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RESEARCH ARTICLE

Cognitive Functioning in Egyptian Behçet's disease patients: clinical, psychiatric, and Brain MRI evaluation

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Abstract

Objectives: Investigation of the cognitive profile of the Egyptian behcet disease (BD) patients in comparison to healthy subjects. **Introduction**: Neurological involvement of BD either in the form focal parenchymal involvement or cerebral venous sinus thrombosis. The impact of BD on cognitive functions is still poorly understood. **Materials and methods:** Forty BD patients were included in this study (20 of them had history of neurological involvement (Neuro-BD) and the other 20 patients had no current or past neurological manifestations). All were recruited from Zagazig University Hospitals- Egypt. Twenty healthy subjects, with no history of neurological or psychiatric disorders were taken as a control group. Disease activity assessed by Behçet's Disease Current Activity Form (BDCAF). Cognitive functions assessed by: Montreal Cognitive Assessment (MoCA) and Trail Making Test (TMT) (part A and B). Hospital Anxiety and Depression Scale (HADS) was used to assess severity of depression and anxiety. Brain MRI imaging for patients was analyzed by the age-related white matter changes (ARWMC) scale. **Results**: All tests of cognition (MoCA, TMT-A and TMT-B) were impaired in both Neuro-BD and BD patients, compared to healthy subjects (p= 0.00). MRI scans showed positive findings in; frontal lobes, parieto-occipital region, and basal ganglia. Patients with white matter changes on the frontal lobes had poorer performance on the (MoCA, TMT- A and TMT- B tests) than those without (p= 0.03, 0.00, 0.00 respectively). **Conclusion:** Silent neurological BD patients represented 20% of Egyptian BD patients. Periodic psychometric testing along with brain MRI is recommended.

Objectives:

This study aimed to investigate the cognitive profile of the Egyptian Neurobehcet Disease (NBD) patients and BD patients without neurologic involvement in comparison to healthy subjects (HS) using neuropsychological tests and brain magnetic resonance imaging (MRI), also to assess possibly associated clinical predictive variables.

Introduction

Behcet's disease (BD) is a heterogeneous, multisystemic, recurrent, inflammatory disorder with a chronic course and an unknown cause. It is a relatively rare condition, with the highest prevalence in countries along the ancient Silk Road from Japan to the Middle East and the Mediterranean basin [1]. Genetic susceptibility has been found in these regions, that is, HLAB ∗ 51 is more common among Behcet's disease patients [2].

Behcet's disease hallmark characteristics are recurrent oral and genital aphthous ulcers and relapsing uveitis. (BD) may affect eyes, the skin and mucosa, the joints, the vascular system (mainly veins), the lungs, the gastrointestinal tract, and the nervous system. It is currently well established that neurological complications are a high contributor to morbidity and mortality in (BD) [3].

Neurological involvement in (BD) may be sub classified into two major forms: one, which is seen in the majority of patients, may be characterized as a vascular inflammatory CNS disease, with focal or multifocal parenchymal involvement; the other, which has few symptoms and a better neurological prognosis, may be caused by isolated cerebral venous sinus thrombosis and intracranial hypertension. These two types rarely occur in the same individual, and their pathogenesis is likely to be different. A nonstructural vascular type headache is relatively common, whereas isolated behavioral syndromes and peripheral nervous system involvement are rare [4, 5]. Histopathologically, parenchymal lesions represent inflammatory cellular infiltration of mononuclear cells around small vessels, and, as the lesions become more chronic, excessive gliosis and atrophy become more prominent [6]. The neurological symptoms usually develop abruptly and generally clear completely within weeks [7].

The impact of Behcet's disease on higher cognitive functions is still poorly understood. The few reports that have collected objective neuropsychological data of Behcet's disease patients with neurological involvement suggested that attention and working memory, retrieval abilities, and executive functions may be particularly vulnerable to dysfunction [8, 9]. Subclinical neurological abnormalities have been detected in neuroradiological [10, 11], neurophysiological [12], or neuropsychological [13] examinations of 27–75% of Behcet's disease patients without overt neurological manifestations.

MRI is the most sensitive imaging technique that can be used for diagnosing NBD. For the parenchymal NBD, doctors mainly monitor the upper brainstem lesion and it is possible that lesions extend to thalamus and basal ganglia. MRI can distinguish NBD from non-NBD neural disease. When only spinal cord is affected by NBD, brain looks perfectly normal. Therefore, it is necessary to scan the spinal cord as well when diagnosing possible NBD involvement [14].

Materials and methods:

Subjects:

Forty patients with Behcet's disease were included in this study. They were diagnosed according to the International Study Group for Behcet's disease criteria [15]. All were recruited from the out-patient clinics and follow-up units of the Rheumatology and Rehabilitation Department of Zagazig University Hospitals. They were divided into two groups. The first group (I): included 20 patients had history of neurological involvement (Neuro-BD). The second group (II): included 20 patients had no current or past neurological manifestations (BD), other than episodic headache and/or migraine. Both Neuro-BD and BD patients were in the inactive phase of the disease (i.e., no exacerbation in more than 1 month). A third (ш) group of 20 apparently healthy subjects (HS), with no history of neurological or psychiatric disorders and matched for age, sex, total years of education, and social backgrounds were included and taken as a control group. All subjects included in this study were provided with full detailed information about the reason and aim of the study. Informed written consent from all subjects to participate in this study was present before entering the study, as required by the Declaration of Helsinki. This study was approved by the institutional ethics committee. Demographic data for each group were as follows: the Neuro-BD group consisted of 14 (70.0%) males and 6 (30.0%) females, with their age ranged between 26- 40 years (mean ± SD 31.8± 4.3 years), disease duration ranged between 1-5 years (median of 3 years) and the range of their age at onset of neurological symptoms was 25-36 years (mean ±SD 28.8±3.5 years). In BD group there were 13 (65.0%) males and 7 (35.0%) females, their average age was 26- 37 years (mean ± SD 31.2± 3.8years) and with disease duration ranged between 1-4 years (median of 2.5 years). In the HS (control) group the number of male subjects was14 (70.0%) and female subjects was 6 (30.0%), with an average age of 27- 38 years (mean ± SD 31.5± 4.0) years. There was no significant difference between groups as a regard to: sex, age, age at onset of neurological manifestations or disease duration (p =0.87, 0.65, and 0.64 respectively). Prednisone dosage at the time of assessment ranged from 0 to 30 mg/day [mean ± SD 7.57 ±5.95 mg/day].

Disease activity

Disease activity was assessed using the Behçet's Disease Current Activity Form (BDCAF) [16]. The completed BDCAF included 12 items as well as the two questions which assess disease activity from the patient's and clinician's perspective. These items were: a Likert scale, represented by 'smiley' faces ranging from very bad to very good, to indicate how the patient or the clinician felt the disease had been over the past 4 weeks, and the presence or absence (over the last 4 weeks prior to the clinic visit) of arthralgia, arthritis, diarrhoea, erythema nodosum, eye inflammation, genital ulcers, headaches, mouth ulcers, nausea/vomiting, new central nervous system involvement, new major vessel inflammation, and pustules. The average of BDCAF in neuro- BD group and in BD group was 3**.0**±0.81, 3.1±0.82 respectively, without any significant difference (t=0.34, p =0.71).

Neurological Examination

A careful history was taken and a full neurological examination was done to all BD patients. Medical records were also reviewed thoroughly. Patients with current or past neurological findings suggestive of involvement of the nervous system by the disease were classified as cases of Neuro- BD. Patients without current or past symptoms or signs of neurological involvement were classified BD.

Assessment of cognitive functions was done by:

A-The Montreal Cognitive Assessment (MoCA) is a rapid screening instrument for cognitive dysfunction [17]. It is a paper-and-pencil tool that requires approximately 10 minutes to administer. The MoCA assesses 8 cognitive domains including attention, concentration, visuospatial/ executive functions, memory, language, abstraction, calculation and orientation. The total possible score is 30 points; a score of 26 or above is considered normal, while a score of 25 or below indicates impairment. Each MoCA sub-test/domain assesses various neuro-anatomical areas. The MoCA provided good sensitivity and specificity in detection of cognitive impairment tasks of the frontal executive functioning and attention [18].

B- Trail Making Test (TMT) (part A and B)" The trail making tests A and B requires immediate recognition of the symbolic significance of number and letters, ability to scan the page continuously to identify the next number or letter in sequence, flexibility in integrating the numerical and alphabetical series, and completion of the these requirements under the pressure of time [19]. Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. Part A assesses visual perception rapidity and psychomotor rapidity. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). Part B assesses mental shifting and the subject's attention ability. The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper [20]. *Scoring Trails A and B:* 1.Part A and B are scored separately. The score for each part is the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. 2. If the time to complete trail B longer than 240 seconds; the test is stopped and the number of the figures in the allotted time as well as the number of the errors are noted. 3. Trail A between (28-33 seconds) is average and > 78 seconds is deficient. 4. Trail B between (60-84 seconds) is average and > 273 seconds is deficient. [19].

Assessment of Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) [21] is an easily administered 14-item self-report measure. The HADS takes only 2-5 minutes to complete. Its aim is to detect the presence and severity of depression and anxiety in both non somatic and psychiatric cases [22]. The measure comprises 14 items divided equally between the two mood states (7 items for anxiety and 7 items for depression). The total score is the sum of 14 items, and for each subscale the score is the sum of the respective 7 items ranging from (0- 21), on 4-point Likert rating scales (0= best to 3= worst) for each item [23].

Neuroimaging Brain MRI

MR imaging of the brain was performed for all patients on Philips Achieva class II MRI 1.5-T scanner (Philips Medical Systems- Best- Netherlands). The imaging sequences consisted of:

1. T2-weighted fast-spin echo sequence in the axial plane [TR/TE = 8500/83 ms, slice thickness 2 mm, gap 0, matrix size 256 x 192 pixels, field of view 220 mm);
2. T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence in the axial plane (TR/TE/TI = 9800/126/8500 ms, slice thickness 2 mm, gap 0, matrix size 256 x 192 pixels, field of view 240 mm).
3. T1-weighted spoiled gradient-echo two dimensional sequence in the coronal plane (TR/TE = 26/7 ms, flip angle 30, slice thickness 1.6 mm, gap 0, matrix size 256 x 256 pixels, field of view 240 mm).

The age-related white matter changes (ARWMC) scale [24] was used to analyze the scans. White matter changes on MRI were defined as bright lesions ≥5 mm. The ARWMC scale was rated on a 4-point scale (0- 3) for each of the following brain areas: frontal, parieto-occipital, temporal, infratentorial/ cerebellum, and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, and insula). The left and right hemispheres were rated separately. The score zero means: no visible lesion, score 1 means: 1 focal lesion ≥5 mm, score 2 means: >1 focal lesion and score 3 means: confluent lesions) was found in the scans. The neuroradiologist was blind to patient's clinical information or cognitive performance.

Statistical analysis: Quantitative variables were described using means, standard deviations (SD), ranges, and analyzed by Analysis Of Variance (ANOVA) F test, Student *t*-test and Mann Whitney U test. Qualitative variables were summarized using number and percentage, and analyzed by Chi-square test (x^2). Pearson's correlation coefficient (r) was used to find the strength of association between two continuous variables. Data were analyzed using the Statistical package for social sciences SPSS software version16.0 (SPSS, Chicago, IL, USA), with 80% power of study, 95% confidence interval CIs and P<0.05 as a level of significance.

Results:

The results of tests and the statistical analysis were tabulated and evaluated as follows.

The clinical manifestations and steroid intake among neuro-BD and BD patients are given in Table (1).

Table (1) Clinical manifestations of patients with Behçet's disease

Symptoms	Neuro-BD Number (%)	BD Number (%)	x^2	*P*
Headache	14(70.0%)	12(60.0%)	0.61	0.42
Oral ulcers	8 (40.0%)	14(70.0%)	1.67	0.19
Genital ulcers	2(10.0%)	8 (40.0%)	4.80	0.03*
Erythema nodosum	0 (0.0%)	2(10.0%)	2.11	0.15
Pastular lesions	2 (10.0%)	8 (40.0%)	4.80	0.03*
Arthralgia	6 (30.0%)	8 (40.0%)	0.62	0.43
Arthritis	4 (40.0%)	8 (40.0%)	1.90	0.17
Abdominal pain	0 (0.0%)	2 (10.0%)	5.7	0.07
Nausea/vomiting	4 (20.0%)	0 (0.0%)	6.11	0.04*
Diarrhea+ altered/frank blood per rectum	0 (0.0%)	0 (0.0%)	_	_
Eye involvement				
a red eye/a painful eye	2 (10.0%)	4(20.0%)	0.87	0.94
blurred or reduced vision	12 (60.0%)	12 (60.0%)	2.67	0.26

New central nervous system involvement				
-Black out	0 (0.0%)	0 (0.0%)	-	–
-Difficult speech	0 (0.0%)	0 (0.0%)	-	–
-Blurred vision	6 (30.0%)	0 (0.0%)	7.00	0.01*
-Difficult hearing	4 (20.0%)	0 (0.0%)		
-Weakness or diminished sensation of face	0 (0.0%)	0 (0.0%)	4.45	0.03*
-Weakness or diminished sensation of arm and leg	8 (40.0%)	0 (0.0%)		
-Memory loss and/ or impaired cognition	8 (40.0%)	0 (0.0%)	-	-
-Loss of balance	4 (20.0%)	0 (0.0%)	7.22	0.01*
			7.22	0.01*
			3.4	0.09
New major vessel inflammation	4 (20.0%)	6 (30.0%)	4.96	0.18
• Chest pain	0 (0.0%)	2 (10.0%)	0.23	0.97
• Breathlessness	0 (0.0%)	0 (0.0%)	-	-
• Coughed up blood	0 (0.0%)	0 (0.0%)	-	-
• Pain/swelling/discoloration of the face	0 (0.0%)	0 (0.0%)	-	-
• Pain/swelling/discoloration of the arm	0 (0.0%)	0 (0.0%)	-	-
• Pain/swelling/discoloration of the leg	4 (20.0%)	4 (20.0%)	-	-
BDCAF (Mean ±SD) Range	3.**0**±0.81 2-4	3.1±0.82 2-4	0.34	0.71
Steroid [Prednisone]	5 (25.0%)	7(35.0%)	0.43	0.7

Abbreviations: Neuro-BD: Bechcet disease patients with neurological symptoms, BD: Bechcet disease patients, HS: healthy subjects, BDCAF: Behçet's Disease Current Activity Form

Pattern of Cognitive Impairment

In comparison to healthy demographically matched subjects, both Neuro-BD and BD patients were found to be impaired on neuropsychological tests of attention, learning and executive performance on measures of attention and working memory, delayed memory recall, and executive functions with highly statistical significant difference (p= 0.00); however, these impairment in each of neuropsychological measure was of no statistical significant difference between the two groups of BD patients (Table 2).

Table (2) Comparison of neuropsychological measures between groups

	Neuro-BD *n*=**20**	**BD** *n*=**20**	**HS** *n*=**20**	**F**	***P***
HADS–Anxiety	11.7±3.4[a] 5-16	12.1±3.1[a] 6-17	4.5±1.5[b] 3-7	17.4	0.00*
HADS–Depression	17.3±5.4[a] 6-20	16.8±4.3[a] 7-21	4.6±1.3[b] 2-6	22.3	0.00*
MoCA	16.7±7.5[a] 9-27	18.8±3.9[a] 15-27	28.3±1.6[b] 26-32	12.7	0.00*
TMT A–time	53.2±23.6[a] 29-86	43.4±9.7[a] 30-60	29.7±1.8[b] 27-33	30.9	0.00*
TMT B–time	251.7±60.4[a] 160-321	248±68.0 [a] 130-330	70.7±5.9[b] 61-84	85.2	0.00*

Abbreviations: MoCA: Montreal Cognitive Assessment, TMT: trail-making test, HADS: Hospital Anxiety and Depression Scale

- The identical alphabetical coding is not significant.
- The different alphabetical coding is significant.

Analysis of HADS results demonstrated that; eighteen (90%) neuro- BD patients had anxiety and depression scores above the normal range versus nineteen (95%) of the BD group. Results of the neuropsychological tests revealed that; for neuro-BD group MoCA was below normal in 11(55.0%), TMT-A was prolonged in 12(60.0%) and TMT-B prolonged in 15(75.0%) of patients, while for BD group MoCA was low in 8(40.0%), TMT-A was prolonged in 11(55.0%) and TMT-B prolonged in 13(65.0%) of patients (Table 3).

Table (3) Severity of anxiety, depression and cognitive impairment in neuro- BD and BD patients

	Neuro-BD *n*=**20** (%)	**BD** *n*=**20** (%)	x^2	***P***
Anxiety				
Non- case (normal) (0-7)	2(10.0%)	1(5.0%)		
Borderline case (8-10)	14(70.0%)	15(75.0%)	0.66	0.59
Case of anxiety (11-21)	4(20.0%)	4(20.0%)		
Depression				
Non- case (normal) (0-7)	2(10.0%)	1(5.0%)		
Borderline case (8-10)	5(25.0%)	3(15.0%)	0.47	0.49
Case of depression (11-21)	13(65.0%)	16(80.0%)		
MoCA				
Low<26	11(55.0%)	8(40.0%)	**0.40**	**0.52**
Normal(26-30)	9(45.0%)	12(60.0%)		
TMT A–time				
Normal (28-33) sec	8(40.0%)	9(45.0%)	**0.79**	**0.37**
Prolonged > 33 sec	12(60.0%)	11(55.0%)		
TMT B–time				
Normal (60-84) sec	5(25.0%)	7(35.0%)	**0.12**	**0.73**
Prolonged > 84 sec	15(75.0%)	13(65.0%)		

Neuro-BD patients' disease duration, time since onset of neurological symptoms, disease activity level of anxiety and level of depression were not significantly correlated with any of the neuropsychological measures. Neuro-BD patients not taking prednisone had significantly more cognitive impairments (p= 0.02). BD patients' level of anxiety was significantly correlated with MoCA and trail-making test–part A and part B (P= 0.00). BD patients' level of depression was significantly correlated with MoCA and trail-making test–part A (P= 0.00). None of the neuropsychological measures were found to be related to disease duration (p= 0.22). BD patients with headaches tended to be more frequently impaired on the neuropsychological measures (p= 0.00); however the frequency of

impairment on each neuropsychological measure was not significantly different in patients taking versus not taking prednisone (Table 4).

Table (4) Correlation between cognitive functions tests and clinical variables

	Neuro-BD						BD					
	MoCA		TMT- A		TMT– B		MoCA		TMT– A		TMT –B	
	r	p	r	p	r	p	r	p	r	p	r	p
Disease duration	**0.14**	**0.44**	**-0.28**	**0.22**	**-0.30**	**0.24**	**0.19**	**0.41**	**-0.22**	**0.18**	**-0.29**	**0.23**
Onset of neurological symptoms	**0.38**	**0.09**	**0.34**	**0.15**	**0.28**	**0.22**	-	-	-	-	-	-
(BDCAF)	**-0.40**	**0.07**	**0.15**	**0.54**	**-0.33**	**0.09**	**0.44**	**0.10**	**0.19**	**0.58**	**-0.40**	**0.08**
Headache	**-0.42**	**0.07**	**0.28**	**0.22**	**-0.42**	**0.88**	**0.64**	**0.00***	**-0.96**	**0.00***	**-0.55**	**0.00***
HADS–Anxiety	**-0.39**	**0.08**	**0.27**	**0.22**	**-0.40**	**0.87**	**0.61**	**0.00***	**-0.97**	**0.00***	**-0.51**	**0.00***
HADS–Depression	**-0.38**	**0.08**	**0.26**	**0.28**	**0.35**	**0.13**	**0.65**	**0.00***	**0.77**	**0.00***	**0.34**	**0.15**

Brain MRI Findings

Brain MRI scans for neuro-BD patients showed that; (twelve patients scored 1, six patients scored 2 and two patients scored 3 on the ARWMC scale) versus only four BD patients scored 1on the same scale. The only three brain regions with positive findings were the frontal lobes, the parieto-occipital region, and the basal ganglia. Evidence of temporal, infratentorial/ cerebellum infarct was not found in any patient (Table 5).

Table (5) Results of Brain MRI on (ARWMC) Rating Scale

According to Location	**Neuro-BD** *n*=**20**	**BD** *n*=**20**	x^2	***P***
parieto-occipital lobes	6 (30.0%)	0 (0.0%)	7.06	0.01*
Frontal lobe	10 (50.0%)	4 (20.0%)	0.59	0.41
basal ganglia	4 (20.0%)	0 (0.0%)	4.9	0.08
Temporal, infratentorial/ cerebellum infarct	0 (0.0%)	0 (0.0%)	-	-
According to rating scores (0 –3)				
0	0 (0.0%)	0 (0.0%)		
1	12 (60.0%)	4 (20.0%)	12.9	0.00*
2	6 (30.0%)	0 (0.0%)	7.06	0.01*
3	2 (10.0%)	0 (0.0%)	2.71	0.15

Abbreviations: MRI**;** magnetic resonance imaging- (ARWMC); Age-Related White Matter Changes

MRI scans demonstrated that, patients with white matter changes on the frontal lobes had poorer performance on the neuropsychological tests; (MoCA, TMT- A and TMT- B) than those without (p= 0.03, 0.00, 0.00 respectively). No association was found between positive findings on the parieto-occipital region or basal ganglia and cognitive functioning (Table 6).

Table (6) Relationship between anatomically affected brain regions and cognitive function

	Parieto-occipital lobes	Frontal lobe	Basal Ganglia	Temporal, infratentorial/ cerebellum	F	P
MoCA	***19.3±4.4[a]*** ***18-27***	27.3±5.3[b] 16-25	14.5±0.7[a] 14-15	18.9±0.7[a] 18-19	5.7	0.03*
TMT- A	31.3±1.03[a] 30-32	75.8±6.5[b] 70-86	30±0.5[a] 29-31	29.5±0.5[a] 28-30	139.5	0.00*
TMT- B	285.2±25.4[a] 230-300	307.8±12.8[b] 290-321	297±10.8[a] 290-308	291±8.7[a] 289-300	7.34	0.00*

- The identical alphabetical coding is not significant.
- The different alphabetical coding is significant.

Discussion

Behcet disease is a symptom complex. Neurological involvement has been reported in about 2.2- 50% of BD patients [25]. Neurological manifestations of BD are caused by primary neural parenchymal lesions or secondary to vascular involvement [26]. These manifestations are considered as adverse prognostic factor [14]. Studies of cognitive functions in BD patients were limited. The majority of these studies have been carried out on patients with NBD and revealed that the most frequent neuropsychological impairments were in measures of attention, memory and executive functions [4, 9, 14, 27]. Other studies suggested that cognitive impairment might be seen also in BD patients without neurological involvement (BD-only) [28, 29, 30, and 31]. The present study showed high prevalence of neuropsychiatric affection of both NBD and BD patients compared to healthy controls detected by abnormal scores of psychometric tests (anxiety, depression, MoCA, TMT-A and TMT-B) together with abnormal brain MRI.

In the current study we reported that 18 (90%) neuro- BD patients had anxiety and depression scores above the normal range (14 patients having moderate anxiety, 4 patients having severe anxiety , 5 having moderate depression and 13 patients having severe depressive symptoms) versus 19 (95%) of the BD patients (15 patients having moderate anxiety, 4 patients having severe anxiety , 3 having moderate depression and 16 patients having severe depressive symptoms); while none of the control was anxious or depressed. The mean HADS score for anxiety and depression was (11.7±3.4, 12.1±3.1 respectively) for NBD and it was (17.3±5.4, 16.8±4.3 respectively) for BD without statistical significant differences between NBD and BD patients; while results of HADS for anxiety and depression was (4.5±1.5, 4.6±1.3 respectively) for control group with highly statistical significant differences between between the two groups of BD and control group (P= 0.00). This was in consistent with the study of Zayed et al. [29] who reported that twenty-three (92%) of BD patients had anxiety scores above the normal range versus none of the control group and with 7 patients having mild, 12 patients having moderate, and 4 patients severe anxiety symptoms. Twenty-four (96%) patients had depression scores that were above the normal range versus none of the controls, with 3 patients having mild, 4 patients having moderate, and 17 patients having severe depressive symptoms. Similarly; results of the study of Tanriverdi et al. [32] showed an increased susceptibility to anxiety and depression in BD patients relative to control group. Whereas the BD group had a mean depression score of 20.08 (± 12.96), the control group had a mean score of only 11.44 (± 9.71). A similar pattern was found for anxiety, with the BD patients scoring a mean of 22.09 (± 14.52) and the control group scoring a mean of 8.69 (± 8.17) on the anxiety scale. This was in agreement with a cross-sectional study conducted on a sample of 101 randomly selected patients with BD in Shiraz, Southwest of Iran [33], revealed that the most prevalent psychological symptoms in patients with BD were; somatization (91.7%), anxiety (78%), and depression (77.78%). Similarly; results of many studies demonstrated that not only do BD patients tend to score high on the depression scales and fulfill the criteria for depression compared to healthy control groups, but that BD patients often yield the highest mean scores even when compared to patients suffering from other severe and chronic diseases such Psoriasis, Rheumatoid Arthritis and Major Depression [34, 35, 36].

The risk of developing psychiatric co-morbidities is further heightened by the fact that BD is autoimmune in origin, progressive in nature, threatens to deform body structures to an extent that necessitates rehabilitation and it denies any hope of the patient for a cure [37]. Still, it is also possible for depression and anxiety to be generated and even aggravated by chronic medication and its effects. For example, the indiscriminate use of corticosteroids so commonly included in the treatment plan may cause depression in cases of prolonged use. Finally, the changes in habit experienced by patients may serve as a trigger of co-morbid psychiatric disorders. Often, chronic pathologies alter the habits of a patient's life, especially upon diagnosis and at the beginning of treatment [38].

In the present study we reported that memory impairment was the major and early finding among NB and BD patients. The most severely affected memory process was delayed recall in the verbal and/or visual modalities, followed by deficits of executive functions of frontal system and visuospatial abilities.

In the comparison of HS to NBD and BD patients, a poorer performance was observed in both groups of patients in almost all of the neurocognitive functions; verbal memory, executive functions, information processing speed, complex visual perception, attention and psychomotor speed, verbal attention and concentration with highly statistical significant difference ($p= 0.00$). Although there was no significant difference in the scores of neuropsychological tests between both groups of patients, NBD patients revealed further impairment on memory, executive functions, information processing speed, visual perception, attention and psychomotor speed, verbal attention and concentration compared to BD patients. Our findings were in line with previous studies showing that both NBD and BD patients have deficits on learning, immediate memory, working memory, verbal fluency and attention tasks comparing to healthy subjects ($p\leq0.003$) [14, 27, 29, 30].

The present work demonstrated that Neuro-BD patients not taking prednisone ($p= 0.02$) or with parenchymal involvement ($p= 0.00$) had significantly more cognitive impairments. This finding was in accordance with previous studies reporting poorer performance on memory, executive functions, complex visual perception and verbal attention among Neuro-BD patients with parenchymal involvement rather than those with cerebral sinus thrombosis [4, 27, 39, and 40]. Also, we found that the frequency of cognitive impairments of NBD patients was not found to be associated with disease duration, time since onset of neurological symptoms, and levels of anxiety and level of depression.

MRI is a useful tool for detecting CNS lesions in patients suffering from Behçet's disease [41]. Neuro-imaging studies on NBD patients have shown that these lesions are generally located within the brain stem, occasionally with an extension to the diencephalons, or less commonly within the periventricular and subcortical white matter [42]. These lesions are generally observed as high signal intensity on the T2-weighed images [41]. The lesion predilection for the brain stem together with the sparseness of cortical lesions might explain the rarity or lack of higher cortical function disturbances in the NBD patients. The reason for the lesion predilection in the brain stem, basal ganglia and diencephalons is not known. It has been hypothesized that inflammation of the small-to-medium sized veins of those regions might be responsible for causing venous infarcts [43]. Although this appears to be reasonable, more pathological studies are needed to support this hypothesis.

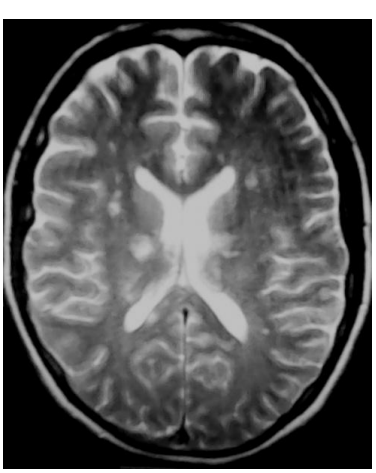
In the present study, twenty patients were diagnosed as having NBD and all of them (100%) had brain lesions on MRI. Most lesions were of high signal intensity on T2-weighted images and located in the white matter of the frontal lobe 10 patients (50%), parieto-occipital lobes 6 patients (30%) and basal ganglia 4 patients (20%). Brain MRI showed there were no temporal, infratentorial or cerebellum infarct was found in any of our NBD patient (Table 5). According to ARWMC scale of the Brain MRI scans for neuro-BD patients, there were twelve patients scored 1, six patients scored 2 and two patients scored 3(Table 5). This was in consistent with the study of Park et al. [44] who reported that, fourteen of 18 BD patients were diagnosed as having NBD and 12 NBD patients (86%) had brain lesions on MRI. Most lesions were of high signal intensity on T2-weighted images and located in the midbrain, pons, basal ganglia, and white matter.

Patients with abnormal findings on neuropsychological and/or neuroradiological studies, but with normal neurological examination and with no neurological complaints except for tension-type headache and/or migraine, may represent a subset of what has been called silent CNS involvement [4]. In the current study the brain MRI scans of BD patients without overt neurological manifestations but with neuropsychological impairments demonstrated changes in 4 patients (20%). All lesions were of high signal intensity on T2-weighted images and located in the white matter of the frontal lobe only without any abnormalities detected in temporal, infratentorial or cerebellum and all scored 1 on the ARWMC scale of the Brain MRI (Table 5). This was in agreement with the study of Park, et al. showed that BD patients with silent CNS involvement, the cerebral white matter was most commonly involved, but almost half the MRI studies were normal [44]. On the other hand, the prevalence of silent CNS involvement in BD

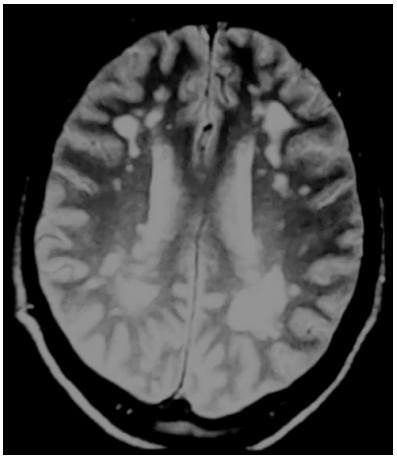
patients was around (40%) as reported by previous series [10, 11, 13, 27,29]. However, we should be cautious in the interpretation of the results of the previous studies because not all BD patients underwent MRI examination and no healthy demographically matched neuroimaging data were obtained [27].

One of the most devastating presentations of BD is the involvement of the nervous system. The systematic exploration of higher brain functions and structural neuroimaging may contribute to a better understanding of the neurological complications of this autoimmune disease and in the future be used to optimize treatment procedures. The present study demonstrated that BD patients MRI changes of the white matter of the frontal lobes had poorer performance on the neuropsychological tests (MoCA, TMT- A and TMT- B) than those without (p= 0.03, 0.00, 0.00 respectively) and there was no association was found between positive MRI findings on the parieto-occipital region or basal ganglia and cognitive functioning (Table 6). This was in accordance with a study of Cavaco, et al. [27] who found that among BD patients with available MRI scans, those with mild white matter changes on the frontal lobes had poorer performance on the nine hole peg test–dominant hand (P = 0.003) and nondominant hand (P = 0.040), digit span– forward (P = 0.014), and Corsi block-tapping test (P = 0.049) and P = 0.025) and were more frequently impaired (80%) on digit span–forward (Fisher's exact test, P = 0.031) than patients without white matter changes on the frontal lobes (20%) [27].

Fig.1 MRI Axial T2 (A & B) shows high signal intensity lesions seen at the bilateral frontal, basal ganglia regions, patchy foci of hyperintense lesions are seen around the surrounding capsule.

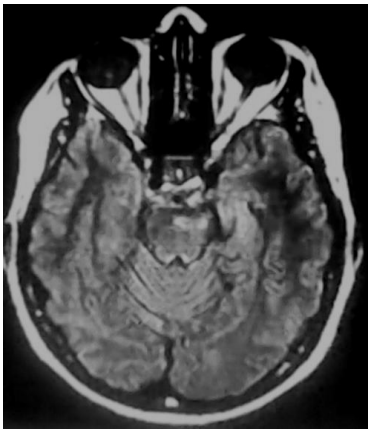


(A)

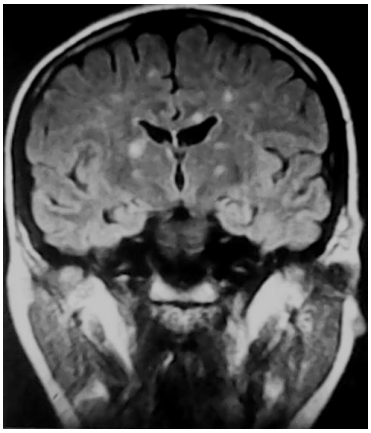


(B)

Fig.2 MRI Axial T1 Contrast and coronal T1 contrast (C & D) shows high signal intensity lesions seen at the posterior fossa, parietal & basal ganglia regions. Following gadolinium administration, patchy foci of enhancement are seen around the surrounding capsule.



(C)



(D)

Conclusion

Our multidimensional neuropsychological and neuroradiological brain MRI approach study provided strong evidence for the occurrence of silent neurological involvement in approximately 20% of Egyptian BD disease patients without the neurological syndrome. Memory impairment and executive functions abnormalities were frequently found in silent neurological BD patients. Since patients with silent NBD tend to progress during follow-up, close clinical monitoring and periodic psychometric testing along with brain MRI are recommended.

Conflicts of Interest

The authors have no conflict of interest to declare.

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