Brief Report

Pseudotumoral Behçet’s Disease

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A R T I C L E   I N F O

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A B S T R A C T

Behçet’s disease is a systemic vasculitis characterized by the presence of oral and genital ulcers. Neurological involvement or neuro-Behçet is an uncommon manifestation. It manifestation has predominance in the male gender appearing 2–4 years after the first clinical manifestation.

However, neuro-Behçet disease sometimes occurs with pseudotumoral brain lesions. Herein, we present the cases of two patients diagnosed with neuro-Behçet after detection of pseudotumoral brain lesions. A review of the literature is performed.

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Introduction

Behçet’s disease (BD) is a recurrent systemic vasculitis that is diagnosed on the basis of clinical criteria. Neurological involvement, although uncommon, is among the causes of higher morbidity and mortality rates, and is included in the differential diagnosis of inflammatory and demyelinating diseases of the central nervous system. The prevalence of neuro-BD (NBD) ranges between 1% and 59%, according to different series, and it is more common among men. Neurological involvement frequently develops 5 years after the diagnosis of BD, but may be a form of onset, which masks the diagnosis because of its atypical presentation.

Parenchymal or extraparenchymal involvement can be observed and, in rare cases, it has been reported to present in the form of a pseudotumor.

We present the cases of 2 patients who were diagnosed with NBD when pseudotumors of the brain were detected.

Case reports

Case no. 1

The patient was a 63-year-old man who presented with a 1-month history of behavioral changes in the form of irritability, aggressiveness and emotional lability, as well as difficulty in...
Table 1
Clinical Characteristics of the Cases Reported in the Literature.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (years)</th>
<th>Sex</th>
<th>History of Behçet's disease (years)</th>
<th>Lesion site</th>
<th>Lumbar puncture</th>
<th>Pathological findings</th>
<th>Outcome</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litvan</td>
<td>14 1987</td>
<td>M</td>
<td></td>
<td>Left parieto-occipital region</td>
<td>Increased proteins in cerebrospinal fluid with negative cultures</td>
<td>–</td>
<td>Partial improvement</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Neudorfer</td>
<td>27 1993</td>
<td>M</td>
<td>No history prior to diagnosis</td>
<td>Right lentiform nucleus</td>
<td>–</td>
<td>–</td>
<td>Improvement</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Genys</td>
<td>14 1993</td>
<td>M</td>
<td></td>
<td>Thalamocapsular region</td>
<td>–</td>
<td>Nonspecific. No evidence of tumor.</td>
<td>Improvement</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Dupin</td>
<td>20 1996</td>
<td>M</td>
<td>No history prior to diagnosis</td>
<td>Cerebellum</td>
<td>–</td>
<td>–</td>
<td>Improvement</td>
<td>Glucocorticoids, colchicine, azathioprine</td>
</tr>
<tr>
<td>Visaga</td>
<td>16 1996</td>
<td>F</td>
<td>2</td>
<td>From bulbomedullary junction to cerebral peduncle</td>
<td>No</td>
<td>No</td>
<td>Improvement</td>
<td>Glucocorticoids, chlorambucil</td>
</tr>
<tr>
<td>Yoshimura</td>
<td>41 2001</td>
<td>F</td>
<td>Several</td>
<td>Left thalamo-identical region</td>
<td>Pleocytosis</td>
<td>Nonspecific. No evidence of tumor.</td>
<td>Improvement</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Ben Taarit</td>
<td>26 2002</td>
<td>M</td>
<td>–</td>
<td>Protuberance and right cerebral peduncle</td>
<td>–</td>
<td>No</td>
<td>Improvement</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Imoto</td>
<td>50 2002</td>
<td>M</td>
<td>No history prior to diagnosis</td>
<td>Basal ganglia, brainstem and white matter</td>
<td>No</td>
<td>Inflammatory cells and perivascular infiltrate</td>
<td>Reduced size</td>
<td>3 glucocorticoid boluses</td>
</tr>
<tr>
<td>Park</td>
<td>52 2002</td>
<td>F</td>
<td>No history prior to diagnosis</td>
<td>Right cerebellar hemisphere extending to 3rd ventricle</td>
<td>Lymphocytes 25μL, proteins 300 mg/dL, glucose normal. No oligoclonal bands.</td>
<td>Lymphocytic vasculitis</td>
<td>Initial disappearance, Three episodes of recurrence, Death</td>
<td>Glucocorticoids, azathioprine</td>
</tr>
<tr>
<td>Tuzgen</td>
<td>59 2003</td>
<td>F</td>
<td>No history prior to diagnosis</td>
<td>Right frontotemporal region</td>
<td>No</td>
<td>Gliosis, panvasculitis, thrombosis, extensive infarction and vascular proliferation No</td>
<td>Radiological improvement. Persistant left hemiparesis</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Bennett</td>
<td>23 2004</td>
<td>M</td>
<td>–</td>
<td>Left diencephalic-mesencephalic junction</td>
<td>No</td>
<td>Perivascular inflammatory infiltrate</td>
<td>Clinical and radiological improvement</td>
<td>Glucocorticoids, azathioprine</td>
</tr>
<tr>
<td>Matsuo</td>
<td>33 2005</td>
<td>M</td>
<td>7</td>
<td>Basal ganglia</td>
<td>Pleocytosis 26 mm(^3) (mononuclear), normal glucose and protein levels. No oligoclonal bands</td>
<td>Reactive gliosis with inflammatory infiltrate</td>
<td>Improvement</td>
<td>3 glucocorticoid boluses</td>
</tr>
<tr>
<td>Schmolck</td>
<td>39 2005</td>
<td>M</td>
<td>5</td>
<td>Left thalamus</td>
<td>No</td>
<td>No</td>
<td>Radiological improvement</td>
<td>Dexamethasone, monthly cyclophosphamide boluses</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Age (years)</td>
<td>Sex</td>
<td>History of Behçet’s disease (years)</td>
<td>Lesion site</td>
<td>Lumbar puncture</td>
<td>Pathological findings</td>
<td>Outcome</td>
</tr>
<tr>
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</tr>
<tr>
<td>Darmoul et al.</td>
<td>2006</td>
<td>38</td>
<td>M</td>
<td>–</td>
<td>Left thalamus</td>
<td>–</td>
<td>No</td>
<td>Radiological improvement</td>
</tr>
<tr>
<td>Appenzeller</td>
<td>2006</td>
<td>43</td>
<td>F</td>
<td>20</td>
<td>Right thalamus, lentiform nucleus, subthalamic area and peduncle</td>
<td>No</td>
<td>Gliosis with gemistocytic astrocyte</td>
<td>Disappearance of the mass</td>
</tr>
<tr>
<td>Kösters</td>
<td>2006</td>
<td>30</td>
<td>M</td>
<td>No history prior to diagnosis</td>
<td>Frontoparietal region</td>
<td>Normal cell counts, glucose levels and protein levels. No malignant cells</td>
<td>Lymphocytic vasculitis of small vessels</td>
<td>Improvement</td>
</tr>
<tr>
<td>Heo</td>
<td>2008</td>
<td>47</td>
<td>M</td>
<td>10</td>
<td>Multiple masses in left pons region and left parietal cortex</td>
<td>No</td>
<td>Perivascular lymphocytic infiltrate, focal necrosis, gliosis, foamy histiocytes</td>
<td>Reduced mass size</td>
</tr>
<tr>
<td>Varoglu</td>
<td>2010</td>
<td>38</td>
<td>M</td>
<td>–</td>
<td>Mesencephalon, bilateral basal ganglia, posterior limb of internal capsule and centrum semiovale</td>
<td>No</td>
<td>Nontumoral lesions</td>
<td>Reduced lesion size</td>
</tr>
<tr>
<td>Bouomrani</td>
<td>2010</td>
<td>45</td>
<td>M</td>
<td>17</td>
<td>Brainstem</td>
<td>–</td>
<td>No</td>
<td>Improvement</td>
</tr>
<tr>
<td>Noel</td>
<td>2012</td>
<td>57</td>
<td>F</td>
<td>11</td>
<td>Lenticulocapsular</td>
<td>Aseptic meningitis</td>
<td>–</td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47</td>
<td>M</td>
<td>3</td>
<td>Peduncles, basal ganglia</td>
<td>Lenticulocapsular</td>
<td>Aseptic meningitis</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>M</td>
<td>10</td>
<td>–</td>
<td>Aseptic meningitis</td>
<td>Necrosis with inflammatory infiltrate, and infiltration by neutrophils, lymphocytes and macrophages compatible with vasculitis</td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>M</td>
<td>No history prior to diagnosis</td>
<td>Thalamocapsular</td>
<td>–</td>
<td>–</td>
<td>Improvement</td>
</tr>
<tr>
<td>Shapiro</td>
<td>2012</td>
<td>30</td>
<td>M</td>
<td>3</td>
<td>Lenticulocapsular</td>
<td>Aseptic meningitis</td>
<td>–</td>
<td>Improvement</td>
</tr>
<tr>
<td>Martínez-Estupián</td>
<td>2014</td>
<td>23</td>
<td>M</td>
<td>4</td>
<td>Cerebellum</td>
<td>Aseptic meningitis</td>
<td>Reactive changes</td>
<td>Poor response</td>
</tr>
</tbody>
</table>

--- unknown; F: female; IV: intravenous; M: male.
walking and agraphia. He mentioned a 35-year history of recurrent oral ulcers, and that sores had appeared on his genitals over the preceding 6 months, accompanied by folliculitis in the genital region and lower extremities. In the physical examination, he was found to have temporospatial disorientation; bradypsychia; right facial, brachial and femoral paresis (4/5); and tendency to list or veer toward the right when walking; together with oral and genital ulcers. The most noteworthy laboratory findings were elevated acute phase reactant levels, negative results in serological tests for Brucella, syphilis, hepatitis B virus, hepatitis C virus and human immunodeficiency virus, and negative findings in an autoimmunity study. He tested positive for HLA B51. Brain magnetic resonance imaging (MRI) revealed the presence of a space-occupying lesion in left thalamus (Fig. 1.1). An angiographic study of the supra-aortic trunks revealed small-vessel disease and atheromatous lesions in the carotid bifurcations, as well as saccular aneurysms and infundibula, with images of vascular nidi in the left carotid territory suggestive of vasculitis. Thoracoabdominal computed tomography was normal. Lumbar puncture yielded clear cerebrospinal fluid, with an unremarkable protein content, without oligoclonal bands. As NBD was suspected, treatment was initiated with methylprednisolone pulse therapy, followed
by oral prednisone (1 mg/kg body weight [bw]/day), colchicine (1 mg/12 h) and oral azathioprine (2 mg/kg bw/day). The patient’s clinical status improved, his genital ulcers disappeared and there was no evidence of the neurological manifestations. After 3 months of treatment, he underwent follow-up brain MRI which revealed the complete resolution of the lesion (Fig. 1.2). After 15 years of follow-up, the patient has no clinical neurological symptoms and is receiving absolutely no treatment. However, he has had sporadic oral aphthae, which have responded well to colchicine.

Case no. 2

The second patient was a 35-year-old woman who had generalized seizures and a 2-month history of paresthesia in the right malar region. The results of the physical examination were normal. Laboratory analyses showed elevated acute phase reactant levels, negative results in serological tests for human immunodeficiency virus, hepatitis B virus and hepatitis C virus, and a negative autoimmune study. Brain MRI revealed the presence of an intraparenchymal infiltrative lesion affecting left frontoparietal region, with enhanced images following gadolinium administration (Fig. 1.3), which was diagnosed as a brain tumor. Lumbar puncture yielded clear, acellular fluid with slightly elevated protein content and no oligoclonal bands. Treatment was begun with intravenous dexamethasone (12 mg/day), which was subsequently tapered. Twenty days later, brain MRI showed a significant reduction in the size of the lesion (Fig. 1.4). 11C-methionine positron emission tomography (PET) of the brain suggested the presence of cerebral lymphoma (Figs. 1.7 and 1.8). The brain mass was biopsied, and the histological study revealed the presence of a focal necrotizing granulomatous infiltrate with lymphocytic vasculitis (Figs. 1.5 and 1.6). Ziehl-Neelsen, periodic acid Schiff (PAS) and silver stains were negative. The results of thoracoabdominal computed tomography, 67gallium scintigraphy and a transbronchial biopsy ruled out sarcoidosis. Three months later, the patient developed oral and genital ulcers. She tested positive for HLA B51. With findings indicative of NBD, treatment was begun with monthly cyclophosphamide pulses (1 g/month) plus tapering glucocorticoid doses. After 5 months with this treatment, she had another seizure, and brain MRI performed at that time showed that the lesion had increased in size. As cyclophosphamide was considered to be ineffective, it was replaced by oral azathioprine (2 mg/kg bw/day) and the prednisone dose was increased to 30 mg/day, after which it was tapered. Four months later, there was no evidence of improvement in the lesion on brain MRI, and the decision was made to start treatment with intravenous infliximab (3 mg/kg bw every 8 weeks). After 8 doses of infliximab, there was a significant reduction in the size of the mass, but the patient developed diffuse joint pain and refused to continue the treatment. It was replaced by adalimumab, which she tolerated well. At the time of this writing, 5 years later, she continues to receive subcutaneous adalimumab (40 mg/15 days) as single-drug therapy. Her tolerance is well and the brain lesion has not progressed. Over the course of the disease, she has had episodes of oral ulcers that responded to symptomatic treatment.

Discussion

The clinical presentation and course of NBD complicate the diagnosis of this condition. It can present either in the acute form, which responds well to treatment with glucocorticoids and immunosuppressive agents, or in the progressive or chronic form (in which high interleukin 6 [IL-6] concentrations have been reported in cerebrospinal fluid), which is normally resistant to glucocorticoid, cyclophosphamide and azathioprine therapy. These patients have been found to have a better response to methotrexate and/or infliximab. The presence of lesions compatible with pseudotumors on brain MRI is very rare in NBD, especially as the form of onset of the disease. The neurological manifestations of BD usually appear from 2 to 4 years after the first clinical sign. However, cases of NBD in which the neurological manifestations preceded other signs of the disease have been reported in the scientific literature. For this reason, when there is a single brain lesion in the absence of other signs, such as oral and genital ulcers, the diagnosis of BD proves to be complicated.

The differential diagnosis of NBD includes multiple sclerosis, infections, vascular disease and tumors. While both computed tomography and MRI of the brain are sensitive imaging techniques for the diagnosis of lesions, the sensitivity of the latter is greater.

In brain MRI, the finding is described as a hypointense signal on T2-weighted images, located predominantly at the diencephalic mesencephalic junction and in the basal ganglia, although the lesion is sometimes found in the periventricular white matter. This makes it difficult to differentiate between NBD and multiple sclerosis. However, multiple locations are reported in the scientific literature (Table 1), and its presentation has even been described as a hypointense mass on T2-weighted images. To differentiate it from a tumor in the definitive diagnosis, it is sometimes necessary to perform a brain biopsy, as in the second case reported here.

The histological study of biopsies of brain pseudotumors in NBD reveals a perivascular inflammatory infiltrate, gliosis, necrosis or neuronal loss.

Treatment with glucocorticoids, as well as the use of other immunosuppressive agents (cyclophosphamide or azathioprine), is accompanied by a rapid response, with a reduction in size or even the disappearance of the lesion.

To date, 27 cases of pseudotumors developing in the course of NBD have been reported in the scientific literature (PubMed: 1987–2014; search terms: neuro-Behcet, pseudotumoral). The Table shows the clinical characteristics of these lesions. The reported cases suggest that pseudotumors develop more often in men (n = 18, 66.7%) than in women, with a mean age at presentation of 38 years (range, 16–59 years); the most common site was the thalamus and basal ganglia. All the patients described were initially treated with high-dose oral or intravenous glucocorticoids. Other immunosuppressive agents, such as azathioprine, cyclophosphamide, methotrexate and chlorambucil, were added.

The patient in our first case responded rapidly to treatment with glucocorticoids and azathioprine, whereas the second patient required biological therapy with anti-tumor necrosis factor-α and infliximab at first and, subsequently, adalimumab. This is one of the few cases of the use of biological therapy for the management of these patients reported in the literature.

A pseudotumor in NBD should be considered in the differential diagnosis of brain masses, especially when a good clinical response is achieved after treatment with glucocorticoids. Biopsy may sometimes be necessary to confirm the diagnosis.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.
Conflicts of Interest

The authors declare they have no conflicts of interest.

References