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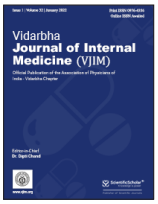

Case Report

Delirium: Fallout of Neuro-Behcet's Disease – A Case Report

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ABSTRACT

Here, we present a case of an elderly male with hypertension and diabetes, who presented to ER with delirium, ataxia, and slurring of speech associated with altered psychomotor behaviour, also features such as anorexia, painful erythematous patches over extremities, tender knee, and ankle joints were conspicuous at presentation. A brain scan on admission revealed multiple lacunar cerebellar infarcts, whereas routine blood investigations did not reveal anything substantial contributions to the cause of presenting symptoms, including negative serology for ANA, DS-DNA, HAL-B51, and anticardiolipin antibodies, done to rule in, presence of systemic autoimmune causes for the gamut of clinical features at presentation. Contemplation over past and associated clinical features, such as ocular ailment, recurrent aphthous ulcers, dermatological lesions (erythema nodosum and peudofolliculitis), and past MRI showing lesions in the thalamus and pons (diencephalon predilection) a diagnosis of Behcet's disease (BD) was considered based on 'International Study Group Diagnostic Criteria for BD'. More so in the event of no better explanation for the neurological involvement, in a diagnosed case of BD, presenting delirium was considered to be the fallout of Neuro-Behcet's Disease (NBD). The Patient responded to steroids and was discharged on a combination of tapering doses of steroids with Azathioprine. Emphasising the fact that the central nervous system affection in a case presenting with signs of systemic inflammation, autoimmune vasculitis as a cause of neurological involvement should be considered, as this is critical for deciding onto the course of treatment. NBD being secondary to systemic vasculitis as compared to atherosclerotic vascular affection seen in regular stroke, require steroids and immunomodulators rather than antiplatelets and anticoagulants.

Keywords: Delirium, Behcet's disease, Neuro-Behcet's disease, Autoimmune, Systemic vasculitis

INTRODUCTION

Behcet's disease (BD) is a chronic, relapsing, multi-systemic vascular-inflammatory disease of unknown origin, characterised by recurrent oral and genital ulcers, skin lesions, and uveitis. As the disease affects many organs and systems and shows a wide range of clinical manifestations and presentations, this ailment can also be seen as a syndrome. Other manifestations include arthritis, a positive pathergy test, thrombophlebitis, central nervous system (CNS), and gastrointestinal affection. The eponym BD is after a Turkish dermatologist, Hulusi Behcet, who first described the disease in 1937.[1] It is commonly observed in the Silk Road countries between the Mediterranian Sea including Spain, Portugal, Turkey, Iran and Far East countries like China and Japan.[2] Demographically, the disease has a male preponderance, with second to fourth decades having the maximum number of cases.

Although the aetiology of BD is not clearly identified, hypothesized pathogenesis is a profound inflammatory response triggered by an infectious agent, HSV-1, and *Streptococcus sanguis*, in a genetically susceptible host. Nervous system involvement, in BD called as Neuro-Behcet's disease (NBD), was first reported in 1941 and occurs in approximately 20% of patients with BD. The growing clinical and imaging evidence suggests that primary neurological involvement in NBD may be sub-classified into two major forms: (i) Parenchymal NBD: Seen in the majority of the patients with NBD, may be characterised as a vascular-inflammatory CNS disease, with focal or multifocal parenchymal involvement mostly presenting with a subacute brainstem syndrome, hemiparesis, pyramidal, extrapyramidal symptoms, personality changes, and psychological disorder. (ii) Non-parenchymal NBD: This has few symptoms and a better neurological prognosis, caused by isolated cerebral venous sinus thrombosis, and presents with features of intracranial hypertension.[3] The core histopathologic phenomenon seems to be T-lymphocyte mediated vasculitis, affecting arterial and venous systems equally. There being no specific radiological, laboratory, and histological criteria for the diagnosis of this BD/NBD, the diagnosis is entirely clinical and based on 'International Study Group (ISG) criteria for the diagnosis of BD [Table 1]'

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and 'International Consensus Recommendation (ICR) for the diagnosis of NBD [Table 2]'. Although certain MRI features of NBD such as typical involvement of diencephalon with predilection towards the brainstem are seen, also laboratory tests such as positive HLA B-51, and anticardiolipin antibodies are said to be associated in 50–80% of patients with BD but are definitely not specific. As NBD is secondary to autoimmune vasculitis, the treatment is immunosuppressants and immunomodulators rather than antiplatelets and anticoagulants.

Treatment options for NBD are limited to steroids in tapering doses over 6 months, symptomatic management, and generally the use of azathioprine, cyclophosphamide, interferon-alpha, and anti-TNF agents for long-term preventive treatment, with doubtful efficacy.[4]

CASE REPORT

A 72-year-old male, pre-morbidly diabetic, and hypertensive for 15 years, presented to ER with the sub-acute onset of delirium, personality changes, insomnia, anorexia, and acute onset dysarthria, ataxia, tremors, associated with red patches over extremities and severe joint and muscle pain on slight movements of extremities, since 4 days.

Table 1: International Study Group criteria for the diagnosis of Behcet's disease.

Mandatory Criteria (Required)	Minor Criteria (At least 2 required)
1.Recurrent oral aphthous ulcers (At least 3 episodes/12 months)	1.Recurrent genital ulcers. 2.Eye lesions 3.Skin lesions 4.Positive pathergy test

Table 2: International Consensus Recommendation criteria for NBD diagnosis.

Definite NBD meeting all of the following three criteria:
1. Satisfy the ISG criteria for BD
2. Neurological symptoms recognises to be caused by BD and supported by relevant and characteristic abnormalities seen on either or both:
   - Neuroimaging
   - CSF
3. No better explanation for the neurological findings

Probable NBD meeting one of the following two criteria in the absence of a better explanation for neurological findings:
1. Neurological syndrome as in definite NBD, with systemic BD features but not satisfying the ISG criteria
2. A non-characteristic neurological syndrome occurring in the context of ISG criteria-supported BD

ISG: International Study Group, BD: Behcet's Disease, NBD: Neuro-Behcet's Disease

Because of features of delirium and parenchymal brain involvement, the patient was admitted to ICU, with the following findings on preliminary physical examination.

General examination

The patient had an average build, was conscious, confused, disoriented, irritable, and had erythematous patches over extremities. Afebrile, pulse – 104/min (regular), respiratory rate – 20/min, blood pressure – 98/70 mmHg, the patient was pale with bilateral pedal oedema and dry tongue, no cyanosis/icterus/lymphadenopathy. He had aphthous ulcer over left buccal mucosa [Figure 1], erythema nodosum over upper extremities [Figure 2], and pseudofolliculitis over the scalp [Figure 3].

Systemic examination

Respiratory system – Air entry bilaterally equal, no adventitial sounds, CVS – S1S2 normal, no murmur, CNS – Confused, drowsy, irritable on arousal, partial response to verbal commands, dysarthria, ataxia and intentional tremors, pupils – no anisocoria with normal reaction to light and planters - flexor bilaterally.

Blood sample was taken for relevant tests and MRI stroke-protocol (NECT Brain + DWI sequence on MRI) was ordered to see for any organic involvement of CNS as to the cause of presenting neurological symptoms.

Blood investigations did not help much to elucidate the cause, significant findings were raised TLC – 16,000/mm^3 and hypoproteinemia. Serum procalcitonin, ammonia and KFT were normal, ruling out any sepsis or metabolic cause for obtundation respectively. Lumbar puncture to see for CNS infection was withheld because of probably deranged coagulation profile as the patient had ecchymotic patches over extremities, and also clinically, there were no signs of encephalomeningitis on systemic examination, except for delirium. A normal coagulation study ruled out haematological factors as the cause of ecchymosis. A brain scan (NECT + DWI image on MRI) revealed multiple lacunar bilateral cerebellar infarcts, attributing to ataxia and intentional tremors, without any component of bleed seen on CT.

As blood investigation, X-ray chest, and brain scan did not come up with substantial reasoning for the presenting mucocutaneous, musculoskeltal and neurological features and their corelation, detail past history was elicited. In the past, the patient had recurrent oral ulcerations, fragile skin with recurrent devolving on minor injuries, choroidal neovascular membrane (CNVM) in both the eye, requiring intra-ocular Bevacizumab, chronic alternating constipation with loose motions, relapsing and remitting arthralgia (knee/ankles). Neurological opinion did not favour the cerebellar lacunar infarct as the cause of entire gamut of neurological

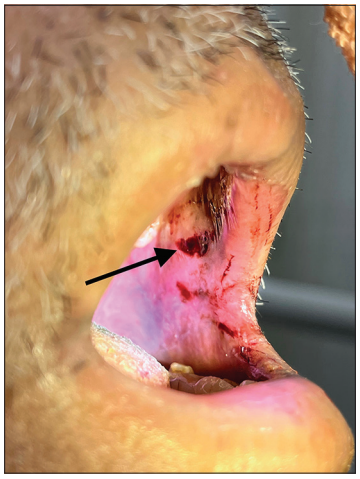

Figure 1: Oral aphthous ulcer (Black arrow).

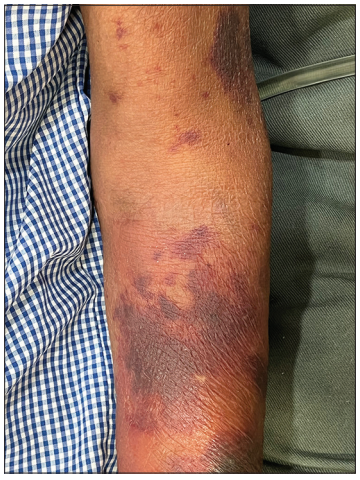

Figure 2: Erythema Nodosum over forearm.

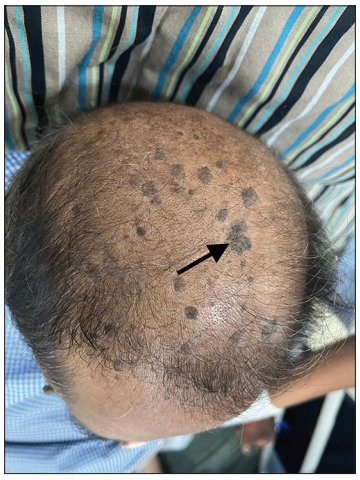

Figure 3: Pseudofolliculitis of Scalp (Black arrow).

manifestation, dermatologist had opined regarding the dermatological lesion to be chronic eczema with ecchymosis and 2D echo ruled out any probability of cardioembolic cause of cerebellar infarct.

A combination of relapsing-remitting oral ulcers, ocular lesion with choroidal involvement, erythema nodosum, pseudofolliculitis, recurrent joint involvement and positive Pathergy test pointed towards BD, as per 'ISG Criteria for Diagnosis of BD' [Table 1], more so concomitant neurological features of altered cognition, personality changes with cerebellar signs, not otherwise explained by any other known systemic or neurological disease or treatment, was taken as NBD, on the basis of 'ICR criteria for NBD diagnosis' [Table 2].

Steroids were started, using 1 mg/kg/day of Methylprenisone, in addition to other on-going ancillary treatment which consisted of PPI, antibiotics, intravenous albumin supplementation, anitplatlets and intravenous multi-vitamins. LMWH was withheld as there were overt subcutaneous haemorrhages and DVT prophylaxis was achieved with non-pharmacological methods. The patient responded well to the given treatment with resolution of CNS obtundation, joint pains, dermal lesions also became less inflamed, the patient started having normal conversation and diet, and was discharged on a tapering dose of steroids. The patient had a relapse of delirium, and personality changes with ataxia as the dose of steroids got tapered over 15 days. The patient again responded to 1 mg/kg/day of Methylprenisone and this time patient was discharged on a slow tapering dose over the period of 6 months in combination with Azathioprine 50 mg once a day.

DISCUSSION

In our case, delirium and other neurological features of parenchymal brain involvement were associated with mucocutaneous, ocular lesions, and musculoskeletal features, the correlation of these individual features into a single entity called BD was established based on 'ISG' criteria for the diagnosis of BD,[5] as our patient had sufficed 4/5 diagnostic criteria [Table 1]. More so in the absence of any radiological, laboratory, and histological diagnostic criteria, ISG criteria are the only criteria for the diagnosis of BD, with the sensitivity of 92% and specificity of 97%. In a diagnosed case of BD, any primary neurological involvement, with no better explanation for the neurological findings, is taken as CNS involvement secondary to BD and is called as NBD. NBD as the cause of neurological features in our case was based on 'ICR' criteria for the diagnosis of NBD[6] [Table 2]. NBD as stated earlier has two subclasses, of which in our case, we encountered parenchymal form, involving diencephalon, thalamus, pons, cerebellum and subcortical white matter including centrum semiovale, corona radiata and pritrigonal area, over the period of disease course.[7] Uveal and choroidal involvement, being one of the diagnostic criteria, was also seen in our case, depicted by presence of CNVM on Optical

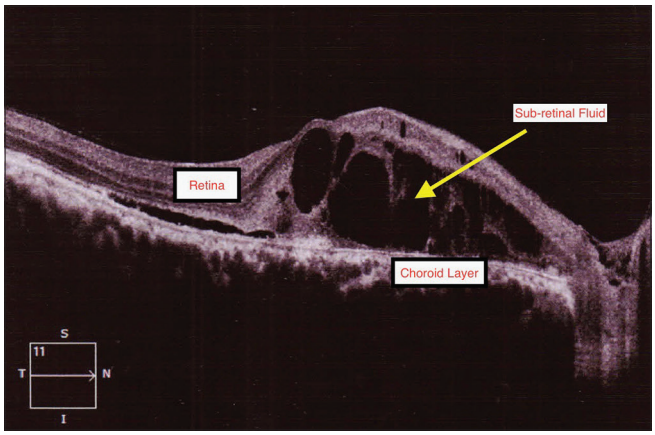

Figure 4: Optical coherence tomography image, showing sub-retinal fluid collection secondary to choroidal neovascular membrane.

Coherence Tomography image [Figure 4], CNVM being a recognised accompaniment of BD,[8] which confirms uveitis in our case. Serological markers such as ANA, DS-DNA, Anti-smith antibody and HLA DR-2 and cANCA/pANCA came negative, differential such as SLE, multiple sclerosis, Sjogren's syndrome and systemic vasculitis secondary to ANCA were ruled out. HLA B-51 and anticardiolipin antibodies though are seen in some cases of BD/NBD but are definitely not diagnostic and were also not found in our case.

On follow-up MRI, resolution of cerebellar lesions at presentation indicates subsidence of vasculitis as a response to immunosuppression by steroids. Delirium being a well-documented neurological feature of NBD,[9] we conclude that delirium in our case with associated mucocutoaneous, ocular, and musculoskeletal features was a fallout of NBD.

CONCLUSION

Delirium and other neurological signs of parenchymal involvement in a case presenting with associated signs of systemic inflammation should always be evaluated as possible fallout of autoimmune systemic vasculitis. In our case, this being NBD, which required treatment with steroids and immunomodulators rather than regular antiplatelets and anticoagulants, required for any regular stroke, secondary to atherosclerotic vascular affection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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