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THERAPY IN PRACTICE

Epidemiology and Management of Neuropsychiatric Disorders in Behçet's Syndrome

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Abstract Behçet's syndrome (BS) is a systemic, chronic, relapsing vasculitis, typically characterized by recurrent orogenital ulcers, ocular inflammation and skin manifestations; articular, vascular, gastroenteric and neurological involvement may also occur. Besides the other clinical features of BS, it seems relatively frequent that patients with BS develop a neurobehavioural syndrome, characterized by euphoria, bipolar disorders and paranoid attitudes, loss of insight/disinhibition, and indifference to their disease, defined as 'neuro-psycho-BS'. To date, the pathogenetic mechanism underlying neuro-psycho-BS has not been determined. It may be secondary to organic neurological involvement, or it may be related to poor quality of life and the relapsing course of the disease. Another engaging theory suggests that it could be related to the frequent observation of psychiatric symptoms during relapses or, in some cases, in the phases preceding reactivation of the disease; these elements suggest that psychiatric disorders in BS could represent a crucial element, whether a psychiatric subset or a distinct clinical feature of the disease. Moreover, it has been reported that cognitive impairment in BS can be seen with or without central nervous system involvement. Globally, psychiatric symptoms have been described as being multifaceted, ranging from anxiety disorders to depressive–bipolar disorders or to psychotic ones. In addition, some psychological characteristics of BS patients seem to predispose them to maladaptive stress management, which may lead to stress-related disorders, including anxiety and depression. Therefore, the aims of this review are to explore the epidemiology of neuro-psycho-BS by evaluating the relationship between the stress system and the multifaceted psychiatric manifestations in BS, and to summarize the therapeutic strategy used.

Key Points

Besides the other clinical features of Behçet's syndrome (BS), it seems relatively frequent that patients with BS develop a neurobehavioural syndrome, characterized by euphoria, bipolar disorders and paranoid attitudes, loss of insight/disinhibition, and indifference to their disease, defined as 'neuro-psycho-BS'.

Anxiety and depression are common psychiatric disorders in BS patients, in some cases representing a clinical feature that precedes the onset of the typical symptoms of BS.

Few data are available on the therapeutic management of neuro-psycho-BS; nevertheless, literature data suggest that these symptoms are usually resistant to conventional psychiatric therapy.

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1 Introduction

Behçet's syndrome (BS) is a systemic, chronic, relapsing vasculitis, typically characterized by recurrent orogenital

ulcers, ocular inflammation and skin manifestations; articular, vascular, gastroenteric and neurological involvement may also occur [1, 2]. The onset of the disease typically occurs in patients in the late third and early fourth decades of life. Although BS has a worldwide distribution, it is most commonly seen in the Middle East, the Far East and the Mediterranean basin—a geographical distribution that is along the ancient Silk Road [3, 4]. Moreover, the prevalence of BS in the endemic areas is strongly correlated with the prevalence of human leukocyte antigen (HLA)-B51 [5]. It is believed that a complex background, with both genetic and environmental factors, contributes to development of the disease. Since there are no established laboratory findings to define BS, the diagnosis remains mainly dependent on identification of the typical clinical picture. In 1990, the International Study Group (ISG) for BS proposed validated classification criteria; to fulfil these criteria, a conditio sine qua non for the diagnosis was the presence of recurrent oral ulcers, together with two or more of the following symptoms: recurrent genital ulcerations, eye lesions, skin lesions or a positive pathergy test [6]. More recently, another set of criteria, with more sensitivity, was created in order to also include major organ involvement [7]. Globally, BS is characterized by a variable spectrum of disease profile: while prevalent mucocutaneous lesions and arthritis represent the only clinical features in a benign disease subset of patients, there are other patients who potentially develop eyesight- or life-threatening manifestations, due to ocular, neurological or major vascular involvement [8].

Besides organ involvement, a number of demographic factors can considerably influence the short- and long-term outcomes of BS: the age at disease onset, duration of disease and sex [9]. Younger male patients are more likely to have more severe disease, due to an increased frequency of both morbidity and mortality, related to ocular, vascular and neurological involvement.

Although neurological involvement is not included in the ISG criteria for BS, it represents the second main cause of mortality, preceded by large-vessel disease [8]. There have been many studies describing the prevalence of neuro-BS in different countries, which varies from 2 to 50 % [10–15]. Despite immunosuppressant therapy, neurological involvement is still considered a worrying complication of the disease, representing an important cause of morbidity and mortality. Although neuro-BS may present with different neurological problems directly or indirectly related to the systemic disease, it is usually categorized into two main groups: parenchymal brain involvement (more frequent, in 80 % of cases) and non-parenchymal or vascular disease. Parenchymal central nervous system (CNS) involvement, mainly affecting the brainstem, occurs with pyramidal signs, cerebellar symptoms, sphincter disturbance and behavioural changes. Vascular disease is generally due to intracranial hypertension secondary to dural sinus thrombosis. Headache undoubtedly represents the most common neurological symptom observed in patients with neuro-BS and can be associated with different aetiologies—namely, parenchymal involvement, cerebral venous sinus thrombosis, ocular inflammation or coexisting primary headache. Parenchymal CNS involvement may present as acute disease or may have a chronic progressive form. The acute form is mainly characterized by acute meningoencephalitis with or without focal lesions; this kind of neurological involvement seems to have a good response to corticosteroids. On the other hand, the chronic progressive form is characterized by a poor response to conventional treatment with corticosteroids, cyclophosphamide or azathioprine, while it seems to be responsive to methotrexate; this form consists mainly of slowly progressive neurobehavioural changes, such as ataxia and dysarthria, which lead to severe disability. Notably, persistent elevation of cerebrospinal fluid interleukin (IL)-6 levels and brainstem atrophy on magnetic resonance imaging (MRI) scans need to be checked for the differential diagnosis of chronic neuro-BS [15, 16]. Parenchymal CNS involvement represents serious morbidity of the disease, often leading to disability and to mortality, if it is not treated early. On the other hand, dural sinus thrombosis is associated with a more favourable outcome than parenchymal involvement. Notably, the onset of CNS involvement seems to occur within the first 10 years, with a higher incidence in the first 5 years [11]. These data have important clinical implications, since the concept that the onset of neuro-BS does not necessary appear in the first stages of BS could strongly influence the frequency of evaluations during follow-up. Indeed, neuro-BS is still related to high rates of morbidity and mortality; early recognition of severe organ involvement could certainly represent an important element in preventing irreversible damage due to the chronic, relapsing course of the disease.

Besides the other clinical features, it seems relatively frequent that patients with BS develop a neurobehavioural syndrome, characterized by euphoria, bipolar disorders and paranoid attitudes, loss of insight/disinhibition, and indifference to their disease, defined as ‘neuro-psycho-BS’ [12, 16–18]. To date, the pathogenetic mechanism underlying neuro-psycho-BS has not been determined. It may be secondary to organic neurological involvement, or it may be related to poor quality of life and the relapsing course of the disease. Another engaging theory suggests that it could be related to the frequent observation of psychiatric symptoms during relapses or, in some cases, in the phases preceding reactivation of the disease; these elements suggest that psychiatric disorders in BS could represent a crucial element, whether a psychiatric subset

or a distinct clinical feature of the disease. Moreover, it has been reported that cognitive impairment in BS can be seen with or without CNS involvement [19]. Globally, psychiatric symptoms have been described as multifaceted, ranging from anxiety disorders to depressive–bipolar disorders or to psychotic ones. In addition, some psychological characteristics of BS patients seem to predispose them to maladaptive stress management, which may lead to stress-related disorders, including anxiety and depression.

Therefore, the aims of this review are to explore the epidemiology of neuro-psycho-BS by evaluating the relationship between the stress system and the multifaceted psychiatric manifestations in BS, and to summarize the therapeutic strategy used.

2 Epidemiology

2.1 Behçet's Syndrome and Stress Reactivity

There is considerable individual variability in the response to stress, which seems to be largely related to the subject's coping mechanisms. The perception and evaluation of a stressor and the specific response to it may have interrelations in different ways, such as sympathetic nervous system activation and induction of the hypothalamic–pituitary–adrenal (HPA) axis, which directly affect the immune system [20–22]. Prolonged exposure to stressors or to severe life events may outweigh the person's coping resources, leading to both medical and psychiatric stress-related diseases. In the stress–disease relationship, the individual's personality characteristics, coping strategies and coping capacities have as great a role as the severity and duration of stress. The total result of the positive and negative variables determines how stress affects the individual and the course of the disease. Moreover, it has been demonstrated that subjects coping with stress show a fast and brief catecholamine response, while others with high defences express signs of more prolonged activation. On the other hand, non-coping individuals show sustained general activation, which may develop into somatic disease or illness [23, 24].

The knowledge of the psychological side of BS is very limited. However, the stress–immune system interaction theory is surely also valid for BS, which is a chronic, recurrent immune–inflammatory disease, with exacerbation and remission periods. Therefore, in the next section, we review evidence regarding the relationship between development of BS and stressful stimuli. Then, we review evidence regarding the stress system, psychological characteristics and stress coping styles of BS patients.

2.2 Stressful Life Events and Behçet's Syndrome Development and Activity

It seems that stressful life events have important implications for both precipitation and relapse of BS. The effect of stress in the relapse and remission cycle of BS has been demonstrated in preliminary studies. Psychosocial stress factors have been described predominantly as occurring prior to the onset of the disease [25, 26]. A study by Karlidag et al. [27] showed that approximately 70 % of BS patients reported a stress factor before the occurrence of the disease; the results of the study also showed that 80 % of patients with BS declared stress in the relapse period. A large proportion of their problems were related to their primary social support group (41.2 %) and their social environment (17.7 %). Beforehand, Epstein et al. [28] studied ten patients with BS, showing that major exacerbations of the somatic illness were associated in each case with situations of stress, especially family conflicts.

2.3 Behçet's Syndrome, Personality Characteristics and Stress Reactivity

Few studies have investigated the personality characteristics of subjects with BS. Koptagel-Ilal et al. [25] investigated 55 BS patients through a psychoanalytically oriented interview and application of the Rorschach test. The personality structures, according to the Rorschach test findings, revealed a weak ego, regressive tendencies, disturbed body image, high anxiety, and difficulties in social adaptation and evaluation of realities, as well as incapacity for adequate expression and handling of affects and emotions. The authors hypothesized that considering the effects of immune mechanisms on the aetiology of this disease, together with the relationships of autonomic system functions to immune reactions and also to psychological stress situations, psychosocial stress and weak personality structures can be assumed to be one of the possible effective factors in the aetiopathogenesis of this disease, at least as a precipitating agent.

Atay et al. [29] conducted a study of 46 BS patients, using Cloninger's psychobiological model of personality [30, 31], which has mostly been used to investigate patients with chronic disorders [32]. According to Cloninger's psychobiological model, personality is a complex system consisting of different psychobiological dimensions of temperament and character. Cloninger et al. [30] identified four temperament dimensions ('novelty-seeking', 'harm avoidance', 'reward dependence' and 'persistence') and three character dimensions ('self-directedness', 'cooperativeness' and 'self-transcendence'). The results of this study demonstrated that BS patients had lower 'exploratory excitability' scores (as a subdimension of novelty-seeking)

than healthy control subjects. In terms of the personality traits in Cloninger's model, patients with BS showed less excitable reactions to pleasant stimuli and had a diminished positive affect and diminished exploratory behaviour. According to this model, such subjects are resistant or slow to engage in new ideas and activities, and they tend to stick with familiar routines. Nevertheless, the scores for the 'shyness with strangers' subdimension of harm avoidance were lower in BS patients. The authors also found lower scores for reward dependence in BS patients than in healthy control subjects. Reward dependence describes maintenance of behaviour in response to cues of social reward. Low scores for reward dependence show that BS patients may have difficulties in social attachment, which may result in relationship problems and susceptibility to psychiatric disorders, such as depression or adjustment problems. Low scorers on the 'attachment' subscale manifest more or less pronounced detachment and disinterest in social relationships. The findings of this study showed that BS patients were low in reward dependence, indicating cold and detached personality traits. Moreover, in the character dimensions, 'self-acceptance' scores were higher in BS patients and 'spiritual acceptance' scores were lower in BS patients than in control subjects. These lower scores represent materialistic personalities. As it has been shown that personality traits play an important role in stress management, depression and anxiety development [30], the authors then hypothesized that these personality traits may make BS subjects more vulnerable to the effect of stress and thus, in turn, more vulnerable to stress-related disorders.

On the basis of the literature data, we can conclude that some personality structures of BS subjects can be assumed to predispose them to development of the disease. In particular, some characteristics may play an important role in stress management, with adoption of stress coping styles that may cause precipitation and relapse of the disease in response to stressful events.

2.4 Behçet's Syndrome and Stress Coping Strategies

Coping strategies more frequently adopted by BS patients have been found to include an active-reliance strategy (41.2 %), avoidance–solitary strategy (26.3 %), distraction strategy (17.7 %) and active-expressive strategy (14.8 %) while they are coping with the disease [27]. In addition, subjects with BS showed a significantly higher score on the Toronto Alexithymia Scale than control subjects. Alexithymia, which is described as a disorder of emotional perception and expression and of the ability to accurately identify and express feelings, can arise as a coping strategy to protect an individual from life-threatening events, severe physical illnesses, traumas, anxiety and depression [33–35]. Indeed, it may result in a maladaptive strategy. Stressful life events can be a stimulatory factor in precipitating and promoting BS disease by impairing homeostasis through activation of the stress system. Thus, the subject may need to adapt through the use of maladaptive coping mechanisms.

2.5 Behçet's Syndrome and the Stress System

BS patients show an alteration of the stress system. Aksoyek et al. [36] reported that BS patients had increased sympathetic and decreased parasympathetic modulation, and they suggested that BS patients may have asymptomatic autonomic nervous system dysfunction. Moreover, Tellioglu and Robertson [37] described autonomic dysfunction accompanied by abnormal catecholamine levels in a BS patient, and they suggested that immunological damage to the components of neural pathways may contribute to the pathogenesis of the autonomic involvement. Sympathetic and parasympathetic autonomic dysfunction in patients with BS have been more recently confirmed [38, 39], which may be related to disease activity. In addition, BS patients show an insufficient antioxidant defence system, suggesting the potential implication of increased oxidative stress [40, 41].

3 Behçet's Syndrome, Anxiety and Mood Disorders

Anxiety and depression are the most commonly encountered psychiatric symptoms in BS. These psychiatric features have an incidence of 86 % after the first manifestations of the disease [28]. Indeed, bipolar disorders have also been described in BS patients. Calikoglu et al. [42] compared the depression and anxiety scores of 23 BS patients with those of psoriasis patients and found that the scores were higher in BS patients. They also suggested that the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were effective tools in detecting depression and anxiety in BS patients. Similar observations were made by Karlidag et al. [27], who studied 25 BS subjects, using the BAI and the Hamilton Depression Rating Scale (HAM-D), and found that levels of anxiety and depressive symptoms were higher in BS than in healthy control subjects.

Other authors have observed similar results and in all cases have reported higher levels of anxiety and depressive symptoms in BS patients than in healthy control subjects [19, 43]. Uğuz et al. [44] studied 25 BS patients, using the BDI, and reported that the scores for major depression were higher in the BS patients than in control subjects, with a negative impact on the BS patients' quality of life. Notably, Lee et al. [45] studied 26 BS subjects, using the State–Trait

Anxiety Inventory (STAI) and the BDI. They found that levels of anxiety and depressive symptoms were higher in BS subjects with fibromyalgia than in those without this comorbidity. Moreover, there are numerous data from observational studies regarding evaluation of depression by means of the BDI and evaluation of anxiety by means of the BAI, which have confirmed a higher prevalence of these disorders in BS patients than in patients with other autoimmune disorders, such as rheumatoid arthritis and psoriasis [46, 47].

In a case report by Nakano et al. [48], the authors described a 53-year-old man with neuropathy, including dysphasia and dyslalia, who developed bipolar mood disorder with anxiety, agitation, depressive mood, talkativeness, hyperkinesia and appetite increase. Brain MRI showed clear swelling of the brain stem area, especially in the pons, in the active phase. At the time of remission, atrophy of the brain stem was shown. The authors hypothesized that this was an early onset of neuro-BS. This case was particularly complex, since it was characterized by an acute neurological involvement, followed by chronic progressive neuro-BS.

In 2004, Alevizos et al. [49] reported the case of a 62-year-old woman suffering from BS since the age of 38 years, who developed treatment-resistant bipolar disorder 6 years after the first manifestations of the syndrome; this case was characterized by a chronic progressive course. The authors concluded that a neurobiological substrate may exist in BS, which could contribute to or generate bipolar disorders.

In light of these data, we can conclude that anxiety and depression are commonly reported in BS patients. As they are important stress-related disorders, some authors have hypothesized that BS patients may develop these disorders through sleep impairment [50]. We can hypothesize that this kind of psychiatric disease develops in the early stage of BS when the disease is still related to stress response.

4 Behçet's Syndrome and Acute Psychosis

There have been several case reports of acute psychosis in BS patients. It has been related to neuro-BS. Nkam and Cottereau [51] described the case of a 31-year-old Haitian woman with a 3-year history of mismanaged BS without parenchymal cerebral involvement, who developed acute psychosis, including hallucinations, misrecognition, psychomotor hyperactivity and a delusion about having had a million childbirths. Similarly, Deniz et al. [52] reported the case of an 18-year-old woman, who developed dysarthria, right hemiparesis, behavioural disturbances, visual and auditory hallucinations, excessive anxiety, weakness, loss of appetite and progressive worsening of communication with family members for 3–4 days before coming to the emergency service centre. A 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 attack, according to the International Classification of Diseases, 10th Revision (ICD-10), or 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). In this case, magnetic resonance flair images showed hyperintensities in the brainstem, the right and left amygdala, the right hippocampal gyrus and the posterior limb of the internal capsule.

Patel et al. [53] described the case of a 17-year-old boy, who presented with acute psychosis and was subsequently diagnosed with neuro-BS. A rare combination of both cerebral venous thrombosis and parenchymal CNS involvement was identified by neuroimaging. All of the cases described here could be characterized by chronic progressive neuro-BS.

In light of these data, we can conclude that psychotic symptoms may be related to a neurological substrate in BS: we can, in fact, hypothesize that this kind of psychiatric disorder develops in the middle and late stages of the disease.

5 Management

5.1 Anxiety and Mood Disorders

Evidence is very scarce regarding therapy for the management of depression and anxiety in BS patients. In a reported case of a 65-year-old BS patient with behavioural disturbances, such as depression and apathy related to cognitive impairment, use of the selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline was shown to be successful in improving psychiatric symptoms [54].

In the case described by Nakano et al. [48], a large lesion in the pons was found. This case was successfully treated with corticosteroids, and total clinical improvement was observed, with a reduction of the lesion size within 9 months. Moreover, in the case described by Alevizos et al. [49], lithium and carbamazepine were ineffective in controlling the affective symptoms, while sodium valproate, combined with low doses of carbamazepine and olanzapine, resulted in sufficient stabilization of the patient's mood state.

Bipolar disorders have been described in rare cases. In 2002, Aydin et al. [55] reported a case of neuro-BS in which the initial onset was hypomania. To date, there have

been no guidelines for treatment of these disorders in BS, probably because bipolar disorders have been studied less frequently than other types of disorder in BS patients. Indeed, these symptoms may be related to a neurological substrate of the syndrome, and we can hypothesize that they develop in the middle stage of the disease. Guidelines are needed to better define the most effective mood-stabilizing medication. A combination of mood-stabilizing drugs, such as sodium valproate, carbamazepine and olanzapine, may produce some improvement in the disease. Finally, we still do not have evidence regarding the most appropriate treatment for anxiety disorders in BS patients. Further studies are urgently needed to understand the type of psychiatric treatment required for both anxiety and depressive disorders in BS patients. In addition, we need to establish, in longitudinal studies, the effects of psychiatric treatments on BS progression.

5.2 Acute Psychosis

The patient described by Nkam and Cottereau [51] developed acute psychotic symptoms and negative symptoms during BS without parenchymal cerebral involvement. Two hypotheses were considered: schizophrenia associated with BS, versus a psychiatric syndrome induced by vasculitis. In the case by Deniz et al. [52], intravenous methylprednisolone treatment was given for 5 days, followed by oral prednisolone. By the end of the pulse steroid treatment, the neurological symptoms (such as dysarthria, right hemiparesis and right central facial paralysis) were ameliorated; however, the psychiatric symptoms persisted. Risperidone (2 mg/day) was added to the treatment. After 3 weeks of treatment, there were significant improvements in self-care, disorganized behaviour and speech, poor attention, hallucinations and insomnia, but complete remission of the psychiatric symptoms was not achieved. The patient was discharged after a 5-week period of hospitalization, with some improvement in psychotic symptoms, and had complete improvement in neurological symptoms. At discharge, the positive symptoms (e.g. hostility), negative symptoms and depressive symptoms were still present, and the patient was scheduled for a follow-up appointment by the psychiatry and neurology outpatient clinic.

In the case described by Patel et al. [53], the patient showed clinical and radiographic improvement with a combination of corticosteroids, anticoagulation and immunosuppressants, including a tumour necrosis factor (TNF)-α-blocking agent.

Indeed, to date, guidelines for the treatment of these disorders have been limited, and we can hypothesize that in addition to corticosteroids, anticoagulation and immunosuppressants, it may be useful to administer a neuroleptic treatment. To date, risperidone or haloperidol have been used, but these drugs seem to increase negative symptoms. Further studies in collaboration with psychiatric units are needed to better understand the use of neuroleptic treatment in this syndrome.

5.3 Influence of Drugs Used to Treat Behçet's Syndrome on Psychiatric Disorders

An important and unresolved issue is how and how much corticosteroid therapy may influence the onset of psychiatric disorders in autoimmune diseases, and since corticosteroids represent important drugs in the treatment of BS, this should be considered in the evaluation of psychiatric disorders. The literature is focused on the somatic side effects of corticosteroids. Poor data are available on neuropsychiatric effects (e.g. depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia and psychosis), probably because of their complexity and the difficulty in studying them [54, 56]. Furthermore, the potential relationship between the incidence of psychiatric manifestations and therapy with corticosteroids has also been considered in systemic lupus erythematosus [57].

The onset of corticosteroid-induced neuropsychiatric symptoms is variable. In some cases, psychiatric disorders have been reported within a few hours of treatment initiation, whereas in other cases, onset of psychiatric symptoms has been reported even when corticosteroids were stopped [53].

So far, we do not know if specific predictors of neuropsychiatric side effects due to corticosteroids exist; considering the complexity of the disease and the high incidence of psychiatric disorders in BS, with or without neurological involvement, a straight evaluation of the potential role of corticosteroids in the worsening of psychiatric symptoms should be mandatory.

Another relevant consideration is the influence that cyclosporine A (CyA) can have on neurological involvement in BS because of its neurotoxicity. Data from case–control studies have supported a higher incidence of CNS involvement in BS patients who have used CyA for eye disease [58]. So far, it is not clear whether this frequency is a result of CyA neurotoxicity or the course of the disease. However, when there is a new onset of neuropsychiatric findings in a patient receiving CyA, the influence of CyA should be considered carefully.

6 Conclusions

The literature data, with results from observational studies and anecdotal reports, suggest that some BS patients may have personality structures that predispose them to

development of the disease. So far, we do not know what the potential biological substrate of this mechanism is, but it seems that some of these characteristics may play an important role in stress management. Moreover, anxiety and depression have been found to be common psychiatric disorders in BS patients, in some cases representing a clinical feature preceding the onset of typical symptoms of BS. Finally, bipolar symptoms and acute psychosis also represent a feature reported in BS but may present at a late stage of the disease. To our knowledge, few data are available on the therapeutic management of neuro-psycho-BS, but, in some reported cases, these symptoms have been resistant to conventional psychiatric therapy. Psychiatric disorder treatment guidelines are needed within a multidisciplinary approach to the disease.

Bearing all of these concepts in mind, neuro-psycho-BS seems to represent an intrinsic aspect of BS and, for this reason, it is deserving of further studies to better define whether psychiatric symptoms may be considered a clinical feature of BS.

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