



## Review Article

# Psychological and neurocognitive impact of Behcet's disease

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## Abstract

**Background:** Behcet's disease is a vasculitis, causing multisystem inflammation and resulting in oral and genital ulcers and eye and skin lesions. A proportion of sufferers also have neurological involvement, termed neuro-Behcet's disease. The purpose of this review was to investigate the psychological and neurocognitive sequelae associated with Behcet's and neuro-Behcet's disease and provide directions for future research.

**Results:** Depression and anxiety are the most researched psychological conditions in Behcet's disease and appear to be the most consistently observed disorders across studies. Depression and anxiety severity is significantly higher relative to controls, and rates are similar across Behcet's and neuro-Behcet's cohorts. A systematic review would be helpful to fully determine the magnitude of these psychological disorders in Behcet's disease and elucidate correlated clinical, regional and demographic factors. Further research is also needed into somatic and psychotic conditions as existing studies have yielded inconsistent results.

Attenuations in neurocognitive functioning appear to be on a continuum. Reduced cognitive functioning is observed in Behcet's disease relative to healthy controls; however, it is observed more frequently in neuro-Behcet's disease, and in a broader range of neurocognitive domains (visual-spatial abilities, working memory, acquired knowledge, processing speed, long-term memory encoding and retrieval). Methodological limitations in existing studies, thus far, have not allowed for further synthesis of the data, such as through meta-analysis, and the field would benefit from several large-sample, multi-site studies using broad cognitive assessment batteries.

**Conclusions:** Assessments of psychological functioning should be included as part of routine practice in clinics treating patients for Behcet's disease. The potential for neurocognitive impairment should also be considered, particularly in those with neuro-Behcet's. Appropriate referral pathways for psychiatric, psychological or neuropsychological intervention and treatment can then be offered, so that the psychological and neurocognitive needs in this patient cohort can be appropriately met.

## Introduction

Behcet's disease is a vasculitis characterised by multisystem inflammation and is chronic in many sufferers. Psychological difficulties and neurocognitive dysfunction have been documented in this patient group for over fifty years [1,2]. Initial information reported in this area was predominantly in the form of case studies and case series papers. However, over the last twenty years a number of group research studies, with small to medium sample sizes, have been conducted providing valuable information about both psychological and neurocognitive sequelae. This review provides an overview of the features and epidemiology of Behcet's disease, and then details what is known about psychological and neurocognitive functioning in this patient group.

The defining features of Behcet's disease, based on the current diagnostic criteria, are oral and genital ulcers, eye and skin lesions, and abnormalities in the vascular and nervous system, although there is no single definitive test for the disease [3,4]. The cause remains unclear. Behcet's may have a genetic component, with environmental or biological triggers the catalyst for the expression of sequelae [5-7]. A number of treatments are available, and currently in use, including corticosteroids, anti-inflammatory agents, calcineurin inhibitors, tumour necrosis factor-blocking agents and mercaptopurine derivatives [8,9]. However, these are often non-curative and many people with Behcet's experience recurrent episodes of the disorder over time. Behcet's has a variable regional prevalence with the epicentre for the disease occurring in Turkey, where prevalence rates are around 400 per 100,000 [10]. Other areas of high prevalence are countries



traditionally associated with the silk road trade route, including Iran, Iraq, Israel, China and Japan, as well as Saudi Arabia [10].

There is also variable regional prevalence in the extent of neurological manifestations observed in the disease. Higher rates of central nervous system abnormalities (between 17 and 44%) have been reported in studies with cohorts from Saudi Arabia, Jordan, Morocco, Italy and Portugal [11–15]. In contrast lower rates (2.3 to 4.6%) have been reported in studies from Iran, Turkey and Korea [16–18]. The subsyndrome of neuro-Behcet's is diagnosed in patients who have neurological manifestations related to their Behcet's disease [19]. This can include parenchymal features such as multifocal and brain stem lesions, cerebral abnormalities, myelopathy and optic neuropathy, as well as non-parenchymal features, such as cerebral venous thrombosis, intracranial hypertension, and meningeal syndrome. Headache is also very common in Behcet's [20,21].

Behcet's disease can compromise the quality of life in sufferers, particularly those with neuro-Behcet's. Features that contribute to increased levels of disability include gait difficulties such as ataxia, postural rigidity, urinary incontinence, sphincter dysfunction, reduced hand eye coordination, dysmetria, diplopia, hemiplegia, dysarthria and headaches [22–25]. Longitudinal data has indicated that 46 percent of individuals with neuro-Behcet's had at least a moderate level of disability as assessed by the modified Rankin Scale, with this proportion requiring some level of help with their daily activities [26].

The purpose of this article is to review what is known about psychological and neurocognitive functioning in Behcet's disease and provide directions for future research in these areas. Research in other chronic conditions, including diabetes, coronary heart disease, stroke and chronic obstructive pulmonary disease has indicated high rates of depression and anxiety in these groups and that this can impact on treatment and care [27–29]. Additionally, other disorders that also involve neurological lesions and physical disability, such as multiple sclerosis, have been associated with high rates of depression and anxiety, and neurocognitive dysfunction [30–33]. The course and nature of Behcet's, and type of disability that can result from the illness, is similar to many of the conditions listed above. Thus, there are many factors that could potentially contribute to poor mental health and neurocognitive impairment in this group. The literature on psychological functioning in Behcet's is reviewed, including the results of broad range assessment studies, followed by a focus on the two most commonly identified mental health conditions. The literature on neurocognitive functioning is discussed for both Behcet's and neuro-Behcet's cohorts and considered in relation to both group studies and the case study/series literature.

## Psychological functioning

Psychological and mental health functioning is an important consideration in all patient groups as it impacts on treatment adherence, treatment response and quality of life [25,34,35].

There is a moderate, and growing, body of literature into psychological functioning in Behcet's disease. Several Behcet's group characterisation studies have been conducted that have utilised broad range psychological assessment measures, designed to assess for symptoms and disorders across a range of psychological conditions. A number of studies have also utilised focused assessment tools to ascertain the presence and severity of specific psychological conditions in Behcet's cohorts relative to healthy controls or other patient groups. There are also a number of published case studies, detailing noteworthy psychological presentations.

## Broad range assessment

In 2007 a study was published by Dursun and colleagues that utilised structured clinical interviews to assess for a broad range of mental health conditions in 73 consecutive outpatients at a Turkish Behcet's dermatology clinic [36]. In this study the Structured Clinical Interview for DSM-IV (SCID-I/CV) was utilised. This measure is comprised of a series of requisite questions pertaining to general psychological issues, with more specific questions administered, pending the interviewee's response to the general questions (i.e. a tiered diagnostic interview approach). As the measure is based on the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV), diagnoses can be provided following assessment. The results from the SCID-I/CV interviews indicated that over 40 percent of patients met the criteria for at least one current mental health disorder [36]. The most prevalent condition was major depression, occurring in 18 percent of the sample, followed by anxiety disorders including specific phobia (16%), generalised anxiety disorder (15%) and social phobia (10%). Other mood and anxiety based disorders were also reported in the sample, including dysthymic disorder (7%), obsessive-compulsive disorder (7%), agoraphobia (4%), panic disorder (1%) and body dysmorphic disorder (1%).

The prevalence rates of depression and anxiety disorders vary from country to country, however, these disorders have the highest lifetime prevalence of all mental health conditions in the general population, globally [37,38]. In this respect, it is not overly surprising that they were the most frequently observed mental health conditions in Behcet's disease. Notably, however, the observed point prevalence rate of depression in Turkish Behcet's patients in the Dursun, et al., study was more than double the standard population average point prevalence for that country (18% vs 4.4–8%) [38,39]. With the rates of reported anxiety disorders also up to four times higher [38,40]. It is reported that none of the patients in the broad range psychological assessment study met criteria for bipolar disorder, schizophrenia and posttraumatic stress disorder, eating disorders, hypochondriasis and somatization disorder. This study explicitly ruled out participants with central nervous system involvement, and thus it is not clear if a similar pattern of results would be present in a neuro-Behcet's sample.

A broad range psychological symptoms assessment measure was also administered to 101 Behcet's patients in a study by Bagheri and colleagues in Iran [41]. This research employed the Symptom Checklist –90–Revised (SCL-90-R). The SCL-



90R is a self-report symptoms inventory that is designed to detect psychological symptoms, but unlike the SCID-I/CV, does not provide a psychiatric diagnosis. Very high rates of psychological symptoms were reported by participants in this study, with responses categorised into *Healthy*, *Borderline*, *Sick* and *Extremely Sick* severity categories, based on Iranian SCL-90R cut-off points. Symptoms of somatization were the most common, with 91.7% scoring outside of the *Healthy* range, and 63.1% considered *Sick* or *Extremely Sick*. The prevalence of anxiety (78% scoring above *Healthy*, 47.6% *Sick* or *Extremely Sick*) and depressive symptoms (77.6% above *Healthy*; 47.4% *Sick* or *Extremely Sick*) were also high, followed by psychosis (69.1% and 51.9%), obsessive compulsive disorder symptoms (69% and 40.5%), paranoid thoughts (34.6% and 10.3%) and phobia (34.1% and 8.5%).

The Bagheri, et al., results differ in a number of ways from the Dursun, et al., study. The results in the area of somatization are particularly disparate, along with the results for psychotic symptoms and paranoia, and disorders with psychotic features (i.e. bipolar disorder or schizophrenia and related disorders). The utilisation of different assessment measures used may explain some of the variance. The SCID-I/CV provides discrete categorical diagnostic classifications, while the SCL-90R provides an indication of the presence psychological symptoms ranging from mild through to severe (i.e. a continuum approach). However, even given this, the discrepancies are marked. The authors of the more recent Bagheri, et al., study do not provide an interpretation of why the results across these two studies have pronounced differences. It is stated that none of the participants in the Bagheri study had a history of mental retardation, brain damage or psychosis. However, it is not clear that central nervous system involvement (i.e. neuro-Behcet's) was ruled out. Thus, it is possible that a higher degree of neurological lesions were present in this patient group. Cultural factors, gender balance differences in the samples, disease severity and the availability of mental health treatment options within the study areas may also have contributed to the differences in the results.

## Depression

The broad range psychological assessment studies indicate that rates of depression and depressive symptoms are elevated in Behcet's, and depression appears to have been the most frequently researched psychological condition in the Behcet's literature using focussed assessment measures [42-52]. Relative to non-Behcet's controls, rates of depression are consistently found to be significantly higher in Behcet's sufferers at levels of clinical importance [42,45,46,50]. The Beck Depression Inventory, Hospital Anxiety and Depression Scale and Hamilton Scale for Depression have frequently been used to assess symptoms of depression. The mean cohort scores for depression vary from study to study, in regard to severity levels, with scores falling between the *Mild* and *Moderate to Severe* ranges [42,45,46]. Depression scores have also been correlated with disease activity, duration of illness, fatigue levels and comorbid symptoms that impact on functioning, including erectile dysfunction in male patients [47,49,51].

When the groups have been separated, rates of depression are generally similar in Behcet's and neuro-Behcet's groups [43,46]. Rates of depression were as high as 60% in one neuro-Behcet's study and depression was also associated with cognitive impairment [48].

## Anxiety

Anxiety has also been relatively well studied in Behcet's patient groups using focussed assessment measures, in keeping with the findings of high levels of anxiety in the broad range assessment studies. It is also highly correlated with depression, and thus, it is perhaps not surprising that elevated levels of anxiety are also commonly found in Behcet's disease [42-46,51-53]. The Hamilton Anxiety Scale, State-Trait Anxiety Inventory, Beck Anxiety Inventory and the Hospital Anxiety and Depression Scale have all been used to assess for anxiety symptoms. Rates of anxiety in Behcet's sufferers are consistently significantly higher than those in healthy controls, scoring at rates of clinical importance [42,46,51]. In studies containing both Behcet's and neuro-Behcet's patients, rates of anxiety are also largely similar across these two patient groups [43,45]. Similar to depression, rates of anxiety are associated with disease factors, such as fatigue and comorbid arthritis [51,53].

## Other disorders

Other psychological and psychiatric disorders have been reported in the literature in patients with Behcet's disease, including bipolar disorder, acute psychosis, behavioural disinhibition and kleptomania, mainly through single case studies [54-57]. At this stage, it is unclear whether these presentations are reflective of the normal 1 to 2 percent prevalence of these disorders within the general population, or that Behcet's disease increases the likelihood of the expression of these disorders, potentially in those with critical levels of neurological disease.

## Future directions

Depression and anxiety appear to be the two most consistently found psychological disorders in Behcet's disease. The literature would benefit from a systematic review, using PRISMA guidelines, to fully summarise and synthesise the existing research in both of these areas. Meta-analysis would provide information about the magnitude of depression and anxiety in Behcet's disease, relative to non-Behcet's controls. It may also help to elucidate contributory mechanisms for the psychological difficulties, such as chronic disease burden, pain, fatigue, or functional restrictions. Given the very high prevalence of these conditions in patients with Behcet's disease, it could be postulated that depression and anxiety are common secondary sequelae of the condition.

The results of broad range screening studies in Behcet's have yielded highly inconsistent results in regard to somatising disorders/symptoms [36,41]. Depression and anxiety are often found to co-occur in somatisation disorder (Lieb, 2007). It has been postulated that there may be a causal relationship between these conditions or that there are mutual etiological factors



that underlie the disorders (Lieb, 2007). There have been recent classification changes to this category of disorders, in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) [58]. Somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder have been removed and replaced with Somatic Symptom Disorder, the primary features of which are somatic symptoms that are very distressing or result in significant disruption of functioning, and excessive and disproportionate thoughts, feelings and behaviors related to those symptoms [58]. As such, further research would be useful in this area in Behcet's disease using the new diagnostic framework, and examining the relationship of somatic symptoms to depression and anxiety in this patient group.

A third area that would benefit from clarification through future research is psychotic features. This includes symptoms such as paranoid thoughts, hallucinations and delusions, and categorically classified disorders, including schizophrenia. Psychotic features have been documented in a number of published Behcet's case studies, but findings have been inconsistent in the broad assessment literature in regard to both the prevalence and severity of psychotic symptoms and disorders [36,41,54]. A large sample study examining both psychotic symptoms and diagnosable disorders would be useful, with screening for neurological involvement an important co-variable to investigate in this area.

### Neurocognitive functioning

Neurocognitive abilities are localised within the brain and can be impacted by acquired neurological damage. Skills that fall under this category include attention, mental manipulation/working memory, information processing, language, memory, visual-spatial and perceptual processing, reasoning, planning, organisation and impulse control. Both disorders that compromise neurological integrity and psychological disorders have been shown to impact on neurocognitive functioning, and can contribute to disease burden and reduced quality of life.

Cognitive deficits in Behcet's disease were first documented in the literature by Wada in 1969, via a published a case series of nine patients, one of which was described a 'disoriented' and had undergone intellectual assessment with an IQ of 68, indicating extremely low cognitive functioning [2]. Since this paper, research into this area has grown over the last 20 years, in particular [2,59]. A recent systematic review indicated that 17 case study or case series papers have been published, containing neurocognitive assessment data, as well as 12 group comparison studies, investigating the neurocognitive skills of Behcet's and neuro-Behcet's patients, relative to comparison groups [59]. However, the authors of this review noted that methodological limitations impacted on the quality of studies within the field. The major limitations were issues with study design (inadequate information about blinding) and reporting (incomplete and selective data reporting) across the field, problems with statistical analysis in the group studies (failure to adjust for multiple comparison), and failure to utilise appropriate normative data or adjust for premorbid ability levels in the case study/series papers.

### Group studies

**Behcet's disease:** Nine studies have investigated neurocognitive functioning in patients with Behcet's disease, compared to healthy control groups [42,43,45,50,60-64]. The collated results of these studies (totalling 258 individuals with Behcet's and 229 healthy controls) across all cognitive domains indicates significant differences in functioning in 18 percent of comparisons between patients with Behcet's disease and controls [59]. However, there are selected cognitive domains that show higher rates of attenuation than others. These are the domains of visual-spatial abilities (40 percent of results significantly poorer in Behcet's; 10 results) acquired knowledge and crystallised ability (33 percent; 3 results), and working memory (30 percent; 10 results). Importantly, it was not clear in all of these studies that neuro-Behcet's was conclusively ruled out in participants, thus some of these patients may have had neurological involvement. Also, where assessed, rates of depression and anxiety were higher in the patient groups, relative to controls.

**Neuro-Behcet's disease:** Cognitive dysfunction in neuro-Behcet's relative to healthy controls has been investigated in four studies [42,45,60,61]. From this collated pool of studies (64 neuro-Behcet's patients, 100 health controls), 31 percent of results, showed significant differences in performances, between the groups [59]. The data in this pool is somewhat limited by the small number of studies and participants, but does appear to indicate higher levels of cognitive attenuation in the following domains: acquired knowledge/crystallised ability (100% significant differences, 1 result), visual-spatial ability (50%; 4 results), processing speed (38%; 16 results), long-term memory, encoding and retrieval (30%; 10 results) and working memory (29%; 7 results). Depression and anxiety ratings were also higher in the neuro-Behcet's patients relative to controls in these studies, were assessed.

**Behcet's vs Neuro-Behcet's:** Direct comparisons of neurocognitive functioning in patients with Behcet's and neuro-Behcet's have only been reported in two studies [45,60]. The participant pool in these studies totals 58 Behcet's patients and 35 neuro-Behcet's patients. The results of these studies indicated 12 percent of results showed group differences. The area with the highest proportion of differences between the two groups was visual-spatial functioning, with 50% of results indicating lower performances in neuro-Behcet's patients.

Thus, the group comparison studies appear to indicate that neurocognitive attenuation in Behcet's disease may be on a continuum: healthy controls < Behcet's disease < neuro-Behcet's disease [59]. Patient's with Behcet's disease show fewer differences from the cognitive functioning of healthy controls, and in fewer cognitive domains, than patients with neuro-Behcet's who differ more frequently from controls and show a proportionally higher rate of differences across more domains. The reduced quality of the studies did not allow for a full synthesis of the existing data through meta-analysis or even forest plots with pooled risk ratios. However, this should be investigated in the future as further research studies are conducted with higher quality study designs and improved data reporting.



## Case studies/series

In the case study and case series literature, empirical cognitive data has been reported for 46 patients (11 Behcet's, 35 neuro-Behcet's) in 17 studies, across 18 papers [2,65-81]. The cognitive data reported in these papers has been in the form of cognitive screening assessment measures, intellectual assessment, or larger scale multi-domain assessment batteries that have included assessment across neurocognitive domains, often with intellectual assessment also. In the overwhelming majority of these cases (45/46) some degree of cognitive attenuation was been reported in participants, as defined by study authors [59].

Cognitive screening measures (i.e. Mini Mental State examination-MMSE, Cognitive Abilities Screening Instrument-CASI, Revised Hasegawa's Dementia Scale - HDS-R), have generally yielded abnormal or impaired results when reported, particularly the MMSE and CASI [75,76,78-81]. When intellectual functioning has been investigated, using full-scale IQ measure the results have been mixed [2,66,68-72,77]. In 58 percent of reported patients with a full scale IQ assessment, authors deemed the results to indicate abnormal or impaired functioning. When separated, verbally based IQ subscales (i.e. VIQ) are reportedly impaired in two-thirds of cases, and perceptually based IQ subscales (i.e. PIQ) in all of the cases that have reported separately on this subscale. At a cognitive domain level, functioning on memory measures were most frequently reported by study authors as abnormal, followed by attention, "frontal" (executive) functioning and verbal fluency.

## Causes of neurocognitive dysfunction

The causes of neurocognitive dysfunction in Behcet's and neuro-Behcet's are likely to be multifactorial. As indicated, both Behcet's and neuro-Behcet's patients appear to experience both depression and anxiety at levels elevated from the general population. Depression and anxiety are both known to impact on cognitive functioning, and thus, at least some of the neurocognitive difficulties observed on Behcet's patients may be related to this [82-84]. A second important factor is that the most commonly used treatment for Behcet's disease, corticosteroids, is also known to affect cognition, with a high proportion of patients in the neurocognitive cognitive studies described above, treated with this medication [85,86]. Finally, the existence of cerebral lesions in neuro-Behcet's disease is a plausible explanation for the increase in the level of cognitive dysfunction seen in this group. Interestingly, the cognitive performances of neuro-Behcet's patients appear to be largely similar to those observed in patients with multiple sclerosis [59]. Multiple sclerosis shares a number of similarities with neuro-Behcet's, as they are both conditions that are characterised by pathological cerebral lesions that develop, resolve or change in size over time, and may occur in similar regions within the brain [74,87-90].

## Future directions

The results of the recent systematic review in this area indicated that methodical limitations in existing studies are an issue in the field. Several well-designed larger sample studies,

directly comparing neurocognitive functioning in Behcet's and neuro-Behcet's to healthy controls, are required that utilise broad neurocognitive test batteries. To strengthen the literature base a number of independently conducted multi-centre studies, using a similar theory driven framework to guide test selection, is recommended. There is also little group data information about the neurocognitive impact of Behcet's and neuro-Behcet's overtime and thus longitudinal group research is also recommended. Further investigation of co-varying factors, such as psychological functioning, medication status (particularly corticosteroids), and neurological lesion burden, would also be useful.

## Conclusion

Depression and anxiety are the most consistently documented psychological conditions in Behcet's disease and are found at relatively similar levels in both Behcet's and neuro-Behcet's patients. As such, it is possible that chronic disease burden, functional disability, and the impact of common treatment agents (e.g. corticosteroids) are the driving factors for these mental health difficulties, rather than frank neurological changes [91,92]. A further possible mechanism may be the inflammatory process that occurs in Behcet's disease, as inflammation has been associated with increased rates of both depression and anxiety [93-97]. Neurocognitive dysfunction is also found in both Behcet's and neuro-Behcet's patients, however, it appears to be more prevalence in neuro-Behcet's patients and occurs across a broader range of domains. Neurological compromise, in the form of cerebral lesions, appears to confer an additional burden to neurocognitive capacity, over and above other common Behcet's disease factors (i.e. depression, anxiety and corticosteroid treatment).

Considering psychological and neurocognitive factors when working with patients who have Behcet's is important, as evidence indicates that many will experience difficulties in one, or both of these areas. It would be useful for screening of high prevalence psychological conditions, such as depression and anxiety, to be made routine in clinics that treat patients with Behcet's. Referral pathways, for clinical psychology or psychiatry intervention can then be provide to those who require assistance. Neurocognitive dysfunction should also be considered, particularly for neuro-Behcet's patients. Patient who show difficulties on cognitive screening measures, or report functional cognitive problems, should be referred for neuropsychological assessment and cognitive rehabilitation, if required.

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