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

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Section 1:
A 36-year-old left-handed dominant Haitian male presented with a one-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 non-pruritic rash for three years. He was found to have a right retinal hemorrhage on a recent eye exam that was treated with ocular VEGF injections without improvement. On examination, he had oral aphthous ulcers and white papulo-pustular lesions on the trunk and extremities. His neurological 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 anatomical localization of these neurological deficits?
2) What is your differential diagnosis?
3) What further diagnostics should be performed?

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 spinothelial pathway involvement and localizes to contralateral midbrain/medulla or ipsilateral/contralateral pons due to decussation of spinothelial pathway, contralateral thalamus, or ipsilateral cerebellum. Loss of sensation to pin-prick localizes to anywhere along the contralateral spinothelial 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, spinothelial, and/or spinothelial 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 work up included a non-contrasted CT head revealing a left basal ganglia hypodensity extending into the superomedial midbrain, pons, and cerebellar peduncle. There was no evidence of hemorrhage. A contrasted cranial MRI was obtained demonstrating restricted diffusion in the left midbrain extending into the pons (Figure 1a). 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 1b, c). Patchy abnormal contrast enhancement and hemosiderin staining was noted within the left brainstem (Figure 1d, e). CT angiography of the head/neck was unremarkable.

Restricted diffusion with patchy contrast enhancement is commonly visualized in vascular insult, however, can be observed in early demyelination, neoplasms, and infections. Inflammatory and neoplastic etiologies of vascular insult were considered including Primary Angitis of the CNS, Neurosarcoidosis, Neurobehcet’s Disease (NBD), and Intravascular Lymphoma. Additional primary inflammatory conditions considered that typically do not affect vasculature, but have a predilection for deep grey/white matter and brainstem include Neuromyelitis Optica Spectrum Disorders (NMOSD) and Bickerstaff Encephalitis. History of vision impairment and systemic symptoms including diffuse papulo-pustules and aphthous ulcers narrowed our differential, and was most concerning for a systemic inflammatory condition involving the central nervous system.

Serum glucose, electrolytes, and calcium were normal. Serological markers for common viral infections (HIV, HBV, EBV, and HCV) were negative. Hypercoagulable work up including proteins C and S deficiency, antithrombin III deficiency, antiphospholipid antibody, anticardiolipin immunoglobulin G and immunoglobulin M, antineutrophilic cytoplasmic antibody, c-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor were all within 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 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 were negative. Gram stain and culture were negative. Cytology and cytometry were negative for B/malignant cells. CT chest, abdomen, and pelvis were unremarkable. Ophthalmic fluorescein angiography was obtained and revealed bilateral chronic vasculitic changes, right vitreous hemorrhage, and left retinal scarring (Figure 1f).

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 1g) further suggestive of NBD.

4) What are the diagnostic criteria for NBD?

Section 3:
Two criteria are widely used for diagnosis of systemic Behcet’s Disease (BD). The International Study Group (ISG), published in 1990, has a sensitivity and specificity rate of 81% and 96% respectively. This criterion requires presence of recurrent oral aphthous ulcerations in combination with 2 of the following: genital ulcerations, skin lesions, eye lesions, or a positive pathergy test. Pathery testing is performed by sterile needle stick to the skin. Positive pathery is defined by development of a papule, pustule, or ulceration within 24-48 hours post-prick 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. 2 points are awarded for ocular lesions, genital, and/or oral aphthosis. 1 point is awarded for skin, neurological or vascular manifestations, and/or positive pathergy test. ICBD was found to have sensitivity and specificity 93.9% and 92.1% respectively.

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

5) What is the treatment and prognosis for NBD?

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. Prognosis of NBD is variable. Retrospective studies suggest patients with severe CNS symptoms involving brainstem lesions have worse outcomes compared to individuals with mild initial disability such as headache. Other factors indicative of poor prognosis includes younger age, male gender, and positive HLA-B51.
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 pan-uveitis 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.

BD is a non-specific inflammatory disease of arterial and venous vasculature involving up-regulation of cytokines, which may be released into CSF. 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. Only 5-30% of BD cases progress to CNS involvement. Headache is the most common neurological presentation followed by pyramidal symptoms. Parenchymal findings are more common than non-parenchymal. 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.

BD is commonly diagnosed in patients of Middle Eastern and Mediterranean descent, and less commonly diagnosed in those of Afro-Caribbean descent like our patient. BD may be under-diagnosed 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. 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.
References:


Figure.
a. axial cranial MRI showing restricted diffusion within left midbrain b. axial cranial MRI revealing T2 hyperintensities within left midbrain and c. pons d. axial cranial MRI showing hemosiderin deposition within left midbrain e. post-contrast coronal cranial MRI revealing patchy contrast enhancement within left midbrain, pons, and cerebral peduncle f. papule formation after needle stick to left forearm after 24 hours indicating positive pathergy g. fluorescein angiography with evidence of neovascularization.
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