cranial nerves deficiencies (6th, 7th, 9th, 10th and 11th), pyramidal and cerebellar symptoms and an impairment of consciousness. The syndrome progresses rapidly and may be fatal, with an overall mortality rate of 51% (15). The CSF often exhibits mild pleocytosis with lymphocyte predominance. CSF and blood sample cultures are positive for only 41% and 61% of cases, respectively. Therefore, negative cultures are not sufficient to rule out its diagnosis (16). MRI features of *Listeria monocytogenes* infection consist of subcortical abscesses in the thalamus, pons and medulla. Early treatment with am-

picillin is crucial to improve prognosis, and certain authors suggest that dexamethasone may be useful as an adjunctive therapy due to this medication's anti-inflammatory activity, reducing neurologic sequelae (17).

Thus, a patient with listerial rhombencephalitis may exhibit clinical, laboratory and imaging features that are very similar to neuro-BD, *i.e.* brainstem symptoms with T2 hyperintense MRI lesions and mild, non-specific CSF abnormalities. Because negative cultures cannot reliably rule out CNS listeriosis, we suggest that empirical ampicillin therapy and corticosteroid therapy should be considered in patients with acute mesodiencephalic lesions that resemble an initial neuro-BD attack.

Herpes simplex virus (HSV)

Although relatively rare (1 case in 250,000 to 500,000 individuals annually) (18), HSV encephalitis is the most common form of viral encephalitis in immunocompetent adults. The diagnosis of this infection is of great importance, given that specific therapy with acyclovir is efficacious and life-saving. If untreated, the mortality rate is approximately 70% (19). The classical pathologic lesions of HSV encephalitis are located in the temporal lobes; however, in nearly half of cases, these lesions may be concentrated in the brainstem (20). Hence, clinical and imaging findings in HSV encephalitis may be similar to those of neuro-BD. Also, caution must be taken before ruling out HSV encephalitis based solely on a negative polymerase chain-reaction (PCR) test. Advanced stage of disease (with insufficient number of genome copies in the CSF) or worldwide variations in the virus genome (precluding its detection by standardised primers) are common reasons for false-negative results (21).

We suggest that empiric acyclovir therapy also should be considered if a first attack of mesodiencephalic neuro-BD is suspected, given that HSV encephalitis is a treatable mimicker (remarkably, HSV infection also causes oral and genital ulcerations). It should be noted that other viruses may also induce rhombencephalitis (enterovirus

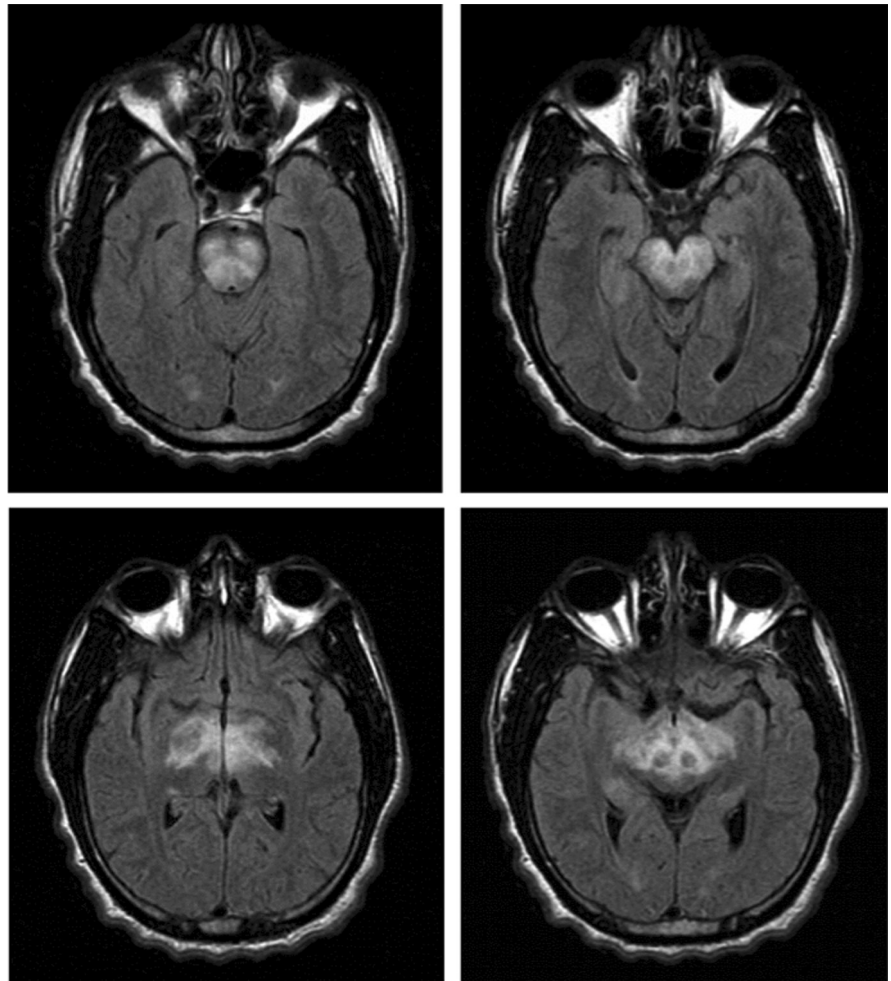


Fig. 3. Axial FLAIR MRI images showing typical neuro-Beçet's disease lesions involving mesodiencephalic junction bilaterally. Besides Beçet's disease, infectious causes of rhombencephalitis should be included in the differential diagnosis (mainly listeriosis, herpesviruses and tuberculosis) and brainstem glioma must also be considered.

71 was the cause of a rhombencephalitis outbreak in Asia) (20); however, these other viral causes have no specific treatments.

Tuberculosis (TB)

Neuro-TB causes a thickening of the basal meninges and may affect the cranial nerves, leading to ophthalmoplegia (22). Granulomas may concentrate in the brainstem, diencephalon and the basal ganglia, where infarctions may also appear due to small vessel vasculitis (23). Headache, fever and neck stiffness are common. The disease process occurs over a few days or weeks and is lethal if untreated (22). The clinical and imaging findings of neuro-TB may resemble neuro-BD (Fig. 4). Another confounder to remember is that uveitis may also occur in tuberculosis.

Two major features aid the clinician in the identification of neuro-TB: the presence of *Mycobacterium tuberculosis*, and the risk factors for tuberculosis. In adults, neuro-TB is common among immunosuppressed individuals (particularly HIV-infected patients, but also with alcoholism, malignancy, diabetes mellitus, corticosteroid or anti-TNF agent treatment) (24). CSF analysis is important for diagnosis; however, there are serious limitations. CSF cell count and protein parameters do not differ from those observed in neuro-BD. It has been reported that *M. tuberculosis* can be isolated by CSF culture in as many as 80% of neuro-TB cases (24). This diagnostic technique, however, requires the analysis of large volumes of CSF obtained in repeated punctures and cannot aid in the initial treatment

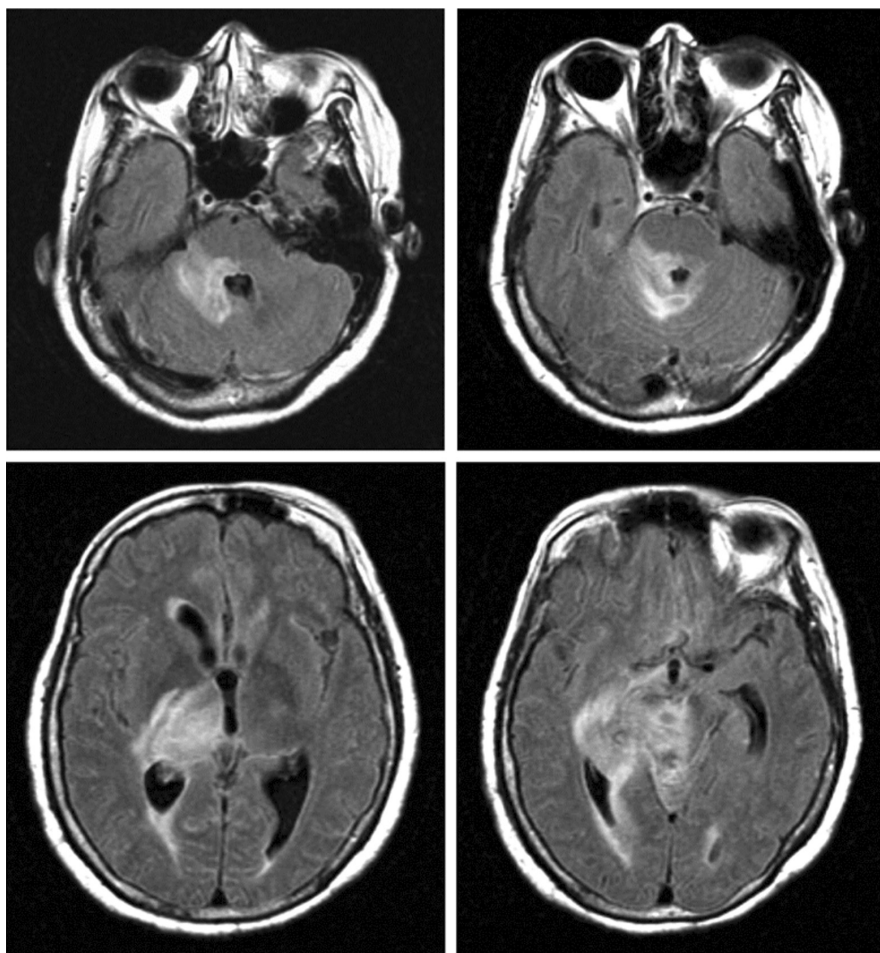


Fig. 4. Axial FLAIR MRI images showing CNS lesions involving brainstem and mesodiencephalic junction in a case of neurotuberculosis, confirmed by the finding of *M. tuberculosis* in cerebrospinal fluid cultures. These imaging findings are very similar to neuro-Beçet's disease (Fig. 3).

decisions, because results may take several weeks. PCR analysis for the presence of *M. tuberculosis* is useful for more rapid results; however, the sensitivity of this test is only 56% (with a specificity of 98%) (25). Therefore, the diagnostic procedures for assessing the presence of *M. tuberculosis* can definitively diagnose the disease when positive; however, negative results cannot rule out an infection. Screening for pulmonary disease is an important aid in diagnosis: in one series, nearly 90% of cases of tuberculous meningitis have alterations in thoracic computed tomography (26), which is not a feature of BD. A sputum culture, bronchoalveolar lavage or a biopsy of accessible tissue may be performed to improve the diagnostic sensitivity.

A confounding factor with respect to neuro-TB is that, in addition to tuberculostatics, high doses of corticoster-

oids are used to treat this infection. By ameliorating the CNS inflammatory process, corticosteroids reduce the risk of disability and mortality in neuro-TB (24). Thus, if corticosteroids are prescribed for a patient with neuro-TB that is mistakenly diagnosed as an autoimmune disease, a clinical improvement will occur in the next days, and the degree of pleocytosis and protein levels in CSF may even be reduced. This treatment may give the clinician a false confidence in his/her incorrect diagnosis. Glucose is a useful CSF parameter in this scenario. Very low CSF glucose levels are uncommon in autoimmune diseases, whereas the ratio CSF glucose/serum glucose is less than 0.5 in 95% of neuro-TB cases (24). If glucose CSF levels continue to decline after steroids are given, neuro-TB should be strongly considered.

Because all of the available methods

that are used to detect *M. tuberculosis* have low sensitivity, the threshold for the empiric treatment for neuro-TB must be low, particularly in countries with high TB prevalence, HIV-infected patients, immunosuppressed patients or individuals who use anti-TNF agents (24). It is particularly difficult to impose this empiric treatment due to its long duration (nine months in Brazilian protocols); however, it is clear that, unless neuro-TB has been convincingly excluded, anti-TNF agents should not be used.

Sarcoidosis

Sarcoidosis is the perfect mimicker of TB and may imitate neuro-BD in certain cases. CNS involvement occurs as parenchymal focal lesions in any location, but the basal cerebral region is commonly affected; granulomatous lesions appear as hyperintense T2 signals, predominantly in the diencephalon (e.g. the hypothalamus and pituitary gland) (27). The involvement of the cranial nerves occurs in up to 75% of cases (27) and imitates the brainstem symptoms of neuro-BD. Unlike neuro-BD, cortical lesions are common in sarcoidosis (28). The CSF is normal in one third of neurosarcoidosis patients and, when altered, exhibits the same mild pleocytosis and protein levels that are observed in BD cases. Oligoclonal bands are also reported in certain cases (29). As in TB: uveitis may be observed in sarcoidosis patients resembling BD, but sarcoidosis patients often present with subclinical pulmonary involvement, which is not a feature of BD. Thoracic high resolution computed tomography (CT) might reveal lung or lymph node disease that is accessible to biopsy. In cases with normal CT findings, whole-body gallium scanning or fluorodeoxyglucose positron emission tomography (FDG-PET) may be used to search for sites of occult inflammation. Fortunately, the distinction between sarcoidosis and neuro-BD is less critical with respect to the therapeutic options. Current therapies that are employed in BD are also useful for sarcoidosis, including anti-TNF agents, which also have been used for refractory neurosarcoidosis (28).

Brainstem glioma

Brainstem tumours are rare occurrences in adults. Most of them are gliomas (30). The median duration of symptoms was 4 months in the largest series, although sudden onset of symptoms may occur, due to intratumoural haemorrhage (31). The main symptoms are gait disturbance due to ataxia or lower limbs weakness, followed by diplopia, difficulty in swallowing and facial paresis, due to cranial nerves involvement. The most common location of tumours are the pons (60%), followed by medulla (25%) (31). Four imaging patterns were described in MRI: (a) diffuse intrinsic low-grade glioma, (b) enhancing malignant glioma, (c) focal tectal glioma, and (d) exophytic glioma (30). In the first pattern, a diffuse infiltrative pontomedullary lesion without contrast enhancement is seen. According Reyes-Botero *et al.* (30) and Guillamo *et al.* (31), in this case a biopsy procedure may be avoided, if the clinical picture is compatible with the diagnosis of glioma, due to the high specificity of this pattern. However, the other patterns (b-d) are due to a contrast enhancement lesion that may be indistinguishable from tuberculosis or BD lesions. Thus, a biopsy is necessary to confirm the diagnosis of glioma in these cases (31). Anti-TNF agents are contraindicated in the presence of neoplastic diseases. Thus, in the case of an isolated contrast-enhancing lesion in brainstem, if systemic features of BD are not clearly evident, we suggest that anti-TNF therapy should be avoided until a biopsy procedure accordingly investigates the possibility of glioma.

Causes of spinal cord or diffuse hemispheric lesions, other than neuro-BD, that should be considered prior to beginning anti-TNF agents: an important role for the careful assessment of other autoimmune diseases

Multiple sclerosis (MS)

MS is the most common primary inflammatory disorder of the CNS and is characterised by demyelination. The disease commonly causes recurrent episodes of localised inflammation involving CNS white matter, leading to

multifocal demyelination over time. The typical features of MS are CNS lesions that are “disseminated in space and time” in the absence of any systemic disease that is capable of producing similar findings. Therefore, MS is diagnosed when a patient suffers from two or more attacks, which are defined by objective abnormalities on neurologic examination and two or more separated lesions. The criteria for diagnosing MS define MRI as the method of choice to provide evidence for the spatiotemporal dissemination of the lesions and to aid in reaching an earlier diagnosis. Spatial dissemination can be demonstrated on MRI, if there are T2 hyperintense lesions in at least 2 of the following CNS areas: periventricular, juxtacortical, infratentorial or in the spinal cord. MRI defines dissemination in time if a new gadolinium-enhancing lesion or a new T2 hyperintense lesion is detected on a follow-up MRI relative to a baseline scan, or there is simultaneous presence of gadolinium-enhancing and nonenhancing lesions at any time (32).

It is noteworthy that certain authors perceive the spatiotemporal dissemination criteria as potentially prognostic of subsequent disease activity (*i.e.* providing the probability of a subsequent relapse) rather than diagnostic criteria (*i.e.* differentiating MS from other diseases) (33). The specificity of MS diagnosis in MRI criteria must rely primarily on the location and extension of lesions. For instance, patients with three periventricular lesions have an odds ratio of 13.8 for MS diagnosis against other neurological diseases. Those patients with one juxtacortical lesion have an odds ratio 6.9 and those with one infratentorial lesion have an odds ratio of 5.4 (33). Each MS lesion is generally less extensive than those that are observed in systemic autoimmune disease. Thus, the presence of small white matter juxtacortical lesions, numerous periventricular lesions or non-longitudinally extensive incomplete transverse myelitis should suggest MS.

However, it should be borne in mind that patients with relapsing-remitting presentations of systemic autoimmune diseases may exhibit CNS lesions that are indistinguishable from those that

are observed in MS. An expert consensus defined 36 main red flags that point to a non-MS diagnosis in a patient with scattered white matter lesions. The majority of these red flags are clinical in nature. For instance, mucosal ulcers are cited as a major red flag (suggesting neuro-BD); lung involvement or cranial neuropathies are also major red flags (suggesting neuro-TB or neuro-sarcoidosis); renal involvement, rash or polyarthralgias are major red flags that indicate SLE or systemic vasculitis; *livedo reticularis* or recurrent abortion points to antiphospholipid syndrome, etc (34). Alternatively, certain non-related features are frequent complaints among the general population. For example, recurrent aphthous ulcerations occur in approximately 1% of the population (3), musculoskeletal pain due to fibromyalgia occurs in 5% of the adult population (35) and low-titer antinuclear antibodies are observed in 13.4% of healthy individuals (36). Hence, many patients with unrelated systemic features still may have MS. CSF analysis is a secondary consideration in MS diagnosis. The CSF in patients with MS should exhibit normal or only slightly elevated cell counts and protein levels, and the finding of oligoclonal bands is unnecessary for MS diagnosis. Moreover, the presence of a small number of oligoclonal bands is not specific to MS, as bands are also observed in other inflammatory diseases that affect the CNS such as neuro-BD and neuro-TB (37).

Type I interferons (IFNs), including IFN- α and IFN- β , are cytokines with both pro- and anti-inflammatory functions depending on the context of the particular pathology. The various forms of IFN- β are commonly prescribed agents for relapsing-remitting MS. Although there is no information regarding the effects of IFN- β on BD, IFN- α is an established therapy for this disease (38). Thus, a case of neuro-BD that is mistakenly diagnosed as MS and which is treated with IFN- β may not present a serious problem. However, the opposite is not true, *i.e.* a patient with MS that is mistakenly diagnosed with neuro-BD and who is given an anti-TNF therapy may suffer adverse events. A clinical trial with an anti-TNF agent (Inercept)

for MS resulted in earlier and more frequent disease exacerbations (39), and there are several reports of demyelinating diseases that are linked to different anti-TNF agents (5). Thus, when CNS lesions are MS-like, we do not recommend anti-TNF treatment unless a BD diagnosis is clearly defined by the diagnostic criteria of this condition.

Neuromyelitis optica (NMO)

NMO is a CNS inflammatory disorder that is characterised by severe and recurrent demyelinating episodes of the optic nerves and the spinal cord. Despite certain similarities to MS, these are different diseases. The observed myelitis in NMO manifests as a complete transversal myelitis and is also longitudinally extensive (involving three or more vertebral segments), whereas the myelitis in MS is generally partial and extends up to only two segments (40). The cerebral lesions that are observed in NMO are less disseminated and are generally limited to periventricular regions. The prognosis is significantly worse for NMO than for MS: over 5 years, more than half of NMO patients will suffer severe vision loss or will be unable to ambulate (41). NMO is associated with the presence of an anti-aquaporin-4 autoantibody (also known as anti-NMO IgG antibody). The sensitivity of this diagnostic parameter ranges from 30% to 91% (with a mean of 62.4%). Thus, a negative result does not rule out a NMO diagnosis; however, the specificity of this test is quite high, and a positive test is highly predictive (41).

NMO must be distinguished from MS because the former requires more aggressive treatment and IFN- β is harmful in NMO patients (42). Immunosuppressive therapies with azathioprine, mycophenolate mofetil or rituximab (an anti-CD20 antibody with activity against B lymphocytes) are indicated in patients with relapsing NMO. Interestingly, these agents are highly efficacious in the treatment of SLE and Sjögren syndrome, which are systemic autoimmune diseases with significant overlapping with NMO (43). The effect of anti-TNF agents in NMO is unknown; however, considering that these agents are likely deleterious in

SLE and similar disorders (6), these treatments are not likely to be effective options for NMO therapy. Therefore, care should be taken to rule out NMO prior to beginning anti-TNF therapy in a suspected neuro-BD case with extensive myelitis or neuritis optica.

Systemic lupus erythematosus (SLE)

SLE is the prototypic multisystemic autoimmune disease due to its ability to affect multiple organ systems (including the CNS). Nearly all nervous structures can be affected by SLE. Moreover, as stated above, there is a strong association between SLE and NMO. SLE myelitis generally exhibits a large longitudinal extension, similar to NMO (40); however, certain neurologic presentations are similar to those observed in MS (*e.g.* disseminated white matter lesions). The diagnosis of SLE must rely on the presence of features in non-CNS organ systems (44, 45). However, these SLE features may not be present simultaneously. Many cases of neuro-SLE may not fulfill the classification criteria at the time of the neurological presentation. The presence of subtle features (*e.g.* mild arthritis or persistent lymphopenia) should raise suspicion of SLE, particularly if antinuclear antibodies (ANAs) are present. The importance of ANAs is based on the extremely high sensitivity of this test for SLE.

The effect of an anti-TNF agent on neuro-SLE is unknown. However, because there are several reports of induced ANA production and drug-induced SLE-like syndromes during anti-TNF treatment for other inflammatory conditions (46), there are serious concerns that this therapy can be deleterious for SLE patients. Therefore, it is wise to rule out SLE prior to beginning anti-TNF treatment in a suspected case of neuro-BD with hemispheric lesions or transverse myelitis. Due to its high sensitivity, a negative ANA finding could be proposed as a first step to define non-SLE cases.

Sjögren's syndrome (SS)

The rationale for neuro-SS is the same as described for neuro-SLE. SS is a systemic autoimmune disease that affects the nervous system in ways that are

quite similar to the effects of SLE. The primary clinical features of neuro-SS are xerostomia and xerophthalmia (*i.e.* sicca syndrome). The diagnosis of SS depends on the evidence of salivary or lachrymal dysfunction in the presence of at least one of the following diagnostic markers: a salivary biopsy revealing lymphocyte infiltration or the presence of anti-SSA/Ro or anti-SSB/La autoantibodies (47). In SS systemic features may be mild (the sicca symptoms are frequently unnoticed by the patient if not specifically mentioned by the clinician). The most common serologic marker, anti-SSA/Ro antibodies, is observed in 60–70% of cases; thus, a third of cases require a salivary biopsy for investigation (48). SS frequently coexists with other autoimmune diseases, including SLE and NMO (43), and its treatment is likewise similar. SS may also cause cerebral white matter lesions and longitudinally extensive myelitis. Neuro-BD may be suggested (in cases with extensive myelitis); however, anti-TNF agents should be avoided if SS cannot be ruled out, similar to the treatment recommendations for SLE and NMO.

Conclusion

Before starting anti-TNF agents or aggressive immunosuppressive treatment for a possible neuro-BD case, we must be assured that the differential diagnosis was fully considered.

For typical neuro-BD lesions (rhombencephalitis), the distinction between neuro-BD, infectious diseases and neoplastic diseases is critical. Listeriosis, herpes simplex encephalitis and neuro-TB may imitate neuro-BD. Because cultures and PCR for these agents are not ideally sensitive, repeated CSF and blood analyses (as well as pulmonary investigations for TB) must be performed. In the acute setting, empiric therapy with ampicillin and acyclovir must be considered. In the scenario of an isolated brainstem lesion, a biopsy procedure must be considered to assess the possibility of a brainstem glioma.

For spinal cord and hemispheric lesions, the distinction between other autoimmune diseases is quite important. MS must be considered prior to anti-TNF therapy, given that such treatment

will likely worsen MS. The presence of small white matter juxtacortical lesions, numerous periventricular lesions or non-longitudinally extensive transverse myelitis should suggest MS. NMO, neuro-SLE and neuro-SS also must be ruled out prior to anti-TNF therapy, and the results of serological tests (*i.e.* for the presence of anti-aquaporin-4, ANA, anti-SSA/Ro and anti-SSB/La antibodies) are useful in this respect.

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