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CASE REPORTS

Rapid, Complete and Sustained Response to Corticosteroids and Pulse Cyclophosphamide Therapy in a Patient with Behçet and Central Nervous Disease

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ABSTRACT

Background: *Approximately eighty-percent of patients with neuro-Behçet have parenchyma CNS disease, probably due to small-vessel vasculitis. The most used treatment is high-dose corticosteroids followed by immunosuppressive medication but efficacy of this combination has not been proven to date*

Methods: *A 23 year-old male Hispanic patient with diagnosis of Behçet's disease, with onset at the age of 18, developed a bout of oral and genital ulcers, fever 39°C to 40°C, joint inflammation, cephalea, diplopia, convergent strabismus and drowsiness. A brain MRI has shown a large T2-weighted hyperintense signal in the right subthalamic nucleus and pontobulbar area. The symptoms remitted after treatment with oral prednisone and monthly pulses of cyclophosphamide and the patient had a complete and sustained neurological recovery up to twelve months of follow-up.*

Results: *We present here the rapid, complete and sustained response to corticosteroids and pulse cyclophosphamide therapy in a patient with Behçet´s disease and subacute central nervous system (CNS) disease*

Conclusions: *The early institution of an aggressive scheme combining high dose corticosteroids and monthly pulse cyclophosphamide therapy in a patient with Behçet disease with CNS manifestations is critical for a rapid, complete and potentially sustained response and to prevent permanent CNS damage.*

Keywords: Neuro-Behçet, cyclophosphamide, Hispanic

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CASE REPORT

A 23 year-old male, of paternal Spanish and maternal Venezuelan ancestry had a history of recurrent painful oral ulcers with onset at the age of 18, with a frequency of approximately four episodes a year. At the age of 22 he had a bout of oral ulcers, fever 39°C to 40° C, joint inflammation affecting wrists, right knee and ankles, and mild cephalea. One month later the cephalea became more intense and unresponsive to acetaminophen, followed by the appearance of diplopia and drowsiness. The physical examination has shown a drowsy patient with convergent strabismus. A lumbar puncture showed a normal opening pressure and the cerebrospinal fluid (CSF) had a clear appearance, with total white cell count 6/mm^3, red blood cells 10/mm^3, protein 14 mg/dL and glucose 55 mg/dL. The Pandy test and bacterial and fungi cultures were negative. A brain MRI has shown a large T2-weighted hyperintense signal and a mass-effect in the right subthalamic nucleus extending into the mid-brain (Figure 1). A pathergy test was negative. The patient was treated with 4 million units intravenous crystalline penicillin every 4 hours during 14 days, becoming afebrile and showing improvement of his neurological symptoms. Five months later he developed three ulcers on his scrotum. A skin biopsy of one of the lesions showed a neutrophilic dermatitis. A diagnosis of Behçet´s disease was established. The cephalea reappeared with increased intensity, accompanied by nausea and vomiting, and he became again drowsy and confused. A paresis of the right external rectum muscle was still present and a peripapillar hemorrhage was observed in the right fundus. The control of conjugate gaze is mediated in the brainstem by the medial longitudinal fasciculus (MLF), a nerve tract that connects the three extraocular motor nuclei (abducens, trochlear and oculomotor) into a single functional unit. Conjugate gaze is important in the initial assessment, even before extraocular movements are assessed. In drowsiness, mild squints, which are not seen in the awaken patient, may become obvious; that is, phorias become manifest tropias. Divergent squints are most common and are exaggerated with upward deviation of the eyes. These signs reflect a decreased level of consciousness, but do not have specific anatomic localization value. With coma and its depending, these oculocephalic reflexes may become overly facile or disappear completely despite maximal stimulation. When an unconscious individual without impairment of vestibulo-oculocephalic reflexes has the head passively turned to the right, the eyes move to the left (in the normal, conscious human being these reflexes cannot be examined clinically due to the voluntary control of the gaze in any area of the visual field). In a comatose individual with severe brainstem lesions, these reflexes are lost. The CSF cytochemical evaluation was normal, and the Gram-stained smear, latex agglutination test and bacterial culture were negative. Cell blood counts, urine sediment and biochemical blood profile were within normal limits. Tests for rheumatoid factor, antinuclear antibodies, anti-DNA, anti-Sm, anti-RNP, anti-Ro, anti-La, and anticardiolipin antibodies were negative. Serum cryoglobulins were not detected. Serology for human immunodeficiency virus, hepatitis B and C viruses was negative. The patient was treated with oral prednisone 1 mg/kg daily and a total of six endovenous pulses of cyclophosphamide, 1 g/m^2, were administered monthly. Two additional trimonthly pulses were given within the next six months. The patient fully recovered his consciousness after the first week of treatment, and the cephalea and diplopia

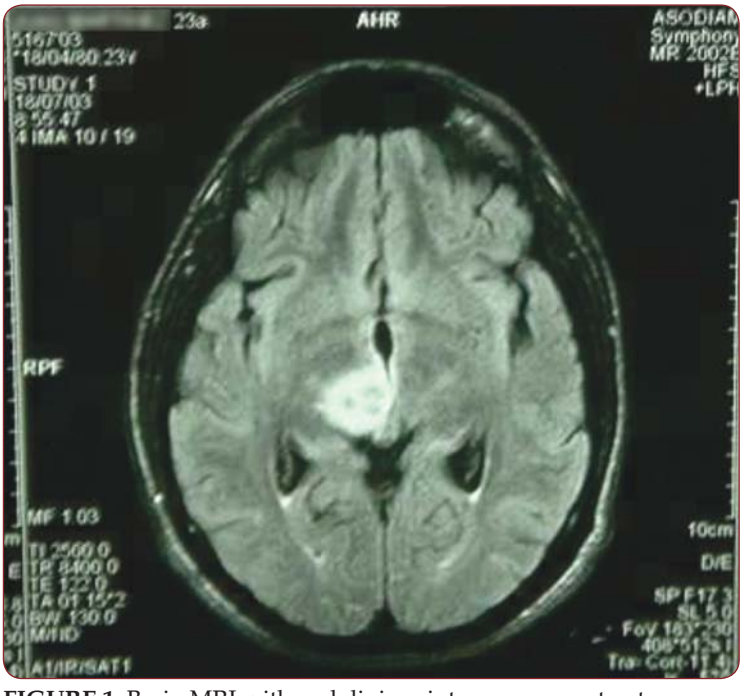

FIGURE 1. Brain MRI with gadolinium intravenous contrast showing a parenchymal inflammatory lesion appearance, marked edema and heterogeneous impregnation center ring, located at level of right basal ganglia and ipsilateral mesencephalic region.

disappeared completely after 2 months of treatment. Oral ulcers recurred upon lowering the prednisone dose below 20 mg daily. The patient was still in complete neurological recovery after 12 months of follow-up. ❑

DISCUSSION

We present here the rapid, complete and sustained response to corticosteroids and pulse cyclophosphamide therapy in a patient with Behçet´s disease and subacute central nervous system (CNS) disease. Behçet´s disease is an uncommon inflammatory disease with a high prevalence in the Silk Route countries. Our patient fulfills diagnostic criteria for this disease (1-3). The main causes of death are neurological and vascular involvement (4,5). Neuro-Behçet occurs more frequently in males (1,6), with a male-female ratio of 4:1. The disease is associated with the HLA-B51 haplotype (3,7-10). The prevalence of this haplotype in Venezuela is 5.85% (11), similar to that reported in Northern Spain (3,12), countries corresponding to our patient`s heritage. Approximately 2% to 49% of Behçet patients develop neurological disease (1). This complication increases the seven-year mortality of Behçet´s disease up to 20% (12-14). Approximately eighty-percent of patients with neuro-Behçet have parenchymal CNS disease (16), probably due to small-vessel vasculitis (4). MRI studies show lesions predominantly at the mesodiencephalic (46%) and the pontobulbar areas (40%). In the series by Akman–Demir et al the CNS lesion was located in the brainstem (51%), brain hemisphere (15%) or spinal chord (14%) (6). Our patient had a focal vascular inflammatory lesion (Figure 1), the most frequent pattern seen in patients with CNS involvement (1). As seen in our patient, cephalea with a vascular pattern and subacute brainstem manifestations are the most common manifestations (17,18). At present, there is no consensus for a standard therapeutic regimen. The most used treatment is high-dose corticosteroids followed by immunosuppressive medication but efficacy of this combination has not been proved to date (10,19,20). Our patient responded rapidly to a combined scheme with oral prednisone and pulse cyclophosphamide therapy. Neurological and mucosal disease remitted completely; oral ulcers recurred after lowering the prednisone below the 20 mg daily dose. One of the cases reported by Lannuzel et al (21), with a CNS lesion with aspect and location very similar to our case remained with neurological sequelae of hemiparesis and pesudobulbar palsy despite intravenous cyclophosphamide therapy (19,21). It is possible that the delay of 2 years in initiation of pulses may explain this patient's unfavourable outcome. Similarly, a fatal case of refractory and fatal case of CNS neuro-Behçet´disease occurred in a female patient starting pulse cyclophosphamide therapy 1 year after the onset of the neurological disease (22). On the contrary, a large thalamic mass seen in a Caribbean patient with neuro-Behçet´disease had complete resolution after monthly IV pulse therapy with cyclophosphamide and dexamethasone (21,23). Our case was treated five months after initiation of neurological symptoms. Cyclophosphamide-resistant cases have been successfully treated with tumor necrosis factor antagonists (24,25).

The early institution of an aggressive scheme combining high dose corticosteroids and monthly pulse cyclophosphamide therapy in a Behçet patient with CNS manifestations is critical for a rapid, complete and potentially sustained response and to prevent permanent CNS damage.

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