Clinical Reasoning: Rare Cause of Hemiparesis and Ataxia in a 36-Year-Old Man

Jessica Decker, DO, and Mini Singh, MD

Neurology® 2022;98:251-255. doi:10.1212/WNL.0000000000013142

Correspondence
Dr. Decker
deckerje@musc.edu

Section 1

A 36-year-old left-hand dominant Haitian man presented with a 1-week history of intractable headache, slurred speech, and right facial and hemibody weakness and numbness. In retrospect, he reported episodes of blurred vision, painful oral ulcers, and a nonpruritic rash for 3 years. He was found to have a right retinal hemorrhage on a recent eye examination that was treated with ocular VEGF injections without improvement. On examination, he had oral aphthous ulcers and white papulopustular lesions on the trunk and extremities. His neurologic examination was significant for right-sided facial weakness in an upper motor neuron type pattern, dysarthria, right-sided hemiparesis and hemianesthesia, and right upper extremity ataxia.

Questions for Consideration:

1. What is the anatomic localization of these neurologic deficits?
2. What is your differential diagnosis?
3. What further diagnostics should be performed?

GO TO SECTION 2

From the Department of Neurology, Medical University of South Carolina.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 2

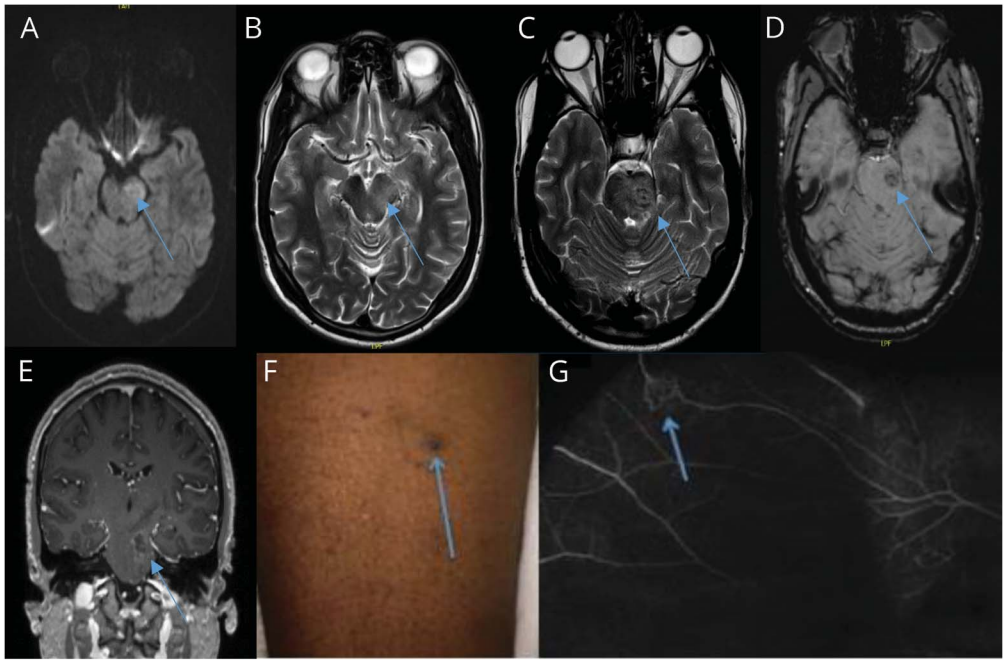
Right hemiparesis with an upper motor neuron pattern of facial weakness localizes anywhere along the corticospinal tract from the contralateral pons at the level of the facial nucleus cephalad. Presence of right-sided ataxia indicates spinocerebellar pathway involvement and localizes to the contralateral midbrain/medulla or ipsilateral/contralateral pons due to decussation of the spinocerebellar pathway, contralateral thalamus, or ipsilateral cerebellum. Loss of sensation to pinprick localizes to anywhere along the contralateral spinothalamic tract from the pons to the somatosensory cortex, as decussation occurs within the spinal cord. The constellation of findings could be seen with a solitary thalamic lesion with internal capsule extension, solitary lesion within the pons, or multiple lesions involving corticospinal, spinothalamic, and/or spinocerebellar pathways. With this clinical picture, the initial differential included infection, various causes of stroke in a young person including vasculitis and connective tissue disorders, and neoplasm.

Initial workup included a noncontrast CT of the head revealing a left basal ganglia hypodensity extending into the superomedial midbrain, pons, and cerebellar peduncle. There was no evidence of hemorrhage. A contrast cranial MRI was obtained, demonstrating restricted diffusion in the left midbrain extending into the pons (Figure, A). T2-sequence revealed a larger area of hyperintensity involving the left basal ganglia, posterior limb of the internal capsule, midbrain, pons, superior cerebellar peduncle, pontomedullary junction, and anterior commissure (Figure, B and C). Patchy abnormal contrast enhancement and hemosiderin staining was noted within the left brainstem (Figure, D and E). CT angiography of the head/neck was unremarkable.

Restricted diffusion with patchy contrast enhancement is commonly visualized in vascular insult; however, it can be observed in early demyelination, neoplasms, and infections. Inflammatory and neoplastic etiologies of vascular insult were considered including primary angiitis of the CNS, neurosarcoidosis, Neuro-Behcet disease (NBD), and intravascular lymphoma. Additional inflammatory conditions considered that typically do not affect vasculature, but have a predilection for deep gray/white matter and brainstem include neuromyelitis optica spectrum disorders (NMOSDs) and Bickerstaff encephalitis. History of vision impairment and systemic symptoms including diffuse papulopustules and aphthous ulcers narrowed our differential and were most concerning for a systemic inflammatory condition involving the CNS.

Serum glucose, electrolytes, and calcium were normal. Serologic markers for common viral infections (HIV, HBV, EBV, and HCV) were negative. Hypercoaguable workup including proteins C and S deficiency, antithrombin III deficiency, antiphospholipid antibody, anticardiolipin immunoglobulin G and immunoglobulin M, antineutrophilic cytoplasmic

Figure



(A) Axial cranial MRI showing restricted diffusion within the left midbrain. (B) Axial cranial MRI revealing T2 hyperintensities within the left midbrain and (C) pons. (D) Axial cranial MRI showing hemosiderin deposition within the left pontomesencephalic junction. (E) Postcontrasted coronal cranial MRI revealing patchy contrast enhancement throughout the left midbrain, pons, and cerebral peduncle. (F) Papule formation (arrow) after needle stick to left forearm after 24 hours indicating positive pathergy. (G) Fluorescein angiography with evidence of neovascularization (arrow).

antibody, C-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor were all within the normal range.

CSF analysis revealed neutrophilic predominant pleocytosis of 36 nucleated cells (rr: 0–8/cumm), mildly elevated protein of 47.5 (rr: 15.0–45.0 mg/dL), and glucose of 47 (rr: 40–70 mg/dL). Oligoclonal bands were absent, and IgG index was normal (rr: 0.28–0.66 ratio). CSF PCR testing for EBV, VZV, VDRL, JCV, HHV-6, and cryptococcal antigen was negative. Gram stain and culture were negative. Cytology and cytometry were negative for B/malignant cells. CT of the chest, abdomen, and pelvis was unremarkable. Ophthalmic fluorescein angiography was obtained and revealed bilateral chronic vasculitic changes, right vitreous hemorrhage, and left retinal scarring (Figure, F).

His overall CSF analysis and imaging features favored an inflammatory process. Evidence of systemic vasculitis on ophthalmologic examination and aphthous oral/genital ulcers raised suspicion for NBD. A pathergy test of skin hypersensitivity was positive (Figure, G), further suggestive of NBD.

Question for Consideration:

1. What are the diagnostic criteria for NBD?

GO TO SECTION 3

Section 3

Two criteria are widely used for diagnosis of systemic Behcet disease (BD). The International Study Group (ISG), published in 1990, has a sensitivity and specificity rate of 81% and 96%, respectively. This criterion requires the presence of recurrent oral aphthous ulcerations in combination with 2 of the following: genital ulcerations, skin lesions, eye lesions, or a positive pathergy test.[1] Pathergy testing is performed by sterile needle stick to the skin. Positive pathergy is defined by development of a papule, pustule, or ulceration within 24–48 hours postprick, indicating skin hypersensitivity. Comparatively, the International Criteria of Behcet's Disease (ICBD), released in 2014, consists of a point-based system in which ≥4 points indicate diagnosis. Two points are awarded for ocular lesions, genital, and/or oral aphthosis. One point is awarded for skin, neurologic or vascular manifestations, and/or positive pathergy test. ICBD was found to have a sensitivity and specificity of 93.9% and 92.1%, respectively.[2]

International consensus recommendations for NBD, released in 2013, describe definitive NBD as meeting 3 of the following: (1) satisfaction of the ISG criteria; (2) neurologic syndrome (with objective signs) recognized to be caused by BD and supported by relevant and characteristic abnormalities seen on either or both: (a) neuroimaging and (b) CSF; and (3) no better explanation for the neurologic findings. Probable NBD meets 1 of the following 2 criteria in the absence of a better explanation: (1) neurologic syndrome as above, with systemic BD features not satisfying the ISG criteria, and (2) noncharacteristic neurologic syndrome occurring in the context of ISG criteria–supported BD.[3]

Question for Consideration:

1. What is the treatment and prognosis for NBD?

GO TO SECTION 4

Section 4

Initial treatment consists of 1 gram IV methylprednisolone for 3–5 days with transition to oral steroid taper over 3–6 months. The optimal choice and duration of immunosuppressive agent is not clear, as there are no high-quality randomized trials addressing this question. Azathioprine is commonly used in BD due to ease of compliance and cost in doses ranging 2–3 mg/kg/day. In patients refractory to azathioprine or with depressed levels of thiomethylpurine transferase concerning for purine toxicity, alternative agents include mycophenolate, methotrexate, cyclophosphamide, and TNF blockers.[4] Prognosis of NBD is variable. Retrospective studies suggest patients with severe CNS symptoms involving brainstem lesions have worse outcomes compared with individuals with mild initial disability such as headache. Other factors indicative of poor prognosis include younger age, male sex, and positive HLA-B51.[5]

Our patient was treated with high-dose methylprednisolone for 5 days followed by a slow prednisone taper. His right hemiparesis improved at the time of discharge. Two months later, he was ambulating without assistance. Long-term immunosuppression with azathioprine was initiated. Follow-up contrasted cranial MRI showed improvement in brainstem lesions and resolution of the left thalamic and capsular lesions. Unfortunately, he had poor visual recovery and underwent a vitrectomy with minimal improvement. He presented with panuveitis 6 months later while on a lower dose of prednisone and was transitioned to a TNF blocker.

Discussion

BD, first described by Hulusi Behcet, is characteristically diagnosed by the presence of recurrent painful mucocutaneous lesions and ocular manifestations. These most commonly present as pseudofolliculitis/erythema nodosum and uveitis/retinitis respectively.[2,3]

BD is a nonspecific inflammatory disease of arterial and venous vasculature involving upregulation of cytokines, which may be released into CSF.[6] Precise triggering factors remain unclear. Both extrinsic variables, including viruses or heat shock proteins, in combination with genetic susceptibility, particularly HLA-B51, may contribute to pathology.[7] Only 5%–30% of BD cases progress to CNS involvement.[8] Headache is the most common neurologic presentation followed by pyramidal symptoms.[3] Parenchymal findings are more common than nonparenchymal. Characteristic MRI findings include large, confluent asymmetric hyperintense T2 signal abnormalities of the upper brainstem extending into thalamus/basal ganglia. Imaging may also reveal smaller areas of restricted diffusion, gadolinium enhancement, and hemosiderin suggesting the edematous nature of NBD.[9]

BD is commonly diagnosed in patients of Middle Eastern and Mediterranean descent[7] and less commonly diagnosed in those of Afro-Caribbean descent like our patient.[10] BD may be underdiagnosed in those of Afro-Caribbean descent, potentially due to reduced sensitivity of the ISG criteria. The higher sensitivity of ICBD allows for earlier recognition of NBD, with broader symptom recognition and not requiring positive pathergy testing. Studies in the Middle East have shown that pathergy testing sensitivity has decreased in recent years.[2] Criteria for NBD, including the International Consensus Recommendations, use the ISG criteria for BD to establish diagnosis. This suggests that the sensitivity of the International Consensus Recommendations for NBD diagnosis would be improved using the more sensitive ICBD, particularly in patients not of Middle Eastern and Mediterranean descent where index of suspicion may be lower.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Jessica Decker, DO	Department of Neurology, Medical University of South Carolina	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Mini Singh, MD	Department of Neurology, Medical University of South Carolina	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Mohan MC, Koya JM, Kandaswamy GV, et al. Neuro-Behcet's: a diagnostic challenge. *Oxf Med Case Rep.* 2015;2015(7):311-313.
2. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol.* 2014;28(3):338-347.
3. Kalra S, Silman A, Akman-Demir G, et al. Diagnosis and management of Neuro Behçet's disease: international consensus recommendations. *J Neurol.* 2014;261(9):1662-1676.
4. Borhani-Haghighi A, Kardeh B, Banerjee S, et al. Neuro-Behcet's disease: an update on diagnosis, differential diagnoses, and treatment. *Mult Scler Relat Disord.* 2019;39:101906.
5. Noel N, Bernard R, Wechsler B, et al. Long-term outcome of Neuro-Behçet's disease. *Arthritis Rheumatol.* 2014;66(5):1306-1314.
6. Hamzaoui K, Borhani-Haghighi A, Kaabachi W, Hamzaoui A. Increased interleukin 33 in patients with Neuro-Behcet's disease: correlation with MCP-1 and IP-10 chemokines. *Cell Mol Immunol.* 2014;11(6):613-616.
7. de Menthon M, Lavalley MP, Maldini C, Guillevin L, Mahr A. HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. *Arthritis Rheum.* 2009;61(10):1287-1296.
8. Borhani Haghighi A, Pourmand R, Nikseresht AR. Neuro-Behçet disease. A review. *Neurologist.* 2005;11(2):80-89.
9. Koçer N, Islak C, Siva A, et al. CNS involvement in Neuro-Behçet syndrome: an MR Study. *AJNR Am J Neuroradiol.* 1999;20(6):1015-1024.
10. Poon W, Verity DH, Larkin GL, Graham EM, Stanford MR. Behçet's disease in patients of west African and Afro-Caribbean origin. *Br J Ophthalmol.* 2003;87(7):876-878.

Clinical Reasoning: Rare Cause of Hemiparesis and Ataxia in a 36-Year-Old Man

Jessica Decker and Mini Singh

Neurology 2022;98;251-255 Published Online before print December 3, 2021
DOI 10.1212/WNL.0000000000013142