



Neuro-Behçets in a Child

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Abstract

We describe a case of neuro-Behçet disease diagnosed in a 12-year-old girl. This patient presented with recurrent oral ulcers, incontinence, spastic gait, blurry vision, and asymmetrical lower extremity hypertonia. Extensive testing revealed punctate lesions through the central nervous system, vitritis, papillitis, and uveitis. A thorough infectious and neoplastic workup was negative. She was treated with pulse steroids and azathioprine with gradual improvement in her gait and ophthalmologic findings. Although rare, primary neuro-Behçet should be considered in pediatric patients with neurologic abnormalities and recurrent aphthous ulcers without other explanation.

Keywords

MRI, uveitis, vitritis, papillitis, hypertonia, incontinence, urinary tract infection, azathioprine

Received July 28, 2014. Received revised July 28, 2014. Accepted for publication August 17, 2014.

Written by Hippocrates of Kos in the fifth century BC, the third volume of *Epidemion* contains a description of a series of patients with relapsing fever, oral and genital ulcers, and “fungal” growths in the eye and eyelids that frequently led to blindness. In 1930, over 2000 years after that first description, another Greek physician, Benediktos Adamantiades, presented a lecture titled “A case of relapsing iritis with hypopyon” in which he described a male patient with oral and genital ulcers, iritis, and arthritis.¹ In 1937, Hulusi Behçet, a dermatologist from Istanbul described the so-called “triple-symptom complex” with symptoms similar to those described by Adamantiades.²

Since that time, cases of Behçet disease have been found along the path of the Silk Road, a 4000-mile long ancient trading route which spanned from the Mediterranean Ocean to China.³ Prevalence varies in countries along the path, ranging from 2 to 370 per 100 000 with the highest prevalence noted in Turkey and Japan. Prevalence in the non-Silk Road countries such as the United States is substantially lower at 0.33 per 100 000³ and even more rare in children, which encompass only 2% to 3% of all cases of Behçet disease.⁴ Additional epidemiologic data have shown an increased relative risk for those with either human lymphocyte antigens (HLA) B5 or B51, with HLA B51 carrying a relative risk for Behçet disease of 6.3.⁵

In this report, we describe an unusual presentation of primary neuro-Behçet disease in a 12-year-old girl.

Case Report

Approximately 2 years prior to her initial neurological evaluation, a 12-year-old girl developed both urinary tract infections in the context of recurrent stress-induced and nocturnal urinary incontinence. One year prior to her presentation, she began to develop recurrent oral ulcers, at the time thought to be “cold sores.” Eight months prior to her presentation, she began to experience intermittent back pain and blurred vision, sporadic abdominal pain, and progressive clumsiness in her lower extremities that caused frequent falls. Two weeks prior to her initial visit at our institution, she was admitted to a psychiatric unit after a suicide attempt.

Due to her progressive symptoms, she was referred to our pediatric neurology clinic for evaluation. At her initial visit, her examination was notable for asymmetric spasticity (right greater than left) in her lower extremities with prolonged ankle

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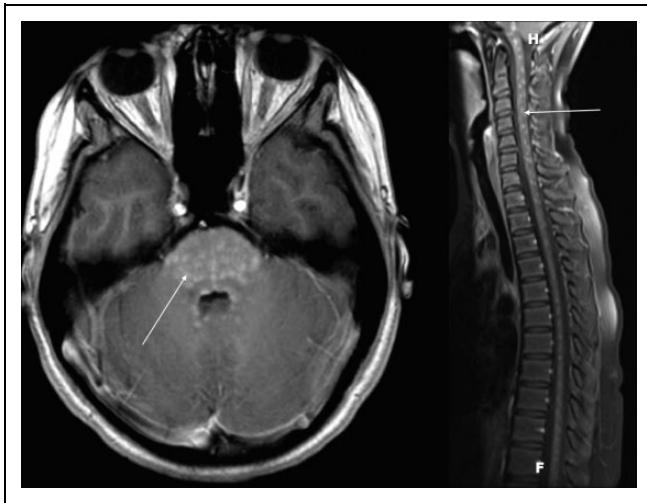


Figure 1. T1 brain and spine images with contrast. On left, axial slice at the level of the brain stem and cerebellum and on the right, sagittal view of spine. Arrows highlight contrast-enhanced lesions seen throughout the spinal axis.

clonus and bilateral extensor plantar responses. Her gait was unsteady, with persistent inversion and circumduction of the right foot, and she was unable to perform a tandem gait maneuver. Her initial visual examination demonstrated normal acuity, pupillary responses, and extraocular movements. No rash, mucosal lesions, or joint symptoms were noted. A brain and spinal magnetic resonance imaging (MRI) with contrast was performed and revealed innumerable contrast enhancing, punctuate lesions throughout her entire cerebrum, brain stem, and spinal cord. The majority of her lesions were infratentorial as shown in Figure 1.

The differential for her symptoms and radiographic findings was broad and included neurosarcoidosis, primary central nervous system lymphoma, central nervous system infection, primary demyelinating diseases, and central nervous system vasculitis. Extensive evaluation for infectious, oncologic, and rheumatologic etiologies was negative except for a positive urine culture (>100 000 colony-forming unit of *Escherichia coli*), positive antinuclear antibody (1:320, speckled pattern), abnormal cerebrospinal fluid indices (20 nucleated cells/high-powered field with 97% lymphocytes—a persistent finding over repeat lumbar punctures, protein 65 mg/dL, and glucose 58 mg/dL), and cerebrospinal fluid angiotensin-converting enzyme level of 7 units/L. A summary of her evaluation is presented in Table 1.

Her visual complaints evolved from a nonspecific “blurring” to loss of perceived acuity that impacted her ability to read. An ophthalmologic examination subsequently revealed vitritis, papillitis, and leakage or extravasation of fluorescein dye during the angiogram consistent with vasculitis as shown in Figure 2. No dermatologic lesions were identified. Given the negative neoplastic and infectious workup, therapy with 2 mg/kg of methylprednisolone was initiated for empiric treatment of a primary central nervous system vasculitis.

Within 3 days of therapy initiation, an improvement in both her gait and vision occurred. She transitioned to 1 mg/kg of prednisone and was discharged home. One month after steroid initiation, a repeat MRI demonstrated that the punctuate lesions previously seen throughout the brain and spinal cord were no longer contrast enhancing. Four months after the start of steroid treatment, the vitritis and papillitis had resolved, she was able to walk a longer distance with less effort and fatigue, and her incontinence had improved substantially. The prednisone was gradually tapered and stopped.

Unfortunately, 2 months after cessation of steroids her gait abnormalities, visual disturbances, arthralgias, and urinary incontinence abruptly worsened, prompting a repeat MRI scan that revealed progression of her contrast-enhancing spinal and brain lesions as compared to the initial study. Given the severity of her symptoms, brain, bone marrow, and conjunctival biopsies were performed. The conjunctival biopsy did not reveal any abnormalities. Three separate central nervous system biopsy specimens were obtained from the dura, parenchyma, and ependymal lining. Both the dural and parenchymal specimens were unremarkable. However, the ependymal biopsy demonstrated atypical areas of well-demarcated inflammation (reactive astrocytes, lymphocytes, macrophages, and activated microglia) and proportional loss of axons and myelin in a perivascular distribution but without clear evidence of vasculitis as shown in Figure 3.

Given the evidence of neuroinflammation on biopsy, an empiric course of intravenous immunoglobulin was initiated. Despite treatment, her visual complaints and gait disturbance continued to worsen. Plasma exchange was then performed a total of 7 times with incremental improvement in her symptoms after each treatment. Given the constellation of her symptoms (visual and gait disturbances, arthralgia, and psychiatric problems), ophthalmologic (vitritis, papillitis, and uveitis) and biopsy findings (proportional loss of myelin and axons in an inflammatory background), and history of recurrent oral ulcers, a presumptive diagnosis of neuro-Beçet disease was made. Azathioprine was initiated at 50 mg/d and was well tolerated. Twenty-four months after starting azathioprine, she regained her original lower extremity strength and visual acuity, has no complaints of abdominal pain, and has not had any further gait disturbance.

Discussion

The cause of Beçet disease remains elusive, although many theories have been proposed. Beçet proposed that the Herpes virus was the cause of the disease² and indeed there is evidence showing a greater presence of herpes simplex virus DNA in saliva in patients with Beçet disease, although nearly 60% of patients with Beçet disease had no herpes simplex virus isolated.⁶

An autoimmune model⁷ for the disease has also been proposed after the observation of CD4+ T cells present in perivascular infiltrates and increased circulating levels of interleukin 8. The autoimmune proposal was bolstered after gene

Table 1. Summary of Diagnostic Workup.

Inflammatory	
ANA	Positive (1:320, speckled)
Angiotensin-converting enzyme (serum)	0 units/L
Angiotensin-converting enzyme (cerebrospinal fluid)	7 units/L
Antineutrophil cytoplasmic antibodies	Normal
Erythrocyte sedimentation rate	Normal
C-reactive protein	Normal
SS-A and SS-B	Normal
C3	Normal
C4	Normal
Oligoclonal bands (serum)	1 band
Oligoclonal bands (cerebrospinal fluid)	3 bands
Neuromyelitis optica antibody (cerebrospinal fluid)	Negative × 3
Infectious	
Urine culture	>100 000 colony-forming unit of <i>Escherichia coli</i>
Cerebrospinal fluid analysis	Glucose 58 mg/dL
	Protein level 65 mg/dL
	Relative lymphocytosis (20 nucleated cells/high-power field, 97% lymphocytes)
Cerebrospinal fluid culture	No growth
Blood culture	No growth
Serologic studies	Negative (<i>Histoplasma capsulatum</i> , <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Cryptococcus neoformans</i> , <i>Treponema pallidum</i> , <i>Bartonella henselae</i> , <i>Borrelia burgdorferi</i> , <i>Toxocara</i> , <i>Brucella</i> , <i>Mycobacterium tuberculosis</i> , <i>Tropheryma whipplei</i> , <i>Varicella</i> , Epstein-Barr virus, cytomegalovirus, human T-lymphotropic virus, human T-lymphotropic virus I and II and human immunodeficiency virus)
Neoplastic	
PET	Normal
Peripheral smear	Normal
Bone marrow biopsy	Normal
Brain biopsy	Atypical inflammatory demyelinating disease with well-demarcated areas of inflammation (reactive astrocytes, lymphocytes, macrophages, and activated microglia) with proportional loss of axons and myelin in a perivascular distribution
Cerebrospinal fluid flow cytometry	Normal

Abbreviations: ANA, antinuclear antibody; PET, positron emission tomography.

Note: Bold items indicate notable findings

sequencing revealed a candidate gene for Behçet disease to be located between the coding regions for HLA B and tumor necrosis factor.⁸

Behçet disease can also be classified as an autoinflammatory disease with a degree of symptom overlap with another autoinflammatory disease, Familial Mediterranean fever. Indeed, one study of patients with Behçet disease revealed a higher than expected mutation rate in the gene associated with Familial Mediterranean fever, *MEFV*.⁹ The presence of neutrophils in the pathologic lesions of Behçet disease further supports the important role of the innate immune system in the development of this disease.

The most common symptoms of Behçet disease in adult and pediatric cases are oral aphthous ulceration (95%-100%) and uveitis (30%-75%).⁴ A broad spectrum of other manifestations have been described, including rashes, arthritis, arterial and venous vasculitis, and central nervous system lesions. When compared to adults, children are less likely to have genital ulcers and vascular lesions but are more likely to have arthralgia and central nervous system symptoms.¹⁰ In 1990, the International Study Group for Behçet Disease¹¹ published criteria

for the diagnosis of Behçet disease requiring the presence one mandatory criteria (recurrent oral aphthous ulcers) and at least 2 minor criteria, which are listed in Table 2.

The spectrum of central nervous system findings in neuro-Behçet disease can vary widely. Metreau-Vastel et al¹² described a series of 12 children with neuro-Behçet disease in 2010. In this report, they describe focal neurologic deficits as the most common symptom, occurring in 4 of 12 patients. Recurrent meningoencephalitis and rhombencephalitis were the second most common findings, each occurring in 2 of 12 patients. Interestingly, one patient in that case series had psychiatric symptoms at disease onset. Nonspecific psychiatric symptoms have been described in other cases, including changes in affect, auditory and visual hallucinations, and suicidal behavior.¹³

No standardized treatment has been proposed for Behçet disease or neuro-Behçet disease as the presentation and involved organ systems vary widely. The European League Against Rheumatism (EULAR) published a set of guidelines, based on an analysis of published literature, for the treatment of Behçet disease organized by affected organ system.¹⁴

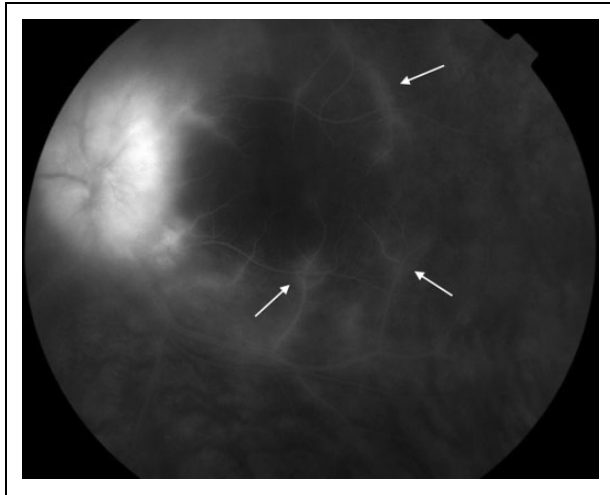


Figure 2. Fluorescein retinal angiography OS. Arrows highlight extravasation of fluorescein dye.

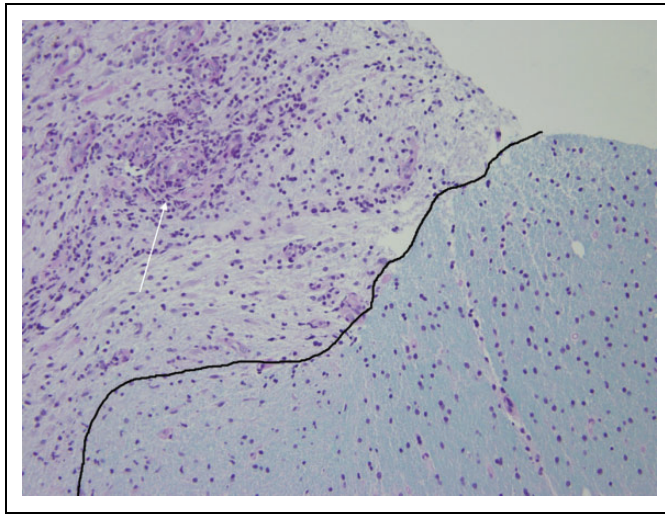


Figure 3. Luxol fast blue/periodic acid Schiff 10 \times . Marked demyelination on the left of the line compared to the normal white matter on the right. On the left, the vessels appear darker. The inflammation extends from these vessels (arrow) and is somewhat clustered around these areas.

In these guidelines, cyclosporine A was described as a highly effective agent for the treatment of ocular disease. However, as later noted, cyclosporine A has been shown to potentiate neurologic symptoms in several cases of Behçet disease and so should not generally be utilized in patients having Behçet disease with preexisting central nervous system symptoms. Although, no randomized, controlled trial has been conducted for the treatment of neuro-Behçet disease, azathioprine, corticosteroids, and methotrexate have been used in published reports.¹⁴ In addition, more recent reports have described the off-label use of antitumor necrosis factor agents (ie, infliximab, etanercept, and adalimumab) with promising results.^{14,15} Due to its use in the treatment of lupus-related neuropsychiatric symptoms and a relatively good side effect profile, we chose

Table 2. International Study Group for Behçet Disease Diagnostic Criteria.

Mandatory criteria (required)	Minor criteria (at least 2 required)
<ul style="list-style-type: none"> Recurrent oral aphthous ulcers (at least 3 occurrences in a 12-month period) 	<ul style="list-style-type: none"> Recurrent genital ulcers Eye lesions Skin lesions (ie, erythema nodosum) Positive pathergy test

to utilize azathioprine as a steroid-sparing agent in our patient and were able to achieve an excellent outcome.

Acknowledgments

The authors wish to thank Nicholas J. Silvestros, OD, for providing the retinal angiography images and the Department of Pathology for the biopsy images.

Author Contributions

ZAV, RG, BWO, and AJW contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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