Radiological neuro-Behçet's associated with bipolar disorder: first presentation of a multisystem disease

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Abstract

Behçet's disease is a chronic, relapsing, systemic inflammatory disease affecting the orogenital mucosa, eyes, joints, blood vessels, nervous system and intestines. The prevalence of neurological involvement varies geographically and can include psychiatric manifestations. Current evidence for a causal association between Behçet's disease and bipolar disorder is limited to a small number of case reports.

We report a case of a patient with a recent diagnosis of bipolar disorder who was subsequently diagnosed with Behçet's disease. The 38-year-old male presented with a 6-month history of right eye visual blurring, 5-month history of mouth ulcers and 3 months of genital ulceration. His inflammatory markers were raised. An MRI of the brain was conducted in the absence of any focal neurological signs or symptoms owing to his past psychiatric history. The MRI showed changes in the medial aspect of the right temporal lobe highly suspicious of neuro-Behçet's disease. His inpatient care was coordinated with neurology, rheumatology, ophthalmology and psychiatry teams, and he was later discharged with outpatient follow up owing to a clinical improvement on high-dose steroids.

This case shows that, although widely unrecognised, neuro-Behçet's can occur in the absence of focal neurology. Additionally, neuro-Behçet's should be considered in patients with bipolar disorder presenting with symptoms suggestive of Behçet's disease. The case emphasises how patients presenting with ulceration, mood disorder and visual changes should not have these symptoms considered in isolation and multisystem disease should be considered. Furthermore, the coordinated multidisciplinary approach required for the care of patients with Behçet's disease is demonstrated.

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Keywords: Behçet's disease, bipolar disorder, neuro-Behçet's disease, ulceration

Financial and Competing Interests: No conflict of interests declared

Introduction

Behçet's disease (BD) is a multisystem, chronic, relapsing, inflammatory disease of multifactorial aetiology.[1,2] BD is characterised by recurrent attacks affecting the orogenital mucosa, eyes, joints, blood vessels, nervous system and intestines.[1,2]

The mean prevalence varies between 1 in 1,000 to 1 in 10,000.[1] The International Criteria for Behçet's Disease (ICBD) (Table 1)[3] has a sensitivity of 93.9% and specificity of 92.1% for diagnosis.[1,4]

Neurological involvement occurs in between 3 and 25% of patients with marked geographical variation[1,5] and can include psychiatric manifestations.[1]

Case presentation

A 38-year-old male with a background of recurrent conjunctivitis and bipolar disorder presented to the acute medical unit (AMU) with a 5-month history of mouth ulcers and a 3-month history of scrotal and penile ulcers. He had also been seen 6 months earlier with a history of right visual blurring, which he was told was 'smoking related'. Seven months prior to his AMU presentation he had required inpatient psychiatric admission for 3 weeks for being acutely suicidal. He was diagnosed with bipolar disorder and started on olanzapine during this psychiatric admission. In retrospect he described feeling depressed and hypomanic for a number of years prior to this.

The patient presented with painful infected scrotal ulcers worsening over 6 weeks. He had self-referred to the walk-

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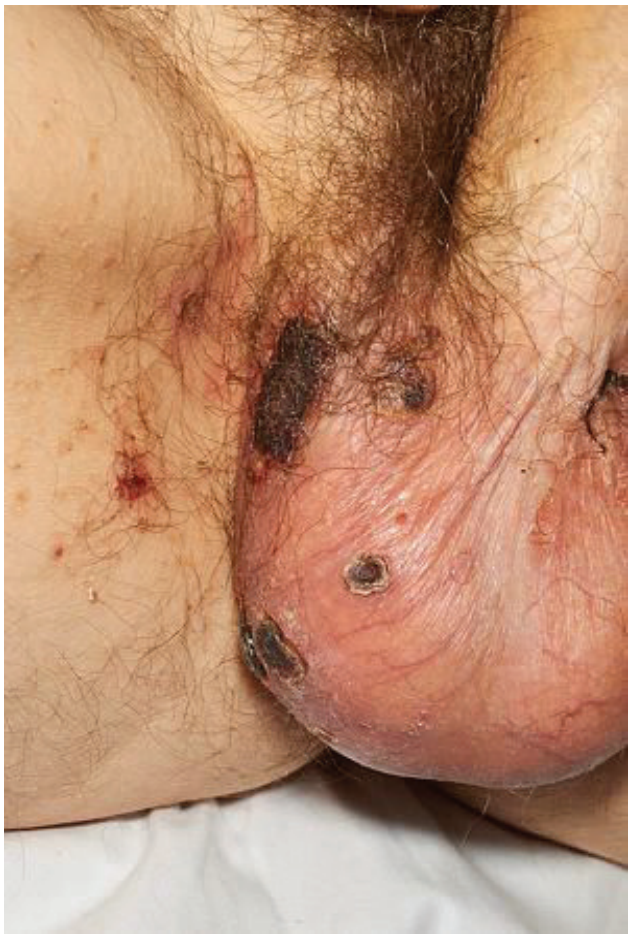
Table 1 International criteria for Behçet's disease point score system: scoring ≥4 indicates Behçet's disease[1,3]

Sign/symptom	Points
Oral aphthosis	2
Genital aphthosis	2
Ocular lesions	2
Skin lesions	1
Neurologic manifestations	1
Vascular manifestations	1
Positive pathergy test*	1*

*Pathergy test is optional and primary scoring system does not include pathergy testing; however, where pathergy testing is conducted one extra point may be assigned for a positive result

Figure 1 Scrotal ulcers in a 38-year-old male



in clinic on multiple occasions and received multiple antibiotic courses that were of minimal help. He did not describe any joint pain, rashes or recent medication change. Cardiorespiratory and abdominal examinations were grossly normal. Multiple scrotal and oromucosal ulcers were present on examination (Figures 1 and 2). There were no focal neurological signs or symptoms. Eye examination revealed a right pupil sluggish to react to light, and visual acuity was reduced to hand movements for this eye. He was stable on olanzapine (20 mg once a day) and did not demonstrate any acute psychiatric symptoms. He was febrile and tachycardic with a heart rate of 110 bpm. Inflammatory markers were raised (Table 2). Flucloxacillin was started for suspected infected scrotal ulcers. When reviewed by ophthalmology his right eye was noted to have right hemi-retinal vein occlusion with macular oedema and retinal neovascularisation.

Further laboratory investigations can be seen in Table 2. An MRI of the brain was conducted owing to his past psychiatric history (Figure 3). Neuroradiology and rheumatology opinions were that in the context of his presentation these changes were highly suspicious of neuro-Behçet's disease (NBD) (Table 2 and Figure 3).

He was reviewed by neurology and rheumatology and the decision made to start him on high-dose steroids because of eye involvement and radiological evidence of neuro-Behçets.

After a week of steroids the patient was clinically improving. A lumbar puncture was considered but not undertaken owing to the clinical improvement on steroids and lack of focal neurology or acute psychiatric disease. He was noted by ophthalmology to have improvement to his macular thickening and was discharged on oral steroids with outpatient neurology, rheumatology and ophthalmology follow up.

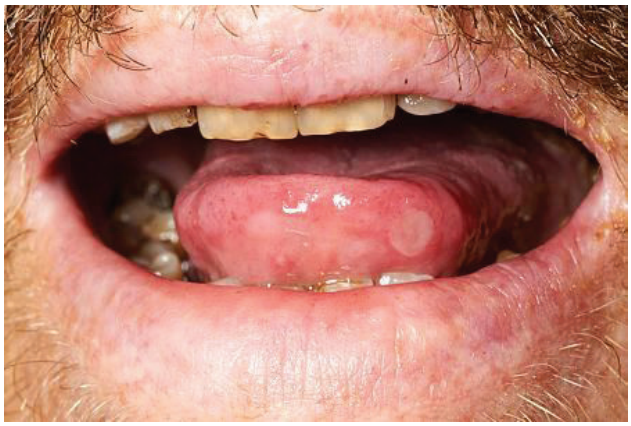
Discussion

This patient met the ICBD diagnostic criteria based upon a history of oral and genital ulcers, ocular involvement and radiological findings suspicious for neuro-Behçets.[3] These lesions were identified on an MRI that was conducted based on his past psychiatric history and in the absence of focal neurology and active psychiatric complaints.

The aetiopathogenesis of BD remains unclear. Current hypotheses suggest that infective, immunological and genetic factors are all contributory.[1,5] Genetics influence the tendency towards BD with HLA-B51 being the strongest susceptibility factor.[1,5,6] Not all patients with BD are HLA-B51 positive.[6] It is postulated that genetic susceptibility combined with an extrinsic trigger factor, such as viral agents, may be responsible for the pathophysiological changes.[1,2,7]

Neurological manifestations of BD include central nervous system (CNS) and peripheral nervous system (PNS) involvement.[1,5,8] CNS involvement is broadly categorised into parenchymal and nonparenchymal lesions.[1,5,8] Parenchymal lesions are found in up to 80% of patients with NBD[1] and typically represent an inflammatory process characterised by multifocal/diffuse, cerebral or brainstem lesions and can manifest as a myelopathy or optic neuropathy.[5,8–10] Nonparenchymal lesions occur secondary to vascular involvement and include cerebral venous thrombosis, intracranial aneurysms and aseptic meningitis.[5,8–10] Parenchymal lesions may be asymptomatic (subclinical) and can also include psychiatric manifestations.[8,9,11]

Figure 2 Oromucosal ulceration in a 38-year-old male



International consensus recommendations for diagnosis and management of NBD[8] recommend that a definite diagnosis of NBD can be made in a patient meeting criteria[3] for BD with neurological symptoms and supporting cerebral spinal fluid (CSF) or radiological evidence, who have no better explanation for these symptoms.[8] A probable diagnosis of NBD can either be made in those with a neurological syndrome and systemic BD features who do not reach the criteria[3] for BD or in those with a noncharacteristic neurological syndrome who do meet criteria[3] for BD.[8]

Investigations for NBD include inflammatory markers, HLA-B51, neuroimaging, CSF, neurophysiological tests and nervous tissue biopsy.[8] MRI findings may include hypointense to isointense lesions on T1-weighted images, hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery images, atrophy or nonspecific white matter lesions.[8,12]

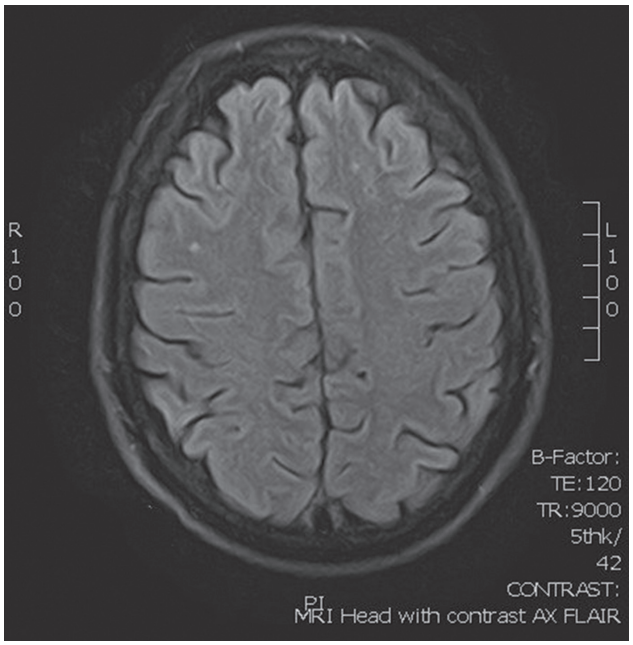
Recommendations for the treatment of acute/subacute parenchymal NBD are high-dose corticosteroids followed by maintenance therapy.[1,8] Disease-modifying therapy with azathioprine as the first line or biological agents, including tumour necrosis factor-α blockers or interferon α, may also be considered based upon disease severity and response to steroids.[1,8]

Evidence for an association between NBD and bipolar disorder is limited to four case reports.[13–16] Two cases involved focal neurological signs,[13,15] another details the presentation of bipolar disorder years after the diagnosis of BD.[14] Van Ham

Table 2 Summary of investigations

Inpatient investigation	Result (reference range)
Inflammatory markers	White cell count: 23 x 10^9/l (3.4–8.4 x 10^9/l) Neutrophils: 17 x 10^9/l (1.6–4.6 x 10^9/l) C-reactive protein: 114 mg/l (0–5 mg/l) Erythrocyte sedimentation rate: 71 mm/h (1–14 mm/h)
Microbiology cultures	Blood cultures: negative Throat swab: negative Scrotal skin swab: mixed skin organisms
Epstein-Barr virus/herpes simplex virus/varicella zoster virus/cytomegalovirus	IgG positive
Human immunodeficiency virus, hepatitis B and C, syphilis viral screen	Negative
Vasculitic and immunology screen	C4/antinuclear antibody/extractable nuclear antigen/ antineutrophil cytoplasmic antibodies/rheumatoid factor/ anticyclic citrullinated peptide/double-stranded DNA/anti-cardiolipin/beta-2 glycoprotein 1/immunoglobulins IgA, IgM, IgG/electrophoresis: negative
HLA-B51	Negative
Testicular ultrasound	No evidence of epididymo-orchitis
CT head venogram	No evidence of cavernous sinus thrombosis
MRI brain with contrast	Few bilateral nonspecific periventicular and subcortical deep white matter focal T2 weighted/fluid-attenuated inversion recovery hyperintensities. Small area of diffuse high T2 weighted and fluid-attenuated inversion recovery signal abnormality in the medial aspect of the right temporal lobe. No corresponding restriction on diffusion-weighted imaging or enhancement post-contrast

Figure 3 MRI of the head with contrast, axial view of fluid-attenuated inversion recovery (FLAIR) images, showing a small diffuse white matter FLAIR hyperintensity in the medial aspect of right temporal lobe and small subcortical hyperintensity in the left frontal lobe



reports a 34-year-old male admitted to a psychiatric hospital with acute mania who proceeded to develop oromucosal and genital ulceration.[16] Although the onset of psychiatric and later dermatological signs and symptoms seems to parallel our case, this was confounded by a retrospective review of the patient's record that revealed he self-discharged from a hospital admission for gait abnormalities 4 years previously, and by the demonstration of a space-occupying lesion on neuroimaging, which was biopsied at the time and showed perivascular inflammation,[16] suggesting that he had preceding focal neurological signs of neuro-Behçet's prior to his psychiatric presentation.

In our case there were no acute psychiatric or neurological symptoms at the time of neuroimaging and the patient was stable on his regular olanzapine. A case–control study involving 49 patients with BD evaluated findings for brainstem evoked potentials in 36 out of 49 patients, single-photon emission computed tomography (SPECT) in 33 out of 49 patients, MRI in 25 out of 49 patients and electroencephalogram (EEG) in 30 out of 49 patients.[12] Patients with BD were excluded if they had any neurological symptoms or signs.[12] The study found that there were more MRI and EEG abnormalities in the BD group than in controls.[12] However, SPECT and brainstem evoked potentials showed no significant difference between the BD group and controls.[12] The detection of MRI and EEG abnormalities in asymptomatic patients suggests that, although largely unrecognised, subclinical NBD may not be so uncommon.[5,12,17] In our patient the parenchymal MRI lesions may be linked to his behavioural disturbance and preceding episode of being acutely suicidal.

Conclusion

This case highlights that patients presenting with oromucosal and genital ulcers, mood disorder and visual changes should not have these symptoms considered in isolation and that BD should be considered. Our patient required coordinated care involving a number of different specialities and this demonstrates the importance of a multidisciplinary approach in managing BD.

It is unclear whether our patient's bipolar mood disorder was directly linked to his parenchymal MRI findings, or whether these findings represented subclinical NBD and independent psychiatric comorbidity. However, the onset of his acute psychiatric symptoms correspond with the onset of orogenital ulceration. It was his past psychiatric history that prompted an MRI. Recognition of our patient's radiological NBD allowed neurology specialist review and follow up, which highlights the importance of considering NBD in patients presenting with BD.

Learning points

- BD should be considered in patients presenting with oromucosal and genital ulcers, mood disorder and visual changes.
- Care of patients with BD should involve a coordinated multidisciplinary approach.
- NBD can occur in the absence of focal neurological signs and symptoms.

Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient for publication of this paper, including accompanying images.

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