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Research Article

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Neuro-Behçet Syndrome Triggered by Illicit Drug Use: Case Presentation and Literature Review

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Abstract

Behcet's disease is a chronic systemic inflammatory disorder that is characterized by recurrent oral and genital aphthous ulcers, skin lesions, uveitis, as well as the involvement of different organs, including the central nervous system (CNS) [1]. Neurological manifestations, better known as neuro-Behcet's (NB), occur in about 5-10% of cases, ranging from headaches and impaired cognition to severe neurological deficits [2,3]. This case report describes a unique case of neuro-Behcet's disease in a patient with substance use in the background, and it adds to knowledge while enhancing further understanding of this complex interplay and its implications regarding management.

Keywords: Behçet's Disease, Neuro-Behçet Syndrome, Drug Abuse, Substance Abuses, Neurological Manifestations

Case Report

Hereby, we present a 29-year-old male patient presented to neurology clinic with syncope and loss of balance problems. He had no prior history of epilepsy, no known chronic conditions, or regular medications. Fainting happened two times and was accompanied by loss of consciousness. In his neurological examination, he had conjugate horizontal gaze palsy towards the left side consistent with 'One and a half syndrome,' diplopia, dysmetria, extremities resting, postural and kinetics tremor, limb ataxia, left Babinski sign positive. Brain magnetic resonance imaging (MRI) showed a hyperintense lesion that extends superiorly to the brainstem at the pontomesencephalic junction and inferiorly towards the left part of the medulla. In the supratentorial area, another intra-axial lesion area was observed on the left side involving the hippocampus-amygdala, partially lateral thalamic, capsular, and extending towards the midline diencephalic regions, characterized by T2/FLAIR hyperintense signals with heterogeneous contrast enhancement.

All lesions showed progression in the next MRI, which was taken two weeks later. A brain biopsy was performed and it was consistent with vasculitis, but a second biopsy was required. A small intracranial hemorrhage located in the left temporal region was seen on contrast MRI. Figure 1 FDG-PET showed no FDG uptake on major vascular structures to be considered in favor of vasculitis and no existence of malignant tissue. His Anti-Nuclear Antibody was weak positive; ENA Profile results came negative, as well as p-ANCA, c-ANCA, Lupus Anti-Coagulant(LAC), and anti-dsDNA. A lumbar puncture and subsequent cerebrospinal fluid examination ruled out any central nervous system infection (Cryptococcus neoformans, Listeria monocytogenes, Neisseria meningitides, H. İnfluenzae, Streptococcus agalactiae, S.Pyogenes, M. pneumoniae, E. Coli K1, VZV, HHV8-DNA, CMV, HSV1 DNA, HSV2 DNA, HHV6 DNA, HHV7 DNA, Enterovirus, Parechovirus, S.Pneumoniae). Cerebrospinal fluid analysis revealed glucose 79mg/dl, protein total 39mg/dl, albumin 30,1mg/dl, chloride 117,6mmol/L, and IgG 39mg/L. Borrelia Burgdoferii IgG and IgM were negative. Sexually transmitted

diseases were also ruled out (including HIV, Hepatitis B, and Hepatitis C). Angiotensin Converting Enzyme(ACE) levels and Immunofixation analysis showed no abnormalities. HLA-B51, however, came positive.

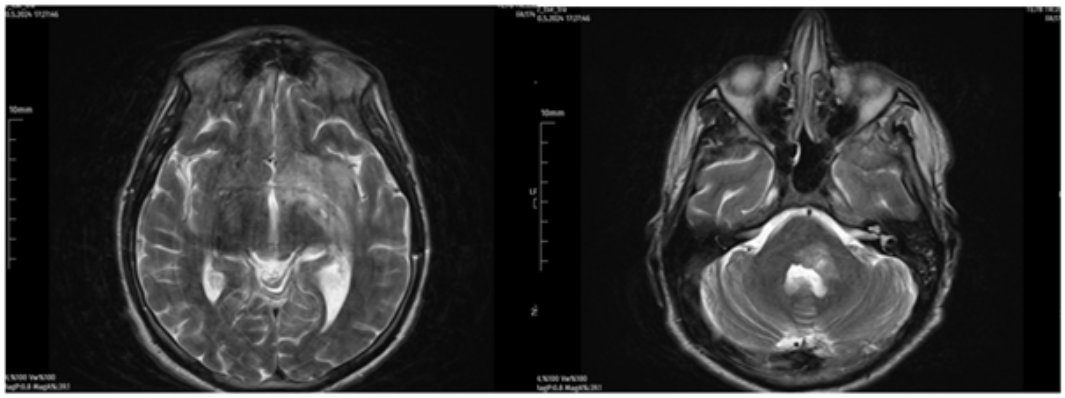

Figure 1: A lesion area is observed in the left superior region of the caudate nucleus, within the deep white matter in the periventricular area, showing hyperintense characteristics on T2-weighted imaging without significant diffusion restriction.Additionally, starting from the left lentiform nucleus and external capsule level and extending downward inferiorly, there are lesion areas on T2-weighted imaging, including hyperintense hemorrhagic foci and regions demonstrating acute diffusion restriction. Furthermore, starting from the midbrain level and extending inferiorly from the posterior of the superior cerebellar peduncle, there are lesion areas showing hyperintense signals on T2-weighted imaging, with some millimetric foci of acute diffusion restriction extending from the posterior pons to the left middle cerebellar peduncle and the left posterior region of the medulla oblongata.

Later, the patient reported having intermittent oral ulcers throughout his life, and pseudofolliculitis was also present upon physical examination. Thus, he was diagnosed with Behcet disease [as the ISG(International Study Group) and ICBD(International Criteria for Behcet's Disease) criteria being fulfilled] and Neuro-Behçet's disease. Therefore, he received 1g/day Pulse steroid (methylprednisolone) treatment for five days and then first cyclophosphamide 250 mg and mesna 400 mg doses. The patient developed dyspnea and bilateral crepitant rales and he was later diagnosed with aspiration pneumonia. Sputum culture revealed Methycillin Resistant Staphylococcus Aureus and Streptococcus Pneumonia. Therefore, he was treated with teicoplanin (2x400mg loading and 1x400mg maintenance) and meropenem (3x1g). The antibiogram and infection markers showed efficacity.

Due to the swallowing function test showing dysphagia and the patient being unable to tolerate the nasogastric tube, still posing an aspiration risk, a percutaneous endoscopic gastrostomy (PEG) was performed, and enteral feeding was initiated. During the hospital stay, the family reported the patient receiving illicit drugs, including LSD, cannabis, MDMA, and methamphetamine, on and off for six years, which he had stopped six months before the first admission. The family reported no regular consumption of all simultaneously but at different intervals.

Once the infection was under control, the second and third doses of cyclophosphamide 500mg and mesna 400 mg were administered once a week. The patient was started on levetiracetam 1000 mg 2x1 for epileptic seizures, but this dose was insufficient, leading to focal seizures, particularly affecting the right upper and lower extremities and status epilepticus. Muscle weakness on the right side was also noticed; thus, diffusion MRI and control EEG were requested. The diffusion MRI did not show acute diffusion restriction compared to the last MRI, which was taken three weeks before, but the EEG showed sharp spikes and slow waves in the left hemisphere.

The levetiracetam dose was gradually increased to 3000 mg/day, but due to the continued seizure activity, phenytoin was also added and gradually increased to 1000mg /day. After the dosage adjustment, the seizures were brought under control. However, the patient developed delirium, likely due to his general condition and prolonged hospital stay, as well as agitation and aggression, possibly as side effects of levetiracetam. Therefore, levetiracetam and phenytoin doses were decreased gradually, and the patient was started on valproic acid and also olanzapine(10mg/day) due to aggression and delirium.

The future treatment plan included infliximab and maintenance of 32mg of methylprednisolone, colchicine 1mg/day, levetiracetam 2000mg/day, valproic acid 2000mg/ day, enoxaparin sodium 4000 IU twice daily, and olanzapine 10 mg/day.

According to the information received from the follow-up doctors and relatives of the patient after his discharge from our clinic, the patient's epileptic complaints completely disappeared after the infliximab doses, and thus, the anti-epileptic dose was reduced.

1. Introduction

Many genetic, environmental, and immune-related factors are involved in the pathogenesis of Behcet's disease [4]. Among the suspected environmental factors, substance abuse may act

on immune regulation and modulate inflammatory pathways. However, the specific impact of neuro-Behcet needs to be explored in more depth in the literature [5]. Recognition of the clinical course and outcomes of neuro-Behcet's in patients with a prior history of substance use is critical for determining individual treatment strategies. This is because substance use, especially that which implies exposure to substances that may disturb immune or vascular function, may modulate inflammatory processes, which are central to the pathogenesis of Behcet's disease [6,7].

2. Dıscussıon

Neuro Behçet disease is presumed to be caused by immune dysregulation and neuroinflammation. It is typified by recurrent inflammatory attacks that impact the central nervous system (CNS), including the brain parenchyma [8]. Cerebrospinal Fluid (CSF) analysis plays an essential role in analyzing the different patterns of NBD. Although the CSF can be completely normal, elevated IL-6 levels, pleocytosis (neutrophilic and lymphocytic), elevated protein levels, and normal glucose levels might be found in parenchymal manifestations [9]. Oligoclonal bands can be seen in a minority of patients, and increased immunoglobulin indices are also an important parameter. However, in a case series, it is shown that oligoclonal bands disappear and immunoglobulin indices decrease after the acute attacks [10,11]. Although there are hypotheses suggesting that Behçet's disease can cross the blood-brain barrier and cause neurological symptoms, there is not enough research to support this hypothesis. However, as we can observe in this particular case, many additional factors may facilitate the development of neuro-Behçet by allowing Behçet's disease to cross the blood-brain barrier.

The blood-brain barrier (BBB) is an essential interface that controls which substances enter the central nervous system (CNS). It contributes to the homeostasis of the brain. The physical barrier is formed by endothelial cell tight junction, adhesion junction protein, non-selective fenestration, and transcytosis. Astrocytes and pericytes are also essential components. Disruption of the tight junctions causing increased paracellular leakage of soluble mediators and upregulation of adhesional molecules causing increased transcellular entry of the inflammatory T cells are the main events occurring during pathological blood-brain barrier disruption Claudin-5 protein level decline also leads to increased paracellular permeability of the BBB. Some studies show that corticosteroids increase the expression of claudin-5 and, by that, strengthen the barrier β2-microglobulin and albumin indexes were significantly elevated in patients with NBD compared with the control patients in another study [12-16]. Functional IL-6 activity in patients with active NBD but lacking progressive NBD has shown marked elevation, with no significant correlation of CSF IL-6 activity with serum IL-6 activity [17]. Patients with chronic progressive NBD, compared with acute NBD, had significantly lower CSF total cell and polymorphonuclear leukocyte counts [18].

Drugs, including stimulants and psychotropic substances which are frequently used for both therapeutic and recreational purposes can penetrate the BBB in several ways. Among these are active transport processes and the possibility of jeopardizing the integrity of the BBB in specific circumstances [19]. Upon entering the central nervous system (CNS), these substances interact with existing immune cells, such as microglia, astrocytes, and neurons. This produces cytokines, chemokines, and reactive oxygen species (ROS), which are markers of an inflammatory response [20]. This inflammatory signaling cascade could exacerbate the condition in neuroinflammatory disorders like Neuro Behçet disease, where chronic neuroinflammation and immunological activation play critical roles in disease progression. Studies reveal that, for example, opioids trigger strong inflammatory responses by activating toll-like-receptors on microglia, which are linked to neuroinflammatory disorders and drug tolerance [21]. Similar to this, it has been demonstrated that stimulants like cocaine and methamphetamine raise oxidative stress and induce the release of pro-inflammatory cytokines in the central nervous system, which can exacerbate the neuroinflammation seen in conditions like Neuro Behçets disease [22].

MDMA, cocaine, and nicotine cause blood-brain barrier (BBB) dysfunction by altering tight junction protein expression and conformation, increasing glial activation, and enhancing enzyme activation related to BBB cytoskeleton remodeling. Additionally, these substances induce neuroinflammatory pathways. Monoamine oxidase inhibition leads to the production of free radicals, resulting in oxidative stress and neuroinflammation. Continuous cocaine use has been shown to increase blood-brain barrier (BBB) permeability by 50% and decrease transendothelial electrical resistance due to the upregulation of matrix metalloproteinase and tumor necrosis factor [23]. Chronic administration of cocaine of 30mg/day/ intraperitoneal route ruptures the neurovascular capillaries and basement membranes of rats [24]. Methamphetamine's high lipophilicity facilitates its rapid passage across the BBB. Additionally, methamphetamine activates microglia and astrocytes within the neurovascular unit, with astroglial reactivity contributing to BBB disruption.

It is shown that a single intraperitoneal injection of either 3 or 9 mg/kg of methamphetamine in rats resulted in blood-brain barrier (BBB) damage in the prefrontal cortex and nucleus accumbens shell, as evidenced by punctate areas of fluorescein isothiocyanate (FITC)-labeled albumin leakage (Kousik et al., 2011) [25]. Other rodent studies have also shown BBB dysfunction following acute methamphetamine treatment, regimens ranging from single doses of 3-40 mg/kg to several acute doses over 24 hours, all of which compromised BBB integrity. A single 30 mg/kg intraperitoneal injection of methamphetamine resulted in elevated expression of TNFα and IL-6 in the hippocampus, frontal cortex, and striatum of mice. Similar increases in TNFα, IL-1β, and IL-6 have been observed following multiple methamphetamine treatments, which may be linked to methamphetamine-induced microglial activation.

In addition to altering blood-brain barrier permeability, [26,27].

This might be related to the neuro-Behcet activation, as mentioned above. MDMA increases the expression of pro-inflammatory cytokines, such as IL-1β, in brain tissue [28]. Morphine induces pro-inflammatory cytokine activity, disrupts intracellular calcium release, and activates myosin light chain kinase, leading to reactive oxygen species (ROS)-mediated neurotoxicity [23]. Chronic nicotine administration compromises the integrity of the blood-brain barrier (BBB) by causing the loss and alteration of tight junction proteins, such as ZO-1, claudin-3, and JAM-1. This disruption affects the regulated transport and receptor systems essential for normal BBB function and reduces the functional activity of ion transporters [29,30].

Cocaine, on the other hand, is shown to contribute to autoimmunity by triggering the development of ANCAs by inducing the release of potentially inflammatory neutrophil extracellular traps [34]. There are also case reports showing the association between cocaine and acute multifocal leukoencephalopathy. This effect might be particularly associated with levamisole contamination, a commonly used cocaine adulterant [35,36]. Another study examined basal and provoked changes in peripheral cytokines among 28 cocaine-dependent individuals and 27 social drinkers, finding that cocaine abusers had decreased basal IL-10, elevated TNFα in response to stress, and lacked the anti-inflammatory responses (IL-10 and IL-1ra) seen in social drinkers [37]. Cocaine use triggers an increase in stress hormones, leading to heightened glucocorticoid receptor gene expression, which enhances the likelihood of continued cocaine use and activates the HPA axis; this activation, coupled with elevated signaling molecules, results in reduced inflammatory responses.

Short-term studies investigating the impact of cocaine on brain signaling and immune modulation yield inconsistent results due to difficulties in managing immune system variables. According to long-term research by Avila et al., chronic cocaine use may lead to enduring changes in immune function, including prolonged T-cell suppression due to persistent corticosteroid release during both active use and withdrawal [38,39]. Cocaine-induced dysregulation of the immune system and stress response may exacerbate Neuro-Behçet's disease by enhancing immune system dysfunction and increasing neuroinflammation. The long-term effects of cocaine, including sustained T cell suppression and disrupted corticosteroid regulation, could lead to more severe neurological symptoms and increased disease flare-ups.

CSF analysis patterns are different in the parenchymal and non-parenchymal subdivisions of NBD. Increased cellularity is an indication of immune activation for both. In half of the parenchymal NBD cases, cellular examination of the CSF has revealed normal findings, whereas the other half revealed pleocytosis, with half showing neutrophilic predominance or both neutrophils and lymphocytes; the other half had higher percentages of mononuclear cells and lower percentages of activated lymphocytes. During active encephalitis, elevated C3 and C4 concentrations, higher percentages of IgM, and, to a lesser degree, IgG and IgA, and the presence of immune complexes were seen in CSF but not in serum. CD8+T cell percentage was also increased, as well as the IgG index in %73 of patients. Oligoclonal bands, on the other hand, are evidence of a humoral response. CSF oligoclonal IgA and IgM were recommended in monitoring CNS disease activity in NBD. %42 of the patients with NBD showed an abnormal barrier function at the same time when assessed with an albumin ratio of CSF to serum [31,32].

Another study highlights that the IgA index in Neuro-Behçet's Disease (NBD) is nearly twice as high as in non-inflammatory neurological disorders (NIND), achieving an accuracy of 84.88% for differential diagnosis with a sensitivity of 75.00% and a specificity of 90.00% at a cutoff of >0.6814. Additionally, the cerebrospinal fluid (CSF) Ig and Ig quotient demonstrate over 90% accuracy in distinguishing NBD from damaged or intact blood-brain barrier (BBB). Clustering analysis identifies two NBD phenotypes: one with BBB damage and lower Ig synthesis and another with intact BBB but increased Ig synthesis at parenchymal sites. Furthermore, the myelin basic protein (MBP) index shows significant correlations with the kappa (KAP) and lambda (LAM) indices ($r = 0.358$ and 0.575, respectively, $P < 0.001$), suggesting that CNS demyelination in NBD triggers excessive intrathecal Ig production and humoral responses [33].

Beside from the neuro-toxic effects of the illicit drugs causing vasculitis and Neurobehcet; chronic behaviour disorders and acute psychosis can also be the first symptoms of the disease, as shown in case report reported by and case study reported by [40,41]. This might be related to our case in a way that vasculitis and seizure history either as a behavioral disorder complication of late diagnosed Neuro-Behcet or vice versa- the CNS stimulating drugs might have triggered his vasculitis.

3. Conclusıon & Importance

Hereby, we presented a patient with Neuro Behçet, whose disease might be activated due to his illicit drug use. For the purpose of creating successful treatment plans, it is essential to comprehend how diseases like Neuro Behçet's disease, neuroinflammation, and drug-induced BBB disruption interact. Therapeutic interventions that target neuroinflammatory responses may be able to reduce the severity and progress of the condition. Furthermore, a deeper comprehension of the effects of various drug classes on CNS inflammatory pathways advances our knowledge of how these drugs affect neurological health. The biology of Neuro Behçet disease and other neuroinflammatory disorders can be better understood by examining the impact of drugs on the BBB and the resulting neuroinflammation. Researchers can improve treatment outcomes for individuals with primary neuroinflammatory disorders and reduce drug-related problems by clarifying these pathways.

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