

Neuropsychiatric Involvement of Behçet's Disease

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INTRODUCTION

Recurrent orogenital ulcers, ocular inflammation and skin lesions are well known findings of the Behçet's disease (**BD**) and this phenomenon was defined by Hulusi Behçet 80 years ago. Today it is accepted that BD is a multi systemic, chronic, relapsing vasculitis and neurological, cardiovascular, pulmonary, articular, and gastrointestinal system can be involved during disease attacks [1,2]. Both genetic and environmental factors play important role in pathogenesis of BD and especially male sex during third decade of life may be affected from disease [3]. BD disease can be seen all over the world, but it is more common in Eastern Asia and Mediterranean region on the ancient Silk Road [4,5]. Because BD has no established laboratory finding, diagnosis of BD is primarily depends on clinical features. Diagnostic criterias of BD was established by International Study Group (**ISG**) in 1990 [6].

Neurological manifestations of the BD is named Neuro-BD (**NBD**). The clinical features of BD are variable. Some patients have mucocutaneous lesions and arthritis, while others have life-threatening neurological and vascular involvement. Although neurological involvement is not included in the ISG criteria for BD, it is the second main cause of mortality. [7]. The prevalence of neuro-BD in studies conducted in various countries has been reported to be 2 to 50 % [8-11]. The first finding in 5-23% of BD patients is neurological symptoms and CNS involvement adversely affects the prognosis in BD [12,13].

CLASSIFICATION OF NBD

NBD is divided into three main groups. The first group is parenchymal group and the second group is non- parenchymal or vascular disease group and finally the third group is mixed parenchymal and non-parenchymal disease group. Parenchymal group is the most common group and estimated frequency is about to 80 %. These groups can be divided into subgroups (Table 1). Parenchymal central nervous system (CNS) involvement may occur with or without meningeal inflammation and mainly brainstem may be affected during disease attack which is related with pyramidal signs, cerebellar symptoms, sphincter disturbance and behavioral changes. Parenchymal CNS involvement may present as acute disease or may have a chronic progressive form. The acute form is mainly characterized by acute meningo encephalitis with or without focal lesions. Chronic progressive form consists of slowly progressive neuro behavioral changes such as dysarthria and ataxia, which lead to severe invalidity. Acute form seems to have a good response to corticosteroids treatment. The chronic progressive form is characterized by a poor response to conventional treatment with corticosteroids but it may respond to methotrexate therapy [11,14]. Spinal fluid analysis (CSF) in the parenchymal form may reveal increased cells and protein, and may also be predominantly neutrophilic. Serum IL-6 levels have been reported to correlate with BD disease activity. CSF IL-6 levels are increased in patients with acute parenchymal NBD and this increase is usually associated with an increase in the number of CSF cells and protein. A smaller rise in IL-6 levels has also been reported in a proportion of progressive parenchymal NBD [15,16].

Table 1: Classification of neuro-Behcet’s disease.

1-Parenchymal
 Multifocal or diffuse
 Cerebral
 Spinal cord
 Brainstem
 Asymptomatic (silent)
 Optic neuropathy
2-Non-parenchymal
 Cerebral venous thrombosis
 Intracranial aneurysm
 Cervical extracranial aneurysm or dissection
 Acute meningeal syndrome
3-Mixed parenchymal and non-parenchymal disease

Dural sinus thrombosis results in intracranial hypertension and vascular disease is usually caused by intracranial hypertension. The most common neurological symptom observed in patients with NBD is headache and 10-15 % of headaches reported in NBD. Because headache may be associated with many different etiologies, other causes of headache should be investigated. For this reason, all BD patients with recurrent headache episodes need to undergo routine neurological examination. Neuroimaging is useful in this context [17,18].

DIAGNOSIS OF NEURO BEHCET DISEASE

Neuroimaging has a significant role in the diagnosis of NBD and MRI is accepted gold-standard method. MRI is extremely useful in differentiating NBD from its mimics and the brainstem thalamic basal ganglia lesions moreover MRI can strongly distinguish the diagnosis of acute/sub acute parenchymal subgroups of the disease [19]. The characteristic MR findings are listed Table 2.

Table 2: Characteristic MRI findings in NBD.

1. Parenchymal NBD
Nature of the lesions
<ul style="list-style-type: none">Acute/subacute lesions are hypo-intense to iso-intense on T1-weighted (T1W) images, commonly enhanced with contrast on Gad-T1W images, are hyper-intense on T2W and FLAIR images, hyper-intense on diffusion-weighted images, and show a restricted apparent diffusion coefficient (ADC) on ADC mapIn chronic phase, smaller lesions might be seen, usually non-enhancing, but might resolve completely. There might be evidence of atrophy especially in the brainstem. Nonspecific white matter lesions can be seen
Location
<ul style="list-style-type: none">The brainstem is the typical predilection site, lesions usually involving the pons, might extend upwards to involve midbrain, basal ganglia, and the diencephalonWith cerebral presentation, multiple small, white matter lesions without a clear predisposition for peri-ventricular regions can be seen. Isolated cerebral hemisphere lesions can be seen, which need differentiation from tumour, abscess, and congenital cysts, etc.Single or multiple inflammatory lesions of variable length involving the cervical or thoracic cord can be seen, mostly in the presence of brainstem, basal ganglia, or cerebral lesions. Isolated spinal cord lesions are rare

PSYCHIATRIC DISORDERS IN BEHCET DISEASE

BD patients may have a syndrome characterized by euphoria, bipolar disorder and paranoid attitudes, loss of insight and insensitivity to the disease. This condition is known as neuro-psycho-BD [15,20-22].

The pathogenesis of neuro-psycho-BD is unknown at present. There are some important hypotheses. Some authors claim that neuro-psycho-BD is a secondary neurological involvement and it may be associated with poor quality of life. According to other authors it could be related to the frequent observation of psychiatric symptoms during relapses or in the phases preceding reactivation of the disease. Psychiatric disorders in BD are very important whether they are a psychiatric subset of the disease or a differential clinical picture. Cognitive impairment in BD may be seen with or without CNS involvement. Psychiatric disorders in neuro-psycho-BD are distributed in a wide range from anxiety disorders and mood disorders to psychotic disorders. In addition, some psychological characteristics of BS patients lead to an inappropriate stress management that may lead to stress-related disorders such as anxiety and depression [23].

ANXIETY AND MOOD DISORDERS IN BEHCET'S DISEASE

Anxiety and depression are the most common psychiatric symptoms in BD. These psychiatric disorders have an incidence of 86 % after the first manifestations of the disease [24]. It has been

shown in some studies that bipolar disorder is present in BS patients. Some BD patients may have personality structures that predispose them to development of the mood disorders. In a study comparing BD patients with psoriasis patients, depression and anxiety scores were found to be higher in BD patients [25]. In a similar study, anxiety and depressive symptoms were found to be higher in BD patients than in healthy volunteers [26]. Similar results were found in other studies [27,28].

In a case report, the authors described a 53-year-old man with neuropathy, including dysphasia and dyslalia, who developed bipolar mood disorder with anxiety, agitation, talkativeness, hyperkinesia and appetite increase. Brain MRI showed clear swelling of the brain stem area, especially in the pons, in the active phase of the disease. At the time of remission, atrophy of the brain stem was shown. The authors hypothesized that this was an early onset of neuro-BD. This case was particularly complex, because it was characterized by an acute neurological involvement, followed by chronic progressive neuro-BD [29]. It is thought that a neurobiological substrate in BS patients may contribute to bipolar disorders [30]. Some authors have hypothesized that mood and anxiety symptoms in BS patients are due to sleep disturbance, as sleep has an important role in stress-related disorders [31]. In these data light, we may come to the conclusion that anxiety and mood disorders are frequently seen in BD patients.

TREATMENT OF ANXIETY AND MOOD DISORDERS IN BEHCET'S DISEASE

Evidence for depression and anxiety treatment in BD patients is unfortunately too weak. Investigators reported that depressive symptoms may be resolved by using of the selective serotonin reuptake inhibitor (**SSRI**) antidepressant sertraline in a BD patient [32]. On the basis of this study it can be considered that the other SSRIs can be used in the treatment of these patients. It has been reported that lithium and carbamazepine were ineffective in controlling mood symptoms in BD. These authors also reported that sodium valproate, combined with low doses of carbamazepine and olanzapine were found successful in controlling these symptoms [30].

To date, there have been no guidelines for treatment of bipolar disorders in BD. Knowledge on the treatment of BD related bipolar disorder is limited to case reports. The combination of mood stabilizers such as sodium valproate, carbamazepine and olanzapine may improve the disease. There has still not enough evidence about the most appropriate treatment for BD related anxiety disorders. Further studies are needed to understand the type of psychiatric treatment required for both anxiety and depressive disorders in BD.

ACUTE PSYCHOSIS IN BEHCET'S SYNDROME

Acute psychosis in BD is rare. There have been only few case reports of acute psychosis related to neuro-BD. A 31-year-old woman with a 3-years history of BD diagnosis without parenchymal brain involvement who developed acute psychosis including hallucinations, misrecognition,

psychomotor hyperactivity and a delusion about having had a million childbirths was described in a case report [33]. In this case, acute psychosis appeared during the course of the disease without brain involvement in the patient. In this case, two hypotheses were considered: schizophrenia associated with BD, a psychiatric syndrome induced by vasculitis. In a similar case report described 18 year old woman who developed behavioural disturbances, visual and auditory hallucinations, dysarthria, right hemiparesis, excessive anxiety, loss of appetite and progressive worsening of communication with family members [34]. Psychiatric examination revealed a decrease in general hygiene, poor attention, disorganized speech and behaviour, labile affect, persecutory delusions, visual and auditory hallucinations, irritability, insomnia and lack of insight. The patient was diagnosed with a psychotic disorder due to a general medical condition, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (**DSM-IV-TR**). Hyperintensities in the brainstem, the right and left amygdala, the right hippocampal gyrus and the posterior limb of the internal capsule were detected in the MR images of the patient.

The latest case report revealed that a 17-year-old boy, who presented with acute psychosis and was subsequently diagnosed with neuro-BD [35]. In the MR images both cerebral venous thrombosis and parenchymal CNS involvement was identified. This case was interesting because of both parenchymal and non-parenchymal involvement. All of the cases described here can be considered as chronic progressive neuro-BD.

TREATMENT OF ACUTE PSYCHOSIS IN BD

Today, guidelines for the treatment of these disorders have been limited. Knowledge of acute psychosis treatment in BD is limited to case reports. Intravenous methylprednisolone and followed by oral prednisolone therapy may be used to treat neurological symptoms such as hemiparesis, dysarthria, central facial paralysis. Combination of corticosteroids, anticoagulation and immunosuppressants, also may be used for treatment of neurological symptoms [35]. These drugs are not effective on psychotic symptoms such as hallucinations, delusion, disorganized behavior and speech, aggression, poor attention, insomnia and psychomotor hyperactivity. Atypical antipsychotic drugs such as risperidone may be used in the treatment of psychiatric symptoms. In a case report patients were administered oral risperidone (2 mg/day) and BD related psychiatric symptoms were successfully resolved [34]. Because BD can involve both psychiatric and neurologic systems, follow-up of these patients in outpatient clinics after discharging from hospital will be an appropriate approach. In order to better understand the treatment of psychiatric symptoms in BD needs to be further studies in collaboration with psychiatry and neurology departments.

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