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Behcet disease: neurological and psychiatric manifestations observed in two patients in the Dos de Mayo National Hospital (Lima, Perú)

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Abstract: The neurological and psychiatric manifestations in two patients who met clinical criteria of Behcet's disease are observed and described throughout several decades. The presence of recurrent oral and genital canker sores is illustrated with images. One of the patients developed thrombosis of the femoral vein, and erythema nodosus was present in both. The ophthalmological evaluation showed absence of uveitis in both patients, and blindness by adult monocular dystrophic maculopathy without signs of retinal vasculitis in the female. Laboratory tests on blood and cerebrospinal fluid evidenced lymphocytic pleocytosis. The patergia skin test was negative. Likewise, laboratory tests determined an absence of findings compatible with other autoimmune diseases. Throughout the evaluation period, the clinical manifestations were correlated with the findings from tomography and brain magnetic resonance magnetic. Similarly, recurrent myelitis and its correlation with the results of medular magnetic resonance imaging are explained. The evaluation and follow-up period through outpatient consultation and hospitalization was prolonged: the 73-year-old male patient, who started the disease at age 35, was followed-up for 34 years; and the 50-year-old female patient, fell ill at the age of 28 and was followed-up for 8 years. This process allowed the understanding of the different morbid factors that influenced the serious evolution of the clinical picture.

Key words: Behcet's disease; neurological; psyquiatric and recurrent myelitis

1 Introduction

Behcet's disease (BD) is considered an autoimmune disease that affects the blood vessels of numerous systems; that is, a multisystemic vasculitis of unknown etiology characterized by oral and genital ulcers and uveitis. It is reported that between 5% and 30% of patients develop neurological manifestations, and in 5% of cases, these constitute the initial presentation; these figures are on the rise due to advances in neuroimaging techniques. However, its etiology remains unknown. The most frequently reported neurological manifestation in the literature is headache [1]. Other manifestations include parenchymal and non-parenchymal lesions, such as pyramidal tract disorders, deficit signs due to cortical lesions, and cognitive and/or behavioral disorders. Bipolar or paranoid disorders have been described, as well as, on occasion, indifference and apathy toward the disease. Anxiety and depression are the most common psychiatric symptoms, with an incidence of up to 86% and a higher prevalence than in other autoimmune disorders [2]. The disease affects men and wom-

-en equally and is usually associated with the development of other autoimmune conditions such as erythema nodosum and noninfectious thrombophlebitis. Neurological involvement, or Neuro-Behcet (NB), occurs most frequently in young adults (ages 26–27). It should be noted that NB is not a new clinical entity, but rather the neurological manifestations of a systemic disease caused by lesions in the blood vessels. The clinical presentation correlates with or should conform to the diagnostic criteria established by the International Consensus Recommendation (ICR) [3]. The purpose of this manuscript is to highlight the disease in its entirety over time, including the general clinical manifestations of Behcet's disease and its neurological and psychiatric complications, as well as the severity of these complications in two patients evaluated and studied from a clinical behavioral perspective; to present the manifestations in their entirety and illustrate them with images; and to report laboratory results—including blood tests, in cerebrospinal fluid, and neuroimaging findings that help elucidate the neurological and psychiatric abnormalities that developed during the clinical follow-up of two patients with NB over the course of several decades.

1.1 Clinical case 1

A 72-year-old man, a native of Ica, with a primary school education, a merchant, married, with five children. His illness began at age 35 when he complained of throbbing headaches without the clinical characteristics of any of the variants of migraine. He remained in this condition for five months. During that period, he developed aphthous lesions on his lips and in his oral cavity, as well as on his scrotum. He did not receive medical treatment. He used analgesics and solutions for the oral lesions. During that period, he reportedly experienced four episodes of oral and inguinal aphthous lesions.

The headache episodes increased in intensity and coincided with the onset of a generalized epileptic seizure. Under these circumstances, he was admitted to the hospital on August 22, 1987. The aforementioned inflammatory lesions were confirmed, alongside painful cutaneous nodules in the tibial regions and aseptic meningism, following an analysis of the cerebrospinal fluid, which revealed lymphocytic pleocytosis of 170 cells. The comprehensive clinical evaluation by system was normal. His mental status was normal. Funduscopic examination revealed normal findings. At no point in the course of the illness were manifestations indicative of external or internal uveitis present or observed. The brain CT scan showed no abnormalities, and blood tests revealed no anomalies. He was discharged with diagnoses of EB, aseptic meningoencephalitis, erythema nodosum, and a seizure disorder. He was prescribed prednisone 60 mg/day for 26 days, with a gradual tapering as the lesions on the mucous membranes of the mouth and scrotum resolved. It was deemed appropriate not to prescribe anticonvulsant medication. The patient returned to the clinic 6 years later because he continued to experience episodes of headache, varying in intensity and frequency, always of a throbbing nature, which were treated with nonsteroidal anti-inflammatory drugs and ergotamine derivatives, without much success. During this period, this symptom was associated with simple partial, generalized, and complex partial epileptic seizures; the latter were accompanied by manual and facial automatisms, as well as more complex episodes in which he would walk for varying durations, maintain good muscle tone, and, on occasion, the seizure would end with leg contractions involving "kicking." He was treated with 800 mg of carbamazepine daily. Apparently, he continued to experience atherosclerotic lesions, which he treated with self-administered prednisone and saw improvement. In addition, he experienced episodes of panic disorder accompanied by intense anxiety and depression. Sleep disturbances were accompanied by delusional and hallucinatory states. The psychiatric evaluation led to treatment with antidepressants and trifluoperazine. His cognitive status and dysthymic disorder were assessed using the following tests: the Folstein Mini-Mental State Examination (23/30) and the Hamilton Depression Rating Scale (4/20), indicating cognitive decline and severe depression. The remainder of the neurological examination, which included an assessment of speech, revealed dysarthria and limb incoordination, as well as

a zigzagging gait; cranial nerves were normal, and motor and sensory function were unaltered. Manual grasping and oral sucking reflexes were present. In September 2004, he presented with pain and swelling in his left lower limb. A Doppler ultrasound confirmed the clinical diagnosis of deep vein thrombosis in the left lower limb. Nine years later, he was admitted to the hospital due to persistent headaches and epileptic seizures. On this occasion, chronic scarring of the scrotal wings and signs of erythema nodosum were noted. A second ophthalmological evaluation revealed: decreased visual acuity in the right eye (OD): 20/30; in the left eye (OS): 20/40; and on fundus examination: signs of vascular sclerosis, with the macula and retina appearing normal (Figure 1). In his worsened neurological state: bradipsychic, episodes of lethargy, emotional indifference, severe intellectual impairment affecting attention, memory, and recall, and persistent echolalia. Signs of intense manual grasping, sucking, and oral exploration. He remained bedridden, disconnected from his surroundings, mute, and exhibiting cat-like movements.

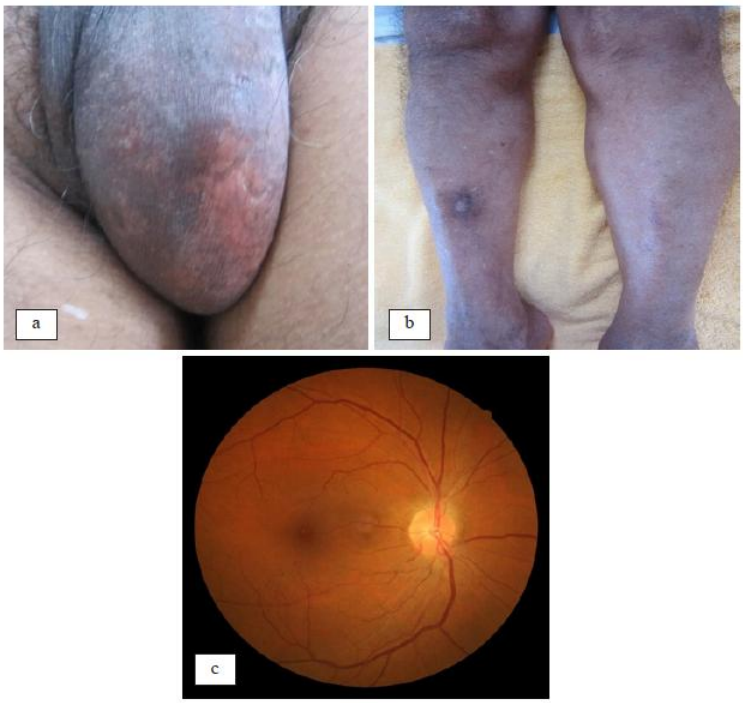

Figure 1. Cicatricial lesions on the scrotums (a), chronic scar from erythema nodosum (b), and fundus with normal characteristics (c)

1.2 Laboratory tests

The complete blood count, hemoglobin, and hematocrit revealed microcytic iron-deficiency anemia. The white blood cell differential was normal. The platelet count, coagulation profile, fasting glucose, liver function tests, electrolytes, and thyroid profiles were normal. Finally, the echocardiogram and tests for autoimmune disease using antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) were nonreactive. Laboratory testing for other forms of autoimmune diseases was also negative. At that time, it was not possible to measure the concentration of interleukin-6 (IL-6) in the CSF, which is indicative of disease activity.

1.3 Neuroimaging study

To determine the extent of the patient's neurological impairment—which would explain the severe cognitive deficits, behavioral disorders, and various types of epilepsy that had occurred over the decades of the disease's progression—studies were conducted using CT scans of the brain, magnetic resonance imaging (MRI) of the brain, and angiography of the carotid and vertebrobasilar systems (Figure 2).

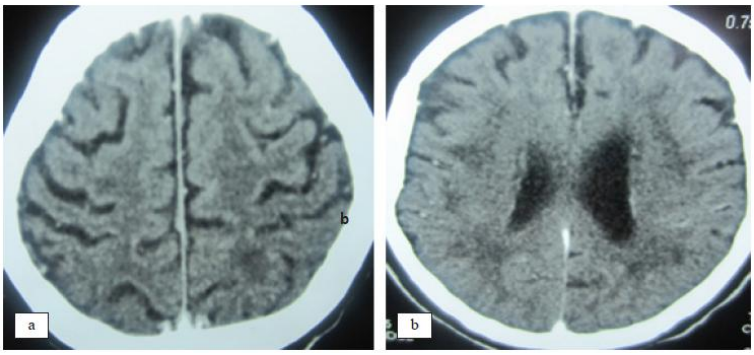

Figure 2. Findings from the brain CT scan. The scan revealed multiple hypodense areas in the subcortical white matter in the frontoparietal regions, predominantly on the left side, in the axial sections (a) and (b)

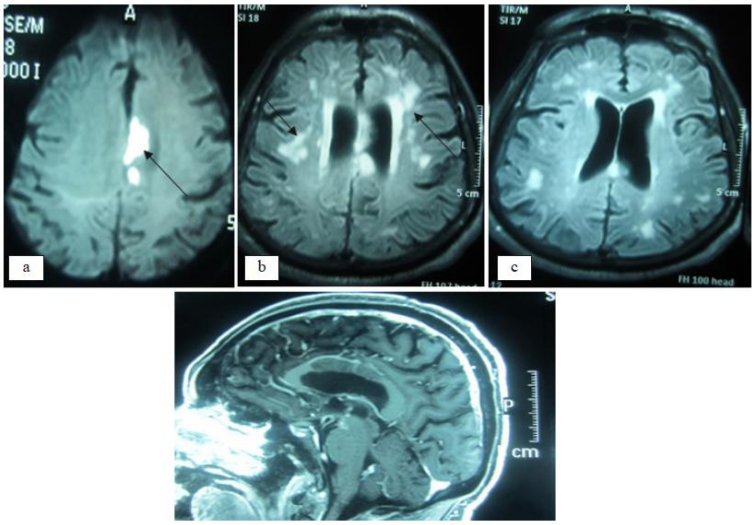

Figure 3. Brain magnetic resonance imaging (MRI) study. The FLAIR MRI scan revealed multiple hyperintense foci in the left parasagittal frontal region (a) and in the bilateral temporal subcortical white matter (b) and (c); on the contrast-enhanced T1-weighted sequence, the sagittal view extensive hypointense signal in the corpus callosum, suggestive of ischemia. All these findings are consistent with chronic ischemic microvascular disease

1.4 Clinical case 2

A 50-year-old patient, born in Lima, completed elementary school, living with a partner, and has five healthy daughters. At the age of 22, she traveled to Buenos Aires to work as a domestic worker. At the age of 28, she developed painful, recurrent lesions on the oral mucosa, in the vulvovaginal regions, and on the buttocks, occurring every four months for six years. She was diagnosed with herpes simplex virus type 2 infection and treated with 1,200 mg/day of acyclovir for 10 days, but the lesions did not improve. She was in Peru at the age of 34 and sought care at Dos de Mayo Hospital, where the aforementioned alveolar lesions were confirmed (Figure 4). These lesions became less frequent, reactivating every six months. One year after her stay, she noticed a marked decrease in visual acuity in her right eye, and one year after the onset of this symptom, she had become blind. The ophthalmological evaluation at that time confirmed blindness in the right eye and visual acuity of 20/40 in the left eye. The fundus could be visualized without difficulty, as the ocular media were clear due to the absence of anterior and posterior uveitis. In the right macular area, an atrophic scar was observed, accompanied by a fibrous reaction and pigment deposits, extending across the entire macular area up to the superior and inferior vascular arcades, suggesting the development of adult dystrophic maculopathy. In the left eye, images corresponding to "drusen" in

the macula are observed, indicating the onset of the aforementioned maculopathy (Figure 5). No signs of vasculitis.

Figure 4. Presence of buccal (a) and vulvovaginal and gluteal (b) inflammatory lesions

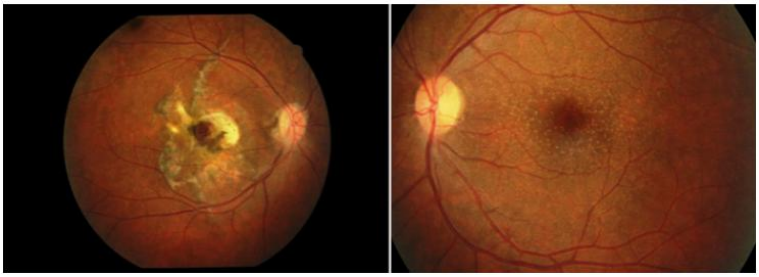

Figure 5. Fundus examination of the patient showing macular atrophic gliosis and the presence of "perimacular drusen"

At that time, the patient had no arthralgias or signs of joint inflammation, and her general condition was good. In June 2015, she acutely developed flaccid paraplegia over a period of approximately two hours, preceded by paresthesias extending from the umbilical region to the soles of her feet, lasting only a few minutes. Neurological examination revealed moderate upper extremity weakness with definite paraplegia, accompanied by hyperreflexia and bilateral Hoffmann's and Babinski signs. Sensory examination was normal in all aspects. She was admitted in this condition to the Department of Infectious and Tropical Diseases at Dos de Mayo Hospital. A medical board was convened, which decided to perform a biopsy of the oral mucosa and of a nodule with erythema nodosum; the findings were reported as indicative of lymphocytic vasculitis, leading to a diagnosis of EB and vasculitis-related myelopathy. Blood and cerebrospinal fluid tests were performed to rule out common in women and, using polymerase chain reaction (PCR), for infection with herpes viruses I and II and HTLV-II. The laboratory results were negative. In the CSF, glucose levels were normal, with elevated albumin and lymphocytic pleocytosis. The pathergy test was negative. Finally, neuroimaging studies using T1- and T2-weighted magnetic resonance imaging (MRI) of the spinal cord revealed filiform ischemic myelopathy extending from the cervical to the dorsal regions (Figure 6).

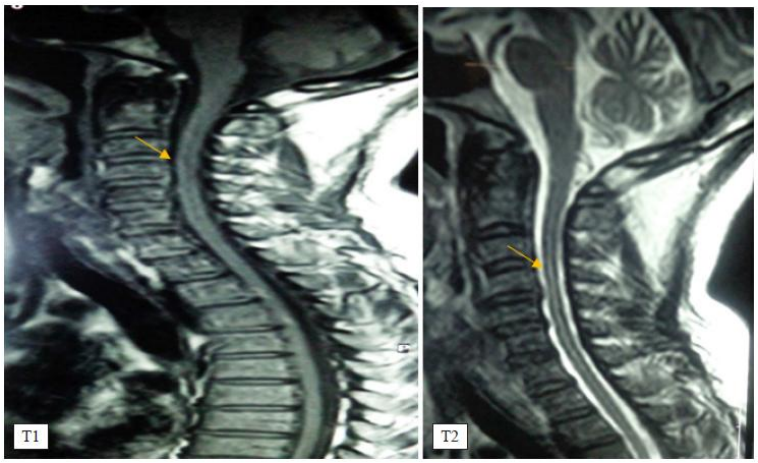

Figure 6. Magnetic resonance imaging of the spinal cord, sagittal section in T1 and T2 sequences showing the signals characteristic of cervicodorsal filiform ischemia

During his two-month hospital stay, he received treatment with 100 mg of azathioprine daily and physical therapy sessions, which led to a favorable outcome, allowing him to walk independently with the aid of crutches. He took the medication for eight consecutive months; however, due to financial difficulties, he had to discontinue it. In August 2016, he was readmitted to the hospital on an emergency basis with the same symptoms as during the first episode. On this occasion, he also presented with flaccid paraplegia accompanied by bilateral Babinski signs and hyperreflexia in all four limbs, without any objective sensory disturbances of any kind. A comprehensive neurological examination revealed no additional abnormalities. She was treated with baclofen for flexor spasms; prednisone 80 mg/day and azathioprine 150 mg/day until the day of her discharge, after a 45-day hospital stay. For reasons unknown to us, we lost track of the patient.

2 Discussion

There is no doubt regarding the diagnosis of EB in both cases, given the α-related manifestations as well as the associations with autoimmune vascular disease in the lower extremities. The CSF findings (lymphocytic pleocytosis with proteinorrachia), as well as the neurological disorders affecting the brain and spinal cord, allow us to classify both cases as NB-related conditions. In the male patient, chronic headache, various forms of epilepsy, progressive cognitive impairment leading to dementia, and depressive dysthymia, alternating with episodes of euphoria and paranoid delusions, constituted the neurological and psychiatric manifestations. These, combined with the findings on TEM and MRI neuroimaging—which show lesions consistent with chronic ischemic vascular angiopathy—constitute the parenchymal subgroup of the disease (NB) [4], which developed over a period of 34 years. It should be noted that the findings in the cerebrospinal fluid and those from neuroimaging are similar to those described in the literature.

In the female patient, the neurological manifestations consisted of the acute onset of strategic spinal cord disease involving the cervicodorsal region in the form of a filiform longitudinal myelopathy, affecting the pyramidal tracts. This neurological involvement occurred after seven years and was preceded by oral and genital α-lesions and the development of a lesion consistent with erythema nodosum. It is therefore concluded that the myelitis took a long time to manifest, and furthermore, that it recurred one year and two months later with the same characteristics. Finally, throughout the course of the disease, there were no neurological manifestations indicating involvement of the cerebral parenchyma.

An additional finding was the loss of vision in the right eye and the presence of "macular drusen" in the left eye, which could be related to adult vitelliform macular dystrophy or Best disease, an autosomal dominant disorder characterized by the accumulation of lipofuscin in the pigment epithelium as a result of a mutation in a transmembrane

calcium protein, due to mutations in the BEST1 gene located on chromosome 11 [5].

Spinal cord involvement, reported in the literature as multifocal transverse myelitis, constitutes a form with a poor prognosis [6]. In the present study, which included clinical follow-up of the patients, the affected woman developed two episodes of filiform myelitis with exclusively motor involvement, a finding not reported in the reviewed literature.

3 Conclusion

We have presented two patients with EB, followed for their neurological and psychiatric manifestations. One of them was a male who, over the course of three decades of the disease, developed numerous neurological and psychiatric manifestations, as documented in the patient's clinical description. Furthermore, we had the opportunity to track the clinical course in a female patient who, during the course of her disease, presented with acute spinal cord involvement on two occasions. In both cases, there were oral and genital lesions. Neither patient presented with uveitis. The diagnoses of NB were supported by neuroimaging and cerebrospinal fluid analysis. We believe that clinical follow-up of patients allows us to assess the severity of the disease. We found no reports in the reviewed literature regarding long-term follow-up of NB cases over the course of the disease. In Peru, NB has been observed on six occasions during the period from 1996 to 2017. The first report of this disease was published by Visaga Maribel et al., describing a pediatric form [7]. Alzamora Barrios Blanca contributed data on patients studied at Arzobispo Loayza Hospital [8], and Roberto A. Molina et al. reported a case [9].

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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