Limbic encephalitis secondary to neuro-Behçet disease: an uncommon presentation

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Introduction. Limbic encephalitis (LE) can have a wide range of etiologies, most frequently infectious (especially viral) or autoimmune. Behçet's disease (BD) can present with heterogeneous neurological manifestations. However, LE is not considered a typical presentation of neuro-Behçet's disease (NBD).

Case report. A 40-years-old male presented with new-onset subacute headaches, memory problems and apathy. A review of systems revealed an unrecorded past history of recurrent oral sores for years, recent malaise and fever, as well as an episode of bilateral panuveitis four months before presentation. His general and neurologic examination revealed slight fever, an isolated oral aphtha, anterograde amnesia and signs of bilateral retinal vasculitis. Brain magnetic resonance imaging displayed a pattern of limbic meningoencephalitis, and his cerebrospinal fluid showed mononuclear inflammation. The patient met BD diagnostic criteria. Considering LE is a very rare presentation of NBD, alternative etiologies were thoroughly assessed and excluded, including infectious, autoimmune and paraneoplastic encephalitis. Therefore, he was diagnosed with NBD, and he recovered well after immunosuppression.

Discussion. Only two cases of NBD presenting with LE have been previously reported. We report a third case of this rare presentation and compare it with the previous two. We aim to highlight this association and contribute to enlarge the rich clinical spectrum of NBD.

Key words. Autoimmune disease. Behçet's disease. Limbic encephalitis. Neurologic disorders. Oral ulcer. Panuveitis.

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Introduction

Limbic encephalitis (LE) is a syndrome typically presenting with subacute short-term memory deficits, neuropsychiatric changes (anxiety, depression, behavioral changes, psychosis) and seizures. It can have a wide range of causes, most frequently infectious (especially viral) or autoimmune [1]. The basic diagnostic workup includes: a) cerebrospinal fluid analysis, usually mildly inflammatory; b) brain magnetic resonance imaging, with typical hyperintensities in the medial temporal lobes and other limbic areas, and occasional gadolinium enhancement; and c) electroencephalography, with temporal lobe epileptiform activity or focal/generalized slow activity. Nonetheless, these studies do not establish the definite etiological diagnosis.

Behçet's disease (BD) is an inflammatory rheumatological multisystemic disease of unknown origin. It is more common in males (3:1) and it predominates in endemic areas of Mediterranean, Middle Eastern and Far Eastern countries. In endemic areas, it is strongly associated with HLA-B*51, considered the best-known risk factor. Recurrent oral aphthae, genital aphthae and posterior uveitis are paramount clinical manifestations of BD. In some cases, it exhibits vascular involvement and/or heterogeneous neurological manifestations [2]. However, LE is not considered a typical presentation of neuro-Behçet's disease (NBD) and only two cases have been previously reported.

Case report

A 40-year-old man presented with two months of progressive memory loss and behavioral disturbance. He became apathetic and forgetful for recent events. His performance as a cashier in a gas station had worsened. A review of systems revealed an unrecorded past history of five years of recurring oral aphthae, occasional acneiform lesions, new-onset holocraneal headaches and episodic fever in the last months. Four months before presentation, he suffered an acute painful blurring of vision and was diagnosed with idiopathic sequential bilateral panuveitis.

Bedside neurologic examination showed a short-term memory deficit, with preserved autobiographi-

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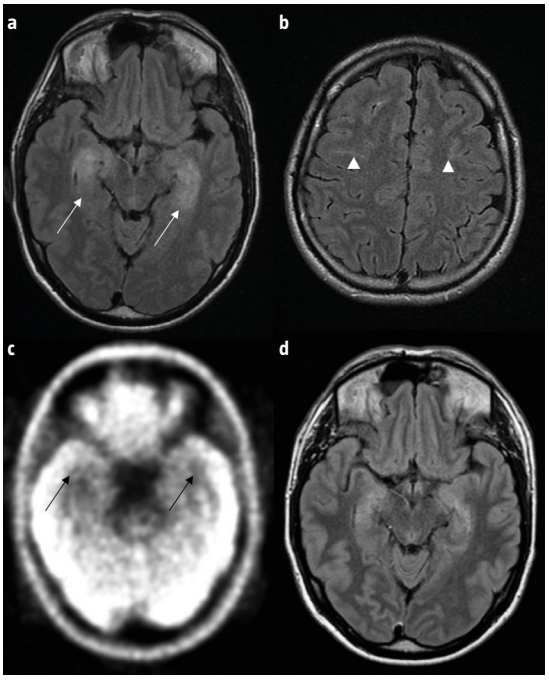
Figure. Magnetic resonance imaging (a, b and d) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (c) of the brain. a) T_2-FLAIR (fluid-attenuated inversion recovery) weighted brain magnetic resonance imaging showing bilateral increased signal intensity in the medial temporal lobes (arrows) involving hippocampus, fornix, amygdala and parahippocampal gyrus; b) T_2-FLAIR brain magnetic resonance imaging after intravenous paramagnetic contrast with leptomeningeal uptake on cerebral sulci (arrowheads); c) Brain ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan showing slight hypometabolism in both anterior temporal poles (arrows); d) Follow-up T_2-FLAIR brain magnetic resonance imaging two months later showing radiological improvement after immunosuppressive treatment.



cal memory. He was only able to recall one of three words spontaneously and another one with semantic clues. Other cortical functions and general neurologic examination were normal. He had no meningeal irritation signs and bedside direct fundoscopy was normal. A thorough general physical exam was unremarkable except for a 37.7 °C axillar temperature and one isolated oral aphtha. Further neuropsychological assessment identified impairment of verbal memory, which did not improve with semantic cues, decreased semantic fluency and nongraphic constructive apraxia.

Laboratory workup showed an elevated C reactive protein (4.32 mg/dL). Head computed tomography, chest radiograph, urinalysis and toxicology screening were normal. A lumbar puncture was performed, with normal opening pressure, normal glucose (49 mg/dL in cerebrospinal fluid, 78 mg/dL in simultaneous serum), hyperproteinorrachia (1.40 g/L) and pleocytosis (440 leucocytes/μL, 80% mononuclear).

Our diagnostic approach was a chronic-to-subacute meningoencephalitis with predominant limbic involvement. The recent bilateral uveitis framed it within the uveo-meningeal syndromes [3], and the history of recurring oral aphthae suggested the possibility of BD.

Brain magnetic resonance imaging (Figure, a-b) showed bilateral hyperintensities in the limbic system, confirming the clinical suspicion of limbic encephalitis (LE), along with leptomeningeal enhancement. Electroencephalography was normal. An extensive serum and cerebrospinal fluid autoimmune and microbiological workup was negative. HLA-B51 was also negative. Ophthalmologic evaluation revealed a bilateral retinal vasculitis without signs of active uveitis.

Recurring oral ulcers and posterior uveitis are hallmarks of BD, and retinal vasculitis is another typical ocular manifestation. Inflammatory meningoencephalitis is a common form of NBD, but LE is not a typical presentation. Therefore, even though the patient fulfilled diagnostic criteria for BD [4], other feasible causes for his neurologic condition had to be thoroughly excluded.

Specially, we aimed to exclude the possibility of a concurrent paraneoplastic LE. Hence, a complete cell binding assay panel of onconeuronal and neuronal surface autoantibodies was requested, all with negative results. Additionally, the possibility of a paraneoplastic LE with negative autoantibodies was addressed [5]. According to present recommendations [6], a whole-body and brain ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan were performed to exclude an underlying tumor. The brain scan showed bilateral temporal lobe hypometabolism (Figure, c), further supporting the LE diagnosis, and the systemic scan ruled out an underlying hidden tumor. Also, a scrotal ultrasound ruled out testicular malignancy.

Consequently, after excluding all other plausible causes for his neurologic presentation, he was diagnosed with NBD. He received treatment with five days high-dose intravenous corticosteroids with clinical and cerebrospinal fluid parameters improvement, followed by an oral prednisone taper, azathioprine and periodic infliximab. A new brain magnetic resonance imaging (Figure, d) two

months later showed almost complete radiological recovery.

Discussion

BD has no specific test and the gold standard for diagnosis remains expert opinion [2]. So, on clinical grounds, the diagnosis relies on clinical criteria [4]. Our patient showed typical manifestations of BD and met diagnostic criteria. The key issue was whether to attribute LE to BD, as NBD is considered a diagnosis of exclusion.

Neurological involvement arises in 5-10% of BD cases and it is the disease debut in about 5% of NBD cases, representing a clinical challenge. Relevant neurological presentations include parenchymal involvement within the central nervous system, with brainstem and basal ganglia predominantly involved, cerebral venous sinus thrombosis and/or isolated intracranial hypertension [7]. On magnetic resonance imaging, large lesions with no distinct borders affecting the brainstem and diencephalon are particularly characteristic. Notwithstanding, NBD presentations can be heterogeneous. Simultaneous parenchymal and cerebral venous sinus thrombosis is very rare, suggesting somewhat different pathogenic mechanisms (small or large vessel vasculitis, respectively, with a predilection for venous vessels). The standard treatment of NBD consists of brisk immunosuppression mainly with high-dose corticosteroids, followed by azathioprine, infliximab or adalimumab [3].

Regarding LE, its diagnostic criteria include bilateral magnetic resonance imaging hyperintensities restricted to the medial temporal lobes, cerebrospinal fluid pleocytosis and/or electroencephalography with epileptic or slow-wave activity involving temporal lobe [1]. Sometimes, the clinical or radiological pattern of extra-limbic involvement might give clues to a certain specific autoimmune syndrome and autoantibody. Screening for occult tumors is mandatory, as autoimmune LE can have a paraneoplastic origin and malignancy may determine the clinical outcome. A significant proportion of autoimmune LE recently estimated at 7% can have negative autoantibodies results [6]. Treatment shares similarities with BD, consisting of brisk immunosuppression.

LE is not considered a typical presentation of BD and the link between LE and BD has been rarely reported in the literature. To the best of our knowledge, only two cases of BD presenting with LE have been previously reported [8,9]. Moreover, one of them was an overlap syndrome of BD and relapsing

Table. Clinical features of our case and the two previously reported cases of neuro-Behçet's disease presenting with limbic encephalitis.

	Present case	Kotan et al (2017)	Kumar et al (2009)
Age and sex	40 years-old male	36 years-old male	29 years-old male
Ethnic origin	Spain	Turkey	Somalia
Prior known BD	No	Yes	No
Past medical history	Recurrent oral sores, malaise and fever, bilateral uveitis four months before	Recurrent oral sores, joint pain and recurrent uveitis	Recurrent oral sores, joint pain and recurrent uveitis. Also, intermittent external ear chondritis
Familial history	No BD history	Two relatives with NBD	Not reported
Neurologic presentation	Headaches, apathy and subacute amnesia	Apathy, language and gait disturbance	Left-sided hyperreflexia finding on examination
Neuropsychological assessment	Amnesic and mild visuospatial impairment	Orientation, attention, and memory impairment	Not reported
Brain MRI findings	Symmetrical mesiotemporal T_2 hyperintensities, with patchy limbic and pial enhancement	Symmetrical mesiotemporal T_2 hyperintensities, without enhancement	Symmetrical mesiotemporal T_2 hyperintensities, without enhancement
EEG	Normal	Not reported	Not reported
CSF	Protein 1.40 g/dL; 440 cells/μL (80% lymphocytes); normal glucose	Normal	Protein 0.60 g/L; 32 cells/μL (predominantly lymphocytes); normal glucose
CSF autoantibodies	Negative	Negative	Not reported
Hidden tumor ruled out	Yes. Body ^{18}F-PET/CT scan and scrotal echography	Yes. Tests not specified	Not reported
HLA-B51 status	Negative	Not reported	Positive
Diagnosis	NBD with limbic meningoencephalitis	NBD with limbic encephalitis	Overlap between relapsing polychondritis and BD with limbic encephalitis
Treatment applied	High-dose steroids, followed by steroid tapper, azathioprine and infliximab	High-dose steroids and intravenous immunoglobulin	Steroids (suboptimal response), substituted by azathioprine and adalimumab
Short-term outcome	Marked improvement	Marked improvement	Marked improvement

BD: Behçet's disease; CSF: cerebrospinal fluid; EEG: electroencephalography; HLA: human leukocyte antigen; MRI: magnetic resonance imaging; NBD: neuro-Behçet's disease.

polychondritis, considering that the latter has a better-established association with LE presentations [10]. We summarize the key clinical features of the three patients in the table. Remarkably, in contrast to our patient who displayed prominent features of aseptic leptomeningeal inflammation (pial enhancement and cerebrospinal fluid parameters), neither of the previous cases showed pial enhancement, while cerebrospinal fluid was normal in one and only mildly inflammatory in the other. The short-term neurological prognosis reported in the three cases was favorable.

In this regard, our case may contribute to highlight this atypical presentation and hence to enlarge the rich clinical spectrum of NBD. Also, it may help clinicians to include multisystem inflammatory diseases like BD or relapsing polychondritis in the differential diagnosis of LE.

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Encefalitis límbica secundaria a neuro-Behçet: una presentación insólita

Introducción. La encefalitis límbica (EL) puede tener un amplio abanico de etiologías, más frecuentemente la infecciosa (sobre todo viral) o autoinmune. La enfermedad de Behçet (EB) puede presentarse con manifestaciones neurológicas heterogéneas. Sin embargo, la EL no se considera una presentación típica del neuro-Behçet (NB).

Caso clínico. Un varón de 40 años consultó por cefalea *de novo* subaguda, problemas de memoria y apatía. La anamnesis por sistemas reveló una historia no conocida previamente de aftas orales recurrentes durante años, fiebre y afectación general reciente, así como un episodio de panuveítis bilateral cuatro meses antes de la presentación. Su exploración general y neurológica reveló febrícula, una afta oral aislada, amnesia anterógrada y signos de vasculitis retiniana bilateral. La resonancia magnética mostró un patrón de afectación de meningoencefalitis límbica y su líquido cefalorraquídeo presentaba inflamación mononuclear. El paciente cumplía los criterios diagnósticos de la EB. Considerando que la EL es una presentación muy rara del NB, se buscaron exhaustivamente y se excluyeron otras etiologías alternativas, incluyendo las encefalitis infecciosas, autoinmunes y paraneoplásicas. En consecuencia, el paciente se diagnosticó de NB y mostró una buena recuperación con tratamiento inmunosupresor.

Discusión. Sólo dos casos de NB con presentación en forma de EL se han publicado previamente. Comunicamos el tercer caso de esta rara manifestación clínica de la EB y lo comparamos con los dos anteriores, con el objetivo de destacar dicha asociación y contribuir a expandir el rico espectro clínico del NB.

Palabras clave. Aftas orales. Enfermedad autoinmune. Enfermedad de Behçet. Encefalitis límbica. Enfermedad neurológica. Panuveítis.