CLINICAL PRACTICE

*Clinical Vignettes***Neuro-Behçet's Disease: An Unusual Cause of Headache**Eric Michael Fountain, MD^{1,2} and Anjali Dhurandhar, MD¹¹University of Colorado School of Medicine, Denver, CO, USA; ²Duke University School of Medicine, Durham, NC, USA.

Neuro-Behçet's disease (NBD) is a potentially fatal complication of Behçet's disease (BD) that can sometimes masquerade as a primary neoplasm, aseptic meningitis or multiple sclerosis. Headache in patients with BD may portend onset of NBD, but the majority of headache in BD is benign. Clinicians who are unaware of the specific neurological manifestations of systemic inflammatory disorders like BD may fail to consider the possibility of serious intracranial pathology. We illustrate these challenges with the case of a 50-year-old woman with a history of BD who presented with headache in the absence of initial focal neurological deficits. The diagnosis of NBD was missed on multiple occasions before the correct diagnosis was made. We describe the etiology of headache in BD, the specific neurological manifestations of BD that suggest NBD, and the utility of routine neurological exams for BD patients with chronic headache. We further discuss the appropriate use of neuroimaging for headache in BD, and we recommend consideration of NBD as a diagnosis for headache in patients suspected of having an underlying systemic disease.

KEY WORDS: headache; Behçet's disease; Neuro-Behçet's disease.

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INTRODUCTION

Headache is one of the most common pain complaints addressed by physicians. A prompt diagnosis of the etiology of headache in patients with systemic inflammatory disorders is critical when concern for serious intracranial pathology exists. When physicians are unaware of the specific neurological manifestations of a given disease, the diagnosis and treatment may be delayed, and patients may suffer a worse outcome. Behçet's disease (BD) is one type of chronic illness with a broad spectrum of neurological involvement in which headache may be an important marker of intracranial pathology. BD is defined as an idiopathic vasculitis characterized by recurrent oral and genital ulcers, uveitis, and pathergy, a hypersensitivity

reaction of the skin seen in the context of minor skin trauma. While more common amongst those of Mediterranean and Asian descent, the prevalence in the United States may be as high as one in 15,000.¹ We describe a case of a patient with BD presenting with acute-onset headache without focal neurological deficits.

CASE REPORT

A 50-year-old woman with a 20-year history of Behçet's disease (BD) and no prior history of headaches presented to clinic with headache upon awakening that morning. She had 8/10 pain located around her eyes and on top of her head, but no visual disturbances or focal neurological symptoms. At the time of her first headache, she was taking prednisone 15 milligrams (mg) for painful genital ulcers. Her physical examination was normal, except for a small oral ulcer, two large genital ulcers, and tenderness over the temporal regions. The headache responded to ibuprofen 400 mg. She was instructed to continue prednisone at the current dose for genital ulcers and to follow up for the headache in 1 week.

Two days later, the patient presented to the Emergency Department for persistent frontal headache of 9/10 severity. Physical examination and non-contrast computed tomography (CT) of the head were both unremarkable. The headache resolved with acetaminophen 1 g, and she was sent home. Four days after her initial presentation, the patient returned to clinic with persistent headache and a new complaint of unsteady gait. This headache worsened with positional changes. Neurologic exam was remarkable for confusion and poor concentration, left-sided dysmetria, slowed rapid alternating hand movements, and difficulty with tandem gait. The patient had intact cranial nerves, normal motor strength, and normal deep tendon reflexes. Otherwise, her physical exam was normal. A lumbar puncture and magnetic resonance imaging (MRI), angiography (MRA), and venography (MRV) of the brain were obtained.

The patient was started on intravenous Acyclovir, Vancomycin, Ampicillin, and Ceftriaxone out of concern for meningoencephalitis given concurrent headache, altered mental status, and a peripheral leukocytosis of 11,800 cells/ μ l. Cerebrospinal fluid (CSF) studies demonstrated a pleocytosis of 128/mm³ with 47 % PMNs, 33 % lympho-

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cytes, and 20 % monocytes. CSF glucose and protein were normal. A Gram stain, bacterial cultures, measurement of oligoclonal bands, VDRL, and PCR for herpes simplex virus (HSV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) of the CSF were negative. MRV and MRA were unremarkable, but MRI demonstrated diffuse enlargement of the pons that effaced the prepontine cistern and partially encircled the basilar artery, initially concerning for a brainstem glioma. After discussing the patient's presentation with the neuroradiologist, the MRI was felt to be highly compatible with Neuro-Behçet's disease (NBD), given the diffuse abnormal signal throughout the pons, which extended into the middle cerebellar peduncles, cerebral peduncles, and partially into the internal capsules. The extension of abnormal signal in the cortical spinal tracts was especially suggestive of NBD (Fig. 1). The patient was treated with intravenous methylprednisolone 250 mg every 6 h. The following day, her neurologic symptoms dramatically improved and she was transitioned to oral prednisone 40 mg twice daily. Her symptoms completely resolved 2 days later and she was discharged on oral prednisone 30 mg twice daily. Subsequent MRI of the brain demonstrated marked improvement (Fig. 1).

DISCUSSION

In the general population, migraine and tension headaches account for the majority of headaches seen by primary care

physicians. A trial of pharmacotherapy for uncomplicated cases of these primary, benign headaches is an accepted diagnostic and treatment modality routinely used in clinical practice.^{3,4} Neuroimaging is typically reserved for headache suggestive of intracranial pathology, as studies have demonstrated that imaging for headache in the absence of neurological symptoms or atypical features rarely reveals a visible abnormality.^{3,4} Commonly accepted red-flag symptoms and signs include focal neurological findings, systemic illness, sudden-onset, and progressive worsening of headache despite appropriate therapy (Text Box 1).^{4,5}

A thorough neurological exam and attention to the red-flag symptoms is particularly important when deciding if neuroimaging is justified in BD patients presenting with new-onset headache, as this may represent one of its most serious sequelae, Neuro-Behçet's disease (NBD). Although no consensus definition for NBD exists, the diagnosis is generally made in a BD patient with headache or neurological symptoms in the presence of compatible abnormalities on neuroimaging.^{2,6,7} Approximately 5–15 % of those with BD subsequently develop NBD,^{6,8} but 45 % of those with NBD will have moderate to severe neurological disability at 10-year follow-up.² It remains unclear if the prompt recognition and specific treatment of NBD would improve long-term prognosis,^{6,8} but the diagnostic approach to headache and use of neuroimaging in BD can be categorized by the types of headaches experienced by BD patients and associated clinical features (Fig. 2).

First, headache is the most common neurologic symptom in BD, with a prevalence of 70 %. Of those, 70 % are migraine

Figure 1. Pre-treatment T2 Fast-Recovery Fast Spin Echo MRI (*left*) demonstrating diffuse enlargement of the pons, which effaces the prepontine cistern and partially encircles the basilar artery, and encephalitis consistent with Neuro-Behçet's Disease. Two weeks after initiation of treatment, T2 Fast-Recovery Fast Spin Echo MRI (*right*) demonstrated markedly diminished signal abnormality in the brainstem and only pontine involvement, with markedly improved encephalitis. Arrows point to the pons.

Figure 2. Approach to headache in Behçet's disease.

and tension headaches, similar to the distribution seen in the general population.⁶ A study of BD patients presenting with migraine or tension headache and a normal neurological exam demonstrated that these patients had normal MRIs.⁹ Neuroimaging for migraine and tension headaches in BD is not recommended unless there are neurological signs, other red-flag symptoms, or worsening presentation.

Second, approximately 10–15 % of headaches reported in BD can be attributed to an ill-defined entity known as “non-structural headache of Behçet’s.”⁶ These headaches do not meet the criteria for either NBD or a primary headache disorder.¹⁰ Focal neurological findings and abnormal neuroimaging are noticeably absent.¹⁰ Particular features of these headaches distinguish them from migraines. These headaches tend to occur with BD flares and improve with systemic corticosteroid therapy. Nearly all BD patients experience their first episode of nonstructural headache after the diagnosis of BD, unlike BD patients with migraines, who usually have their first episode prior to diagnosis of BD. Accompanying symptoms and triggers are less common in nonstructural headache than in migraine.¹⁰

Third, approximately 10–15 % of headaches in BD are consistent with a diagnosis of NBD.⁶ The prevalence of headache in NBD depends on the specific manifestation of neurological involvement. NBD usually presents in two forms: parenchymal or non-parenchymal disease. Parenchymal NBD, the more common form, is described as an inflammatory perivascularitis, often in the form of subacute meningoencephalitis with a predilection for the brainstem. The distribution is typically a unilateral lesion in the upper brainstem extending into the thalamus and basal ganglia. Rarely, patients can have large lesions that may be mistaken for tumor.⁶ Most patients present with pyramidal signs such as rigidity, Babinski sign, hyperreflexia, or clonus. Other common findings during an acute attack

include hemiparesis, behavioral changes, sphincter dysfunction, and headache.⁸ In contrast, venous sinus thrombosis is the most common presentation of the second form of NBD, which is considered non-parenchymal or vascular NBD.^{2,6–9} Nearly all present with headache and papilledema, and less commonly with pyramidal signs.⁸

Therefore, headache in the absence of other signs and symptoms would be an unusual presentation for NBD. In one study, 18.3 % of NBD patients presented with headache as the only symptom. Of those patients, papilledema was present in 87 %, while the remaining 13 % developed additional neurological symptoms during the course of follow-up.² The need for neuroimaging in this subset of BD patients with headache could therefore be justified through careful fundoscopic exam demonstrating papilledema. The remaining 81.7 % of NBD patients presented with additional neurological findings justifying imaging.² Because headache in isolation is rarely indicative of NBD, it is reasonable to conclude that neuroimaging for headaches in BD patients be reserved for the same red-flag symptoms and signs warranting imaging in the general population (Text Box 1).

However, BD patients presenting with headache consistent with a prior history of migraine or tension headache can develop “silent neurological involvement,” defined as the presence of abnormal neurological findings found incidentally on exam in the absence of additional neurological complaint.^{8,11} The exam findings may include sensorial deficits, asymmetric or enhanced deep tendon reflexes, or Babinski sign.¹¹ While it is unclear if “silent neurological involvement” is a direct precursor of NBD or a separate clinical entity, one-fifth of these patients will subsequently develop an acute neurological attack consistent with NBD.^{8,11} Primary, benign headache in the absence of initial neurological findings thus requires close observation in BD,

Text Box 1.**Red Flag Symptoms and Signs [7,8]:**

- Systemic illness – e.g. fever.
- Maximal-at-onset, worst headache of life.
- Focal neurological deficits.
- Papilledema
- Altered mental status
- Presence of seizures
- Early morning headache consistent with increased intracranial pressure.
- Onset of headache secondary to exertion, cough, or equivalent Valsalva maneuvers.
- Progressive worsening, change in character of preexisting headache syndrome.

and routine neurological exams should be considered in all such patients, despite any apparent stability of headache frequency and character.

Additionally, while most develop NBD approximately 3–6 years after BD onset, NBD may be the initial presentation of disease in approximately 6 % of patients.^{6,8} For those without a prior diagnosis of BD, the differential for the neurological manifestations of NBD is broad and often includes multiple sclerosis, aseptic meningitis, sarcoidosis, systemic lupus erythematosus and neoplasms.⁶ Consequently, when considering etiologies of headache and neurological deficit in patients suspected of harboring a systemic disease, NBD should be included in any differential. A

summary of these recommendations can be found in Text Box 2.

It is important to note that a small percentage of headaches in Behçet's disease patients may be related to other etiologies. Up to 7 % are related to ocular inflammation,^{6,10} while a smaller percentage may be due to trigeminal neuralgia or malignancy.^{6–8,10}

Finally, when neuroimaging is justified, MRI is the preferred diagnostic modality for NBD, with MRV additionally recommended if venous thrombosis appears likely.^{6,8,12,13} In one retrospective study of 200 patients with neurological findings consistent with NBD, 31 % of CT scans were found to be abnormal while 70 % of MRI scans were found to be abnormal.⁸ In addition, because CSF analysis often demonstrates a pleocytosis with elevated protein levels in parenchymal NBD, this may be mistaken for infectious meningitis, given the simultaneous presence of meningeal signs and symptoms commonly seen in NBD.⁶ Such studies consequently have equivocal diagnostic value in parenchymal NBD,^{6,7} though abnormal CSF is considered a poor prognostic marker.⁸ Additional markers indicative of poor prognosis include the presence of parenchymal disease, attack recurrence or progression, and residual neurological dysfunction.^{4,6,8} Of note, definitions of NBD vary slightly between studies, and most studies are retrospective with a small sample size, which limits generalizability.

For our patient, neuroimaging was appropriately delayed until red-flag signs and symptoms appeared. While NBD was confirmed through rapid improvement with systemic corticosteroids, the correct diagnosis was delayed due to our lack of awareness of the neurological complications of BD, failure to meet imaging criteria upon initial presentation, and the presence of various nonspecific findings of NBD that can mimic other diseases. In particular, the abnormal CSF studies initially raised the possibility of infectious meningoencephalitis, and the MRI images were initially felt to be consistent with a pontine glioma.

Text Box 2.**Key Points:**

- Headache in Behçet's disease is most likely due to migraine or tension-type headache, and neuroimaging is warranted for the same red flag signs and symptoms as in the general population.
- Routine neurological examinations are recommended for Behçet's patients with history of stable migraine or tension-type headache to identify progression to Neuro-Behçet's disease.
- Neuro-Behçet's disease should be considered in the differential for headache and neurological findings suspected to be secondary to a systemic disease.

CONCLUSION

The majority of headache in BD can be identified as primary, benign headache or “nonstructural headache of Behçet’s,” both of which typically present with normal neuroimaging in the absence of neurologic deficits. Approximately 10–15 % of all headaches in BD can be attributed to NBD, for which neuroimaging is usually required for diagnosis.^{2,6} While NBD is associated with high morbidity, epidemiological data suggests that the approach to headache in BD should be similar to headache in the general population. Therefore, common red flag symptoms should be used to determine when neuroimaging is necessary in BD. A thorough neurological exam is the most useful clinical tool in BD patients presenting with new-onset or chronic headaches. Special consideration should be given to the ophthalmological exam, as papilledema is found in most patients with NBD that initially present with isolated headache. All BD patients with a recurring headache syndrome, regardless of apparent stability of headache character, require routine neurological examinations to identify “silent neurological involvement” predictive of future onset of NBD, and non-localizing pyramidal signs are the typical exam findings.⁸ In addition, NBD should be considered in the differential of any patient with new headache or neurological manifestations suspected to be secondary to an underlying systemic disorder.

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REFERENCES

1. Calamia KT, Wilson FC, Icen M, Crowson CS, Gabriel SE, Kremers HM. Epidemiology and clinical characteristics of Behçet’s disease in the US: a population-based study. *Arthritis Rheum*. 2009;61(5):600–4.
2. Siva A, Kantarci OH, Saip S, et al. Behçet’s disease: diagnostic and prognostic aspects of neurological involvement. *J Neurol*. 2001;248(2):95–103.
3. Tsushima Y, Endo K. MR Imaging in the evaluation of chronic or recurrent headache. *Radiology*. 2005;235(2):575–9.
4. Goadsby PJ. To scan or not to scan in headache. *BMJ*. 2004;329(7464):469–70.
5. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. *Neurology*. 2004;63(3):427–35.
6. Al-Araji A, Kidd DP. Neuro-Behçet’s disease: epidemiology, clinical characteristics, and management. *Lancet Neurol*. 2009;8(2):192–204.
7. Hirohata S, Kikuchi H, Sawada T, et al. Clinical characteristics of Neuro-Behçet’s disease in Japan: a multicenter retrospective analysis. *Mod Rheumatol*. 2012;22(3):405–13.
8. Akman-Demir G, Serdaroglu P, Tasçi B, et al. Clinical patterns of neurological involvement in Behçet’s disease: evaluation of 200 patients. *Brain*. 1999;122(11):2171–82.
9. Gökçay F, Çelebisoy N, Gökçay A, Aksu K, Keser G. Neurological symptoms and signs in Behçet disease. *Neurologist*. 2011;17(3):147–50.
10. Saip S, Siva A, Altintas A, et al. Headache in Behçet’s syndrome. *Headache*. 2005;45(7):911–9.
11. Yesilot N, Shehu M, Oktem-Tanor O, et al. Silent neurological involvement in Behçet’s disease. *Clin Exp Rheumatol*. 2006;24(Suppl. 42):S65–70.
12. Saadoun D, Wechsler B, Resche-Rigon M, et al. Cerebral venous thrombosis in Behçet’s disease. *Arthritis Rheum*. 2009;61(4):518–26.
13. Haghighi AB, Pourmand R, Nikseresht AR. Neuro-Behçet disease. A review. *Neurologist*. 2005;11(2):80–9.