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SECONDARY HEADACHE (K HENRY AND M ROBBINS, SECTION EDITORS)

Headache in Behçet's Syndrome: Review of Literature and NYU Behçet's Syndrome Center Experience

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Abstract Headache, a common and disabling symptom in Behçet's syndrome, may be associated with a variety of neurologic syndromes and ocular inflammation, or may present as an isolated feature. Our objective is to describe the various neurologic and ocular syndromes of Behçet's syndrome of which headache is a symptom, and to review the features of isolated headaches in Behçet's. We also report results of a study of headache in Behçet's syndrome patients who are followed at NYU Hospital for Joint Diseases, the first study of its kind in North American patients, and the first to document prevalence of both episodic and chronic daily headache in Behçet's.

Keywords Behçet's syndrome · Headache · Episodic headache · Chronic daily headache · Migraine · Neuro-Behçet's · Cerebral venous sinus thrombosis · Uveitis · Increased intracranial pressure

Introduction

Behçet's syndrome (BS) is a chronic relapsing multisystem inflammatory disorder originally defined by a triad of oral and genital ulcerations and hypopyon uveitis [1]. The current diagnostic criteria require the presence of recurrent

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oral ulceration (at least three times in a 12-month period) plus any two of the following features: recurrent genital ulceration, ocular inflammation (anterior/posterior uveitis, panuveitis, or retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules), and positive pathergy test [2]. BS affects men and women equally, but is more severe among males [3•]; has peak onset in the 20–35 age group; and is particularly prevalent along the 'Silk Road' that stretches from the Mediterranean to the Far East [4]. The prevalence of BS in Turkey is 5–20 per 10,000, which is at least 10 times higher than in the U.S. [5].

Neurological syndromes due to BS are referred to as 'neuro-Behçet's disease' (NBD), and may be broadly categorized as 'parenchymal' (due to inflammatory lesions in the brain and spinal cord), or 'vascular' (cerebral venous sinus thrombosis, intracranial or extracranial aneurysms). However, mixed parenchymal/vascular presentations and syndromes that do not readily fit into either category, such as increased intracranial pressure, optic neuritis, meningitis, and peripheral nervous system involvement, have been described [5]. The current criteria for NBD [6, 7] require neurological symptoms consistent with BS not explained by another etiology, including neurotoxicity of BS treatments. In addition, there must be objective evidence of neurologic involvement consistent with NBD based on one or more of the following: neurological examination, neuroimaging, neurophysiology, or examination of cerebrospinal fluid (CSF) [6].

Headache is the most common neurological symptom in BS. Headache is not attributed to NBD *unless* it is accompanied by neurological deficits and abnormalities on neuroimaging or CSF [8]. We propose to classify headache in BS into the following six categories: 1) headache associated with parenchymal NBD, 2) headache associated with vascular NBD (e.g., cerebral venous sinus thrombosis), 3) headache associated with increased intracranial pressure without sinus venous thrombosis, 4) headache associated with meningitis, 5) headache associated with ocular inflammation, and 6) isolated headache not accompanied by NBD or uveitis. Because headache is a ubiquitous human experience, many headaches experienced by individuals with BS may not be related to BS. Headache secondary to NBD or uveitis accounts for a minority of headaches in BS, but they are more important to recognize and will be discussed first.

Headache Associated with Neuro-Behçet's Disease

Headaches due to parenchymal NBD typically present in the context of florid neurologic symptomatology that includes behavioral changes and focal neurologic signs such as brainstem signs, hemiparesis, or ataxia [9]. Characteristic MRI lesions of parenchymal NBD are T2-hyperintense and can be located in the brainstem, diencephalon, periventricular, and subcortical white matter [2, 10, 11]. Koçer et al. reported that the three most commonly affected areas in parenchymal NBD were the mesodiencephalic junction (46 %), pontobulbar region (40 %), and hypothalamic/thalamic region (23 %) [12], although other studies have documented frequent involvement of supratentorial white matter [13]. Cerebrospinal fluid (CSF) typically shows pleocytosis, with or without elevation in protein, and occasional oligoclonal banding [11]. Inflammatory changes in CSF can also be seen in meningitis without parenchymal involvement, but this appears to be an uncommon scenario.

Cerebral venous sinus thrombosis is a well-recognized syndrome of BS that presents with symptoms and signs of increased intracranial pressure (ICP): bilateral papilledema, sixth nerve palsies, and progressive bilateral headache. CSF analysis is usually unremarkable but opening pressure is elevated [2, 10, 13]. Headache severity lessens with a decrease in ICP. Diagnosis of sinus thrombosis is confirmed with CT or MR venography. Most commonly affected is the superior sagittal sinus, followed by the lateral sinus, although any of the sinuses can be affected [6]. Intracranial hypertension without thrombosis on imaging has also been reported. Some cases evidence neuroimaging findings consistent with venous sinus thrombosis during recurrence of increased intracranial pressure [14]. Other vascular manifestations such as intracranial hemorrhage are rare, with few reported cases [15, 16].

Headache is common in NBD. In a study of seven patients with BS with neurologic involvement, all patients reported headache [17]. Of the six patients with parenchymal NBD in the study by Ashjazadeh et al., five had headache. Two of the patients had isolated brainstem involvement; three had lesions in the brainstem, thalamus, basal ganglia, and subcortical white matter; and one patient had a stroke-like hemispheric syndrome. Two patients also had an abnormal CSF profile with pleocytosis [18]. Hirohata et al. noted headache in 53.9 % of patients with acute meningoencephalitic NBD, compared to 5.7 % of patients with chronic progressive NBD. Of the Behçet's patients without neurologic deficits, 42.4 % had headache [10]. As such, headache is not specific for NBD.

Headache in patients with BS is attributed to NBD in 5–31 % (18–20) of patients with headache. The wide variation is due, at least in part, to the source of the study population. The highest rates come from neurologic referral studies [18], while rates are lower in more representative samples of patients with BS. Among headaches attributed to NBD in adults, most are due to the parenchymal form, at a ratio of about 7:1. In children, on the other hand, the dominant neurological presentation is dural venous sinus thrombosis [19•].

When patients with BS develop headaches, clinicians often wonder if the headache represents the onset of NBD. In BS patients with headache and normal neurologic examination, brain MRI is normal in approximately half , and in the other

half, MRI most often reveals small white-matter lesions within the cerebral hemispheres, not indicative of NBD [8]. Therefore, the majority of isolated headaches with a normal neurological examination in BS do not imply NBD. At the same time, since missed diagnosis of NBD can be devastating, it is prudent to perform MRI of the brain and lumbar puncture (with opening pressure) in the case of new-onset, atypical, and persistent headache, even in the absence of overt neurologic deficits.

Headache Associated with Ocular Inflammation

Uveitis is the most common ocular manifestation in BS [20] and a significant contributor to disease morbidity. Symptoms include blurred vision, photophobia, decreased visual acuity, and eye pain with conjunctival injection [21, 22]. Headache secondary to uveitis is typically periorbital and temporally related to the evolution of uveitis [23•]. Saip et al. noted that inflammatory eye disease occurred in more than 40 % of patients, but only 4 % complained of headache, which implies that headache is not a frequent feature of uveitis [24]. Similarly, Ashjazadeh et al. reported that only 4.2 % of headache in BS was attributed to recurrent uveitis [18]. Optic neuritis is a much less common manifestation of BS, but it can be a source of headache and eye pain, and may be more difficult to appreciate on examination than overt uveitis.

Isolated Headache

While headache prevalence in BS patients ranges from 56–83 % (Table 1) in most studies, the high prevalence need not imply that headache is overrepresented in BD compared to the general population. A review of 50 studies involving 115,000 participants in 17 European countries reported a 55 % one-year prevalence of headache in the general population [25]. Similarly, a one-year prevalence of primary headache disorders in the U.S. is 40 % for episodic tension-type headache (TTH) and 18 % and 6 % for migraine among women and men, respectively [26–28]. In one study that compared headache prevalence in BS subjects and controls, headache frequency in BS was high but not statistically higher than in controls [13].

Characterization of headache varies among studies. Aykutlu et al. determined that migraine was the predominant cause of headache, reported in 46.4 % of their patients, while 26.8 % had TTH [29]. Similarly, Gökçay et al. found that 54 % of their patients had migraine compared to 15 % of patients with TTH [11]. On the other hand, several other studies have recorded TTH as the predominant headache type in BS. According to Ashjazadeh et al, of the patients who did not have NBD, uveitis, or 'unspecified headaches', 25 % had TTH and only 13.5 % had migraine [18]. Saip et al. reported TTH in 23.6 % of patients versus migraines in 14.9 % [24]. There also was no consensus among the different studies with regard to ratio of migraine with aura to migraine without aura. Some report migraine without aura to be more common than migraine with aura [24], while others have found 'vascular' headaches, with either visual or sensory auras, to be the more common migraine variant [30]. The variance in prevalence of different headache types may be related to differences among ethnic populations, various forms of selection bias (e.g., higher prevalence of headache among BS clinic patients compared to BS patients at large, or BS patients referred to neurology clinics), differences in methodology (e.g., prospective versus retrospective), and importantly, in case definitions of headaches used in the various studies [8, 18, 31].

The question of whether particular characteristics of headache in BS correlate with impending or current systemic relapse was addressed by Saip et al., who suggested that 'the non-structural headache of Behçet's disease', commonly defined as a bilateral, pulsatile, moderately severe headache, is often associated with systemic disease flare-up (including mucosal ulcerations or uveitis), and also improves with the treatment of systemic disease [24]. This finding requires validation.

Review of the literature reveals many gaps in our understanding of the prevalence, characteristics, and significance of headache in BS. A large-scale multicenter prospective study with uniform case definitions of the kind recently reported in SLE [32•] is necessary to determine whether headaches are seen in BS more frequently than would be expected by chance, the frequency of various headache types in BS, and also whether there exists a specific 'Behçet's headache' indicative of active systemic disease or BS relapse.

Episodic and Chronic Daily Headaches in BS: NYU Behçet's Syndrome Center Experience

Episodic headaches (EH) are defined as occurring on fewer than 15 days per month, and chronic daily headaches (CDH) on 15 or more days per month, for at least three months [33]. The characteristics and frequency of EH and CDH in BS have not been investigated. We undertook a study of headache, using standardized International Classification of Headache Disorders (ICHD-2) definitions [23•], among patients attending the Behçet's Syndrome Evaluation, Treatment, and Research Center at NYU Hospital for Joint Diseases in New York.

Forty-four consecutive patients completed our questionnaires from July to December 2009. All patients fulfilled International Study Group criteria for Behçet's Disease [2]. The cohort was largely female (41/44, 93 %), with an average age of 35±13 years and an average disease duration of 8±7 years. Headache within the past year was reported by 38 of 44 patients (86 %). Depression and anxiety were highly prevalent in the headache group: 26 % met criteria for moderate-severe depression (PHQ-9≥15), and 37 % met criteria for moderate-severe generalized anxiety disorder (GAD-7≥10).

Table 1 Summary of recent studies of headache in Behçet's Syndrome

First Author, Year [reference]	Country	Number of patients	Study description	Results
Al-Araji 2003[35]	Iraq	N=140	Prospective study of prevalence/patterns of neurologic involvement in BS.	14 % had NBD. 60 % of NBD patients had headache. 50 % of NBD with parenchymal involvement, 30 % with increased intracranial pressure, and 20 % had amixed pattern.
Aykutlu 2006[29]	Turkey	N=118	Retrospective study of headache characteristics in BS patients seeking neurologic consultation.	83 % of patients had headaches. Migraine - 46.4 %. TTH - 26.8 %. 31 % had 'non-structural headache secondary to BS'.
Ashjazadeh 2003[18]	Iran	N=96 (6 of which had NBD)	Prospective study of neurologic manifestations of BS.	57 % of total cohort had headache. Migraine - 13.5 %. TTH - 25 %. 'Meningeal' - 10.4 %. Not specified - 3.1 %. Headache related to uveitis - 4.2 %. 83.3 % (5/6) of pts w/ NBD had headache.
Borhani Haghighi 2008[30]	Iran	N=180	Case control study of prevalence/ characteristics of BS patients.	65 % w/ headache. Migraine with aura - 1.7 %, without aura - 25 %. TTH - 23.8 %. 8.3 % due to NBD. 3.3 % due to uveitis.
Gokcay 2011[11]	Turkey	N=530	Retrospective study of neurologic manifestations of BS. (54/530 had NBD).	8.7 % had headache (w/o other neurologic signs, negative MRI), of whom 54 % were migraine. TTH - 15 %. Cluster - 2 %. 28 % w/ headache that worsened during systemic BS findings.
Hirohata 2012[10]	Japan	N=144 (76/144 w/ NBD, 35 w/ CP NBD, 33 non-NBD)	Multicenter retrospective analysis of clinical characteristics of NBD.	Headache in 53.9 % of acute NBD, 5.7 % of chronic NBD, 14 % in BS patients without neurologic involvement.
Monastero 2003[13]	Italy	N=27	Case control study of headache in BS without neurologic disease.	88 % had headache, not statistically different from control, near statistical significance (p=0.054).
Reira-Mestre 2010[34]	Spain	N=20	Retrospective study of clinical features of NBD.	60 % reported headache.
Saip 2005 [24]	Turkey	N=228	Multidisciplinary prospective study differentiating headache types in BS patients.	Headaches in 66.2 % of total. 38.6 % had primary headache. TTH - 23.6 %, Migraine - 14.9 %, 5.2 % associated with NBD, 3.9 % due to uveitis. 18.4 % had headaches associated w/ systemic BS but normal neurological exam.
Zayed 2011 [31]	Egypt	N=25	Case control study evaluating silent CNS involvement in BS patients.	60 % of patients with recurrent mostly migraine-like headache with no increase in frequency of abnormal brain SPECT.

Legend: NBD:Neuro-Behçet's disease, BS: Behçet's syndrome, HTN: Hypertension, TTH: Tension-type headache, CP NBD: Chronic progressive Neuro-Behçet's disease, SPECT: Single-photon emission computed tomography

Within the headache cohort, 24 patients (55 %) had EH and 14 patients (32 %) had CDH. The two groups were similar with respect to age, disease duration, male-female ratio, use of pain medications for non-headache reasons, and proportion of patients with strokes, seizures, meningitis, and uveitis (Table 2). Eight patients in the CDH group (57 %) and 13 patients in the EH group (54 %) reported a new type of headache since onset of BS. The two groups did not differ in their scores on assessments of allodynia, depression, anxiety, fatigue, or sleepiness, but as expected, differed widely in their headache impact scores (MIDAS of 179.6 in CDH vs. 50.3 in EH, $p<0.001$). Medication overuse was more common in the CDH (71 %) than the EH (33 %, $p=0.023$) group.

Among patients with EH, 22 (91.7 %) met criteria for migraine or probable migraine, and two (8.3 %) had TTH. Migraine with aura and probable migraine with aura were reported by 13 of 24 patients (54.2 %). Migraine without aura and probable migraine without aura were reported by 9 of 24 patients (37.5 %). Worsening of pre-existing headache severity and frequency since BD onset was more common in patients with migraine without aura (78 %) compared to migraine with aura (54 %; $p=0.004$). Increase in headache severity during BS exacerbations was reported by every patient with migraine without aura (100 %), but only 46 % of patients with migraine with aura ($p=0.007$).

Table 2 Characteristics of patients with episodic and chronic headaches from the NYU Behçet's Syndrome Center study

	Episodic Headache	Chronic Daily Headache	P value*
Number of patients	24	14	
Mean age (years)	36.1	33.1	0.530
Mean duration of BS (years)	8.8	7.4	0.536
% of female patients	88 %	100 %	0.168
New HA since BS onset	13 (54 %)	8 (57 %)	0.666
HA worse with BS onset	14 (58 %)	9 (64 %)	0.514
Acute medications on more than 2 days/week	8 (33 %)	10 (71 %)	0.023**
Non-HA pain treated for more than 1 day/week	13 (54 %)	8 (57 %)	>0.1
Hospitalized for BS	12 (50 %)	8 (57 %)	0.671
Mean MIDAS	50.3	179.6	<0.001**
Mean FSS	41.6	45.6	0.463
Mean ESS	17.9	17	>0.1
Mean ASC	4.5	4.4	0.954
Mean PHQ-9	9.8	11.7	0.421
Seizures	2 (8 %)	1 (7 %)	0.496
Meningitis	7 (29 %)	3 (21 %)	0.601
Cerebrovascular accident/	1 (4 %)	2 (1 %)	0.268
Uveitis	3 (13 %)	2 (14 %)	0.444

* chi-square test was used for categorical variables and two-sided t-test for continuous variables

** $p<0.05$ was considered significant.

HA=headache, MIDAS=migraine disability assessment, FSS=fatigue severity scale, ESS=Epworth sleepiness scale, ASC=allodynia symptom checklist, PHQ-9=patient health questionnaire for depression; NS=non-significant

Among the patients with CDH, 11 (79 %) met criteria for chronic migraine and three (21 %) met criteria for new daily-persistent headache. In the CDH group, 14 (100 %) underwent MRI of the brain and 10 (71 %) underwent lumbar puncture, compared to 15 (63 %) with MRI of the brain and seven (29 %) undergoing lumbar puncture in the EH group.

In conclusion, more than half of the BS patients had EH during the study, and the majority of the headaches were migraine or probable migraine with aura. In contradistinction, TTH predominates in the general population and only a minority of migraine headaches feature aura [26–28]. Most patients with migraine, particularly the migraine without aura subset, reported HA worsening with the onset of the disease and during exacerbations. Compared to CDH prevalence in the general population (2–5 % in most surveys) [36], clinic patients with BS reported CDH at remarkably higher rates: almost one-third of our patients had CDH at the time of the survey. BS patients with CDH and EH differed in headache-related disability and medication overuse, but not in demographics or comorbidities.

Conclusions

Headache is the most common neurological symptom in patients with BS, reported in 56–83 % of cases in most studies [10, 13, 24, 34]. Clinicians evaluating a patient with headache and BS need to be aware of the various neurologic and ocular syndromes of BS of which headache is a symptom. Although headaches associated with NBD or ocular inflammation constitute a minority of headaches in BS, these syndromes need to be excluded, as timely treatment is paramount. A BS patient with new-onset or frequent headache needs to be evaluated for the presence of uveitis, papilledema, meningismus, cranial nerve palsies, and any other focal neurologic deficits. Even a patient with an isolated headache and normal neuro-ophthalmologic and neurologic examination may warrant neuroimaging and lumbar puncture if headache is new-onset, severe, and progressing despite treatments.

Much has been learned about headache and BS during the past decade, but there are still significant gaps in our understanding of their interrelationship and the conflicting conclusions regarding prevalence, headache type, and association with systemic disease and NBD. The NYU Behçet's Syndrome Center study documented remarkably high prevalence of episodic headaches, especially migraine, as well as chronic daily headache. We advocate for a large-scale multicenter prospective study of headache with uniform validated case definitions in order to provide answers to the important questions with respect to the prevalence, characteristics, and significance of headache in patients with BS.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Vijay Vishwanath, Dr. Ericka Wong, Dr. Sara Crystal, Dr. Maria Filopoulos, and Dr. Ilya Kister each declare no potential conflict of interest.

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