A Case of Neuro-Behcet’s Disease Presenting with Central Neurogenic Hyperventilation

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Conflict of interest: None declared

Patient: Female, 46

Final Diagnosis: Central hyperventilation

Symptoms: Hyperventilation

Medication: —

Clinical Procedure: None

Specialty: Neurology

Objective: Unusual clinical course

Background: Behcet’s disease is a chronic inflammatory disorder usually characterized by the triad of oral ulcers, genital ulcers, and uveitis. Central to the pathogenesis of Behcet’s disease is an autoimmune vasculitis. Neurological involvement, so called “Neuro-Behcet’s disease”, occurs in 10–20% of patients, usually from a meningoencephalitis or venous thrombosis.

Case Report: We report the case of a 46-year-old patient with Neuro-Behcet’s disease who presented with central neurogenic hyperventilation as a result of brainstem involvement from venulitis.

Conclusions: To the best of our knowledge, central neurogenic hyperventilation has not previously been described in a patient with Neuro-Behcet’s disease.

MeSH Keywords: Behcet Syndrome • Demyelinating Autoimmune Diseases, CNS • Hyperventilation • Vasculitis, Central Nervous System

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Behcet’s disease is a chronic inflammatory disorder first described in 1937 by Hulusi Behcet, a Turkish dermatologist [1]. Patients typically present with the triad of oral ulcers, genital ulcers, and uveitis but often develop other manifestations, including involvement of the skin, gastrointestinal tract, kidneys, lungs, heart, blood vessels, and the central nervous system. Neurological involvement, so called “neuro-Behcet’s disease”, occurs in 10–20% of patients [1–3]. Here, we report on a patient with neuro-Behcet’s disease who presented with central neurogenic hyperventilation as a result of brainstem involvement from venulitis. Initially described by Plum and Swanson in 1959 [1–3], central neurogenic hyperventilation results from lesions in the medial pontine tegmentum and disruption of cortical inhibitory effects of the medullar respiratory center. To the best of our knowledge, central neurogenic hyperventilation has not previously been described in a patient with neuro-Behcet’s disease.

Case Report

A 46-year-old woman from the Dominican Republic developed progressive dyspnea over a 2-month period. In March 2013 she developed intermittent, dull, left-sided retro-orbital headaches. These were not associated with any typical features of migraine such as nausea, vomiting, photophobia, or visual scintillations, nor were they severe enough to interrupt her daily routine. One month later, in April, she suddenly lost vision in her left eye and was diagnosed with a retinal detachment. In May she started feeling dizzy and developed an ataxic gait. She also appeared withdrawn and had a decreased appetite, which her family attributed to the recent visual loss; by June, she had lost nearly 40 pounds. In July, she started having intermittent episodes of hyperventilation that would resolve spontaneously. Over the next month, however, these episodes became more frequent and prolonged and she developed confusion, drowsiness, and generalized weakness. In August, she was admitted for continuous hyperventilation and respiratory distress. Arterial blood gas analysis revealed a severe respiratory alkalosis with a pH 7.56 and PCO₂ 9 mm Hg. Review of systems revealed no history of fever, infections, rashes, ulcers, myalgias, joint pain, or paresthesias. She denied any exposure to toxins and reported no sick contacts. On general examination, she was a thin woman in mild distress from tachypnea with a respiratory rate of 30 breaths per minute. Oxygen saturation was 100% on 2 liters nasal cannula. She was normotensive with a regular heart rate and rhythm. Her mouth was dry and no ulcers were seen. There were no skin rashes. On neurologic examination, she was drowsy and oriented only to herself but followed simple commands. Her speech was clear. Her right pupil was 3 mm and reactive to light and her left pupil had post-surgical findings. Visual fields were normal in her right eye. She had no vision in her left eye. Eye movements were full, with slightly decreased upgaze. Motor exam revealed a spastic tone in the right limbs compared to the left. There was right arm and leg drift with 4/5 strength. Strength on the left was 4+/5. Sensation was intact. Muscle stretch reflexes were asymmetric, being 3+ in right arm and patella and 2+ in left arm and patella. Clonus was present in both feet but more on the right. Both toes were downgoing. Brain MRI showed extensive hyperintense signal changes on FLAIR and T2-weighted images involving the supratentorial white matter, midbrain, pons, medulla, middle cerebellar peduncles, and part of the basal ganglia and thalami. There was no restriction of diffusion on diffusion-weighted images. There was widespread sulcal effacement and cisternal effacement (Figure 1). Intracranial MRA revealed mild irregularity and stenosis of the supraclinoid segments of both internal carotid arteries and the A1 segment of the right anterior cerebral artery. There was moderate stenosis of the inferior division of the right middle cerebral artery and irregularity and mild fusiform dilatation of the distal M2 segment. There was

Figure 1. Axial brain MRI FLAIR sequences of the patient on admission showing bilateral extensive hyperintense signal changes. The black arrow points to the lesions in the medial pontine tegmentum.
also mild stenosis of the superior division of the left middle cerebral artery and irregularity in the M2 segment (Figure 2). MRI of the cervical spinal cord was normal.

CSF analysis showed lymphocytic pleocytosis and an elevated protein concentration of 52 mg/dL. Testing for oligoclonal bands, myelin basic protein, and IgG index were positive. Serology was negative for ANA, Anti SSB, anti SSA, Anti Jo, Anti chromatin, Anti centromere, Anti ds DNA, Anti ribosomal, Anti smith, and Anti sm/rnp antibodies. ANCA / MPO / PR3 testing was negative. Serology was negative for HIV, HTLV, HSV, and JC virus and a paraneoplastic work-up was negative. Testing for skin pathergy was negative.

Brain biopsy of the right frontal lobe demonstrated necrosis and perivascular inflammation of multiple venules infiltrated predominantly by lymphocytic inflammatory cells (Figure 3). Perivenous demyelination was not identified (confirmed by Luxol Fast Blue and CD68 immunostaining). Neither arteritis nor encephalitis was identified. Histopathological features were felt to be most consistent with neuro-Behcet’s disease.

The patient was treated with methylprednisolone 1000 mg IV once daily for 5 days followed by prednisone 60 mg orally once daily. During this period, an ulceration in the vermillion border of the patient’s left upper lip was noted. After beginning corticosteroids, there was remarkable improvement in her mental status and hyperventilation and she was discharged to a rehabilitation facility.
One month later, however, in September 2013, the patient was readmitted with progressively worsening tachypnea together with weakness in both legs. Repeat brain MRI again showed diffuse supratentorial white matter hyperintense lesions on FLAIR and T2-weighted images. There were also new areas of restricted diffusion involving the left lateral ventricular body, atrium junction and left forceps minor and right medullary pyramid. Repeat cervical cord MRI also showed new hyperintensity on T2-weighted imaging involving the upper cervical cord (from cervical-medullary junction down to C3) with no contrast enhancement.

Further work-up revealed that she harbors the HLA-B51 allele. The patient was again treated with methylprednisolone 1000 mg IV daily for 5 days. However, over the course of the next week, she became quadriplegic. She was treated with cyclophosphamide 500 mg IV and continued on Prednisone 60 mg orally once daily. The patient was discharged to a long-term acute facility but died 3 weeks after discharge.

Discussion

Behcet’s disease is common in the Middle East, with an incidence of 0.58 per 100 000 population and a prevalence in Turkey of 420 per 100 000 population. In the Western hemisphere the exact incidence is less certain but is estimated to be 0.24 per 100 000 population and with a prevalence between 0.12 and 7.5 per 100 000 population [1–5]. The onset usually occurs in the third decade of life with an equal sex predilection (although a male preponderance in Turkey has been described) [1]. Central to the pathogenesis of Behcet’s disease is an autoimmune vasculitis possibly induced by microbial pathogens in genetically susceptible individuals such as those with the HLA-B51 gene [1]. Increased expression of several proinflammatory cytokines seems to be responsible for the enhanced inflammatory reaction in patients with Behcet’s. Specifically, high serum levels of IL-6 and IL-8 have been found during active phases of the disease [1,2]. Polymorphisms in the promoter region of the tumor necrosis factor gene (located in the vicinity of the HLA-B locus) and in the endothelial nitric oxide synthase gene are also thought to play a role [1,2]. While blood vessels of all sizes can be involved, the disease tends to mainly involve small veins.

Clinically, patients typically present with recurrent mouth ulcers that can be severe, involving the soft palate and oropharynx and causing difficulty eating, swallowing, and speaking [1]. Genital ulceration is the second most common manifestation of Behcet’s disease, developing in over half of patients [1]. Ocular disease is seen in 30–70% of patients and usually begins after the mouth ulcers, but in 20% of patients these may be the presenting feature [1]. The most common ocular finding is inflammation of the anterior uvea and the vascular middle layer of the eye. In addition to anterior uveitis, patients can present with a broad range of ophthalmologic conditions, including posterior uveitis (chorioretinitis), retinal vasculitis, and retinal detachment [1].

Neurological manifestations, when they occur, tend to develop late, with average time between onset of the disease and neurological symptoms of about 6 years [1]. In neuro-Behcet’s disease there typically is direct involvement of the brain, usually in the form of a meningoencephalitis with an intense inflammatory infiltration of lymphocytes, eosinophils, and macrophages, and areas of necrosis and apoptotic neuronal loss [1]. In the non-parenchymal form, vascular complications involving thrombosis within large veins and occasionally arteries occur, as well as vasculitis that more often involves small veins [1,2]. In some cases, an obliterative endarteritis of the vasa nervorum can result in focal vascular dilatation and aneurysm formation [1]. The structures within the brainstem, thalamus, basal ganglia, and white matter are all affected to varying degrees. In chronic cases, there can be striking atrophy of brainstem structures seen on MRI [2]. The reason for this propensity of lesion localization in the brainstem is not clear [1–3] but it explains why patients often develop brainstem syndromes, hemiparesis, and ataxia [1,2]. Headache is also common, both migraine and tension type [1]. The course may be relapsing-remitting initially followed by a secondary progressive phase, and occasionally a primary progressive course is seen from the beginning [1].

Our patient presented with a headache and retinal detachment 1 month before she developed neurological symptoms that localized to the brainstem (dizziness and ataxia). As these symptoms worsened, she developed progressive hyperventilation over a 2-month period. Brain MRI showed extensive increased signal on FLAIR and T2-weighted images, mainly affecting the white matter bilaterally but also in the basal ganglia and thalamus, and symmetrically extending from the cerebral hemispheres down to the brainstem and eventually into the upper cervical spinal cord. Intracranial MRA showed several areas of mild irregularity and stenosis suggestive of cerebral vasculitis. Brain biopsy, however, revealed venulitis and necrosis with no evidence of arteritis or demyelination. She was also found to harbor the HLA-B51 allele, which has been closely linked to Behcet’s disease [1]. Thus, the clinical, radiological, and pathological findings were most consistent with neuro-Behcet’s disease, albeit with a rare presentation. Kumral et al. recently reported a similar patient with neuro-Behcet’s disease associated with venulitis affecting the brainstem, although the disease in their patient was much less extensive and the patient had a better outcome than ours [1].
The differential diagnosis in our patient included severe multiple sclerosis and syndromes of demyelination. However, brain biopsy showed no evidence of demyelination (Figure 4). Other uveo-meningitis syndromes such as those associated with sarcoidosis, systemic lupus erythematosus, and Sjögren’s syndrome were considered. However, our patient had no clinical signs or serological evidence of these conditions. Vogt-Koyanagi-Harada (VKH) syndrome is a rare autoimmune disorder that is characterized by bilateral uveitis and retinal detachment, patchy vitiligo, alopecia, hearing loss, tinnitus, headaches, and meningismus [1]. MR imaging has described hyperintense lesions on T2-weighted imaging, including within the brain stem and peduncle, as well as meningeal enhancement [1,2]. However, our patient’s clinical presentation (unilateral retinal detachment), absence of meningeal disease, extensiveness of brain and brainstem involvement, and, most importantly, histopathology showing venulitis, made the diagnosis of VKH unlikely. Neoplastic causes such as lymphoma or glioblastoma cerebri were excluded by brain biopsy. Finally, the intracranial MRA suggested cerebral vasculitis. However, the histopathology revealed only venulitis and not arteritis, a finding typical in Behcet’s disease. However, we cannot exclude the possibility that not finding arteritis may have been a sampling error given the segmental nature of the disease. The development of areas of restricted diffusion on the second MRI would certainly suggest arterial involvement, but it is more likely, given the overall clinical picture, that this vasculitis developed as a manifestation of neuro-Behcet’s disease rather than being a primary CNS vasculitis.

Our case nevertheless is remarkable in several ways. First, almost all patients with Behcet’s disease develop recurrent oral ulcerations. So consistent is this finding that it is a prerequisite for the diagnosis according to the International Criteria for Behcet’s Disease [1]. Our patient did have an oral ulceration, but this came very late in the course and only after her other neurological symptoms appeared. Second, our patient did not have any evidence of genital ulcerations, skin lesions or skin pathergy, or a hyper-reactivity to non-specific physical insults such as a pinprick. Each of these findings generally occurs in 50–60% of patients, although pathergy may be less frequent in patients from the Western hemisphere [1,2]. Third, uveitis is the most frequent ocular manifestation of Behcet’s disease. While retinal detachment has been well described, it is certainly uncommon. Fourth, neuro-Behcet’s disease is rare, occurring in 10–20% of patients with Behcet’s disease. Typically this develops several years after the diagnosis of Behcet’s. To have a patient present with neurological symptoms is very rare. Sixth, the most common presentation of neuro-Behcet’s disease is meningoencephalitis followed by venous thrombosis. While venulitis is typical for Behcet’s disease, it is still uncommon. Finally, symptoms attributable to brainstem involvement have been well reported in patients with Behcet’s disease.
Conclusions

We report the case of a patient with neuro-Behcet’s disease who presented with central neurogenic hyperventilation as a result of brainstem involvement from venulitis. To the best of our knowledge, central neurogenic hyperventilation has not previously been described in a patient with neuro-Behcet’s disease.

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