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Quiescent ulcerative colitis and Crohn's disease have potential effect on cognitive function

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Abstract

Background Ulcerative colitis (UC) and Crohn's disease (CD) imply chronic intestinal inflammation with both local and systemic manifestations. Cognition is a lifelong process of learning and memory processing, which has been identified to be affected by chronic systemic illnesses.

Aim To evaluate the cognitive functions in inflammatory bowel disease (IBD) patients in remission

Patients and methods Inclusion criteria are as follows: 70 IBD patients in remission and a group of 50 healthy control. Mini-mental state examination (MMSE) was used for assessment of global cognitive function and Trail Making Test (TMT) for assessment of executive functions. TMT consists of part A which measures attention and performance speed and part B which measures mental flexibility. Both tests have been previously validated on Arabic-speaking populations.

Results The study included 70 patients (50 UC and 20 CD), who have been in remission for 21 ± 9 months. Of the included cases, about 51 were already on steroids ± azathioprine, and 19 patients were on biologics. Males represented 60% ($n = 42$) while females 40% ($n = 28$), and their mean age was 34 ± 8 years. Both cases and controls were matched for age and sex. The mean score of MMSE among IBD cases was significantly worse than controls (28.5 ± 3 versus 30, $P < 0.001$). Also, the duration of TMT parts A and B was significantly longer in cases than controls. The cases group scored 32 ± 19.5 s in TMT part A, versus 23 s by the controls. In TMT B, the recorded scores were 255 ± 48, versus 234 s in cases and control groups respectively ($P < 0.001$). In the cases group, 6 patients (8%) had below normal MMSE score of less than 24, with mild (3 patients, mean score was 21) to moderate cognitive impairment (3 patients, mean score was 15). The presence of extraintestinal manifestation was the only disease-related factor that was associated with cognitive impairment. Of the patient-related factor: older age, being divorced, and living in rural areas were associated with poorer cognitive functions.

Conclusion IBD patients potentially suffer from cognitive impairment. In our study, factors as extraintestinal complications, older age, marital status, and residence in rural areas could be contributing factors to this impairment.

Keywords Ulcerative colitis, Crohn's disease, Inflammatory bowel disease, Cognitive functions, Extraintestinal manifestations

Introduction

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) is characterized by chronic inflammation of the gastrointestinal (GI) tract which is transmural in CD, while in UC it is limited to the mucosa [1, 2]. In addition to local effects, inflammation

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has extraintestinal manifestations in a variable proportion of IBD patients (6–47%). Classic extraintestinal manifestations include musculoskeletal, dermatologic, ocular, oral, and hepatobiliary manifestations [3]. Neurologic and psychiatric involvement in IBD is not common, but this may be due to under reporting [4]. Neurological complications documented in IBD patients are ischemic cerebrovascular strokes and venous sinus thrombosis with frequency of 0.6 to 4.7% and 1.3 to 6.4%, respectively, as well as peripheral neuropathy with incidence ranging from 0.9 to 38.7% [5], as well as psychiatric problems including depression, anxiety, and fatigue which are twice as common in IBD patients as that in healthy population [6]. Neurological imaging in IBD has showed alterations in the gray matter areas responsible for information processing and memory as well as diffuse hyperintensity in the white matter, in addition to alterations in global network organization and regional connectivity [7].

The pathophysiology of the neuropsychiatric complications may be multifactorial due to pro-thrombotic state, nutritional deficiencies, and adverse effects of medications, but their main mechanism is immunologically mediated [8]. Also, microbiota-gut-brain axis is postulated to play an important role given that it is a bidirectional communication pathway. Inflammatory cytokines can alter neurological signaling leading to mood disorders and cognitive dysfunction, through effects on the pathways [9].

Cognitive function encompasses the lifelong process of learning, ranging from quantitative reasoning to memory formation [10]. Considering that IBD is a lifelong illness, its impact on cognition should be evaluated.

Patients and methods

This cross-sectional observational study was performed at Tropical Medicine Department, Ain Shams University, during the time between August 2022 and January 2023. About 120 previously diagnosed IBD patients, who were attending at our specialized outpatient clinic for follow-up, were recruited. Of whom, 70 IBD cases (50 UC and 20 CD) fulfilled the following criteria and were enrolled for assessment of cognitive functions. IBD diagnosis has been previously confirmed via colonoscopy and biopsy. Also, 50 healthy controls were included for comparison. Consent for participation was obtained from all the cases and controls.

Inclusion criteria

Only IBD patients in remission were included. In UC, remission was identified by the absence of any systemic illness and the absence of mucoid or bloody motions in addition to normal inflammatory markers and classified as asymptomatic (S0) according to Montreal classification of extent and severity [11]. Remission in CD patients included those with a score less than 150 on Crohn's disease activity index "CDAI" [12]. All cases and controls were adults, aged 18 to 60 years old, and had at least elementary school education.

Exclusion criteria

Newly diagnosed IBD patients with illness duration of less than 1 year. Clinically significant debilitating comorbid conditions, including stroke with neurological sequalae, visual impairment, sleep disorders or malignancy, participants with history of substance or alcohol abuse, and those receiving antipsychotic drugs were excluded from the study.

Baseline demographic and clinical characteristics were recorded. Disease characteristics, duration, duration of remission, type of instituted therapy, presence of extraintestinal manifestations, were also documented.

Cognitive function tests

1. The Folstein mini-mental state examination (MMSE) [13] (Appendix A)

   a MMSE consists of several short questions and problems grouped into eight items: orientation to time and place, registration, attention and calculation, recall, language skills, repetition, and complex commands. Each item was scored, and a summary score of maximal 30 points was calculated with higher scores indicating better cognitive performance.

   b In the present study, a MMSE value of 24 or more was considered normal, with lower value indicating mild (19–23 points), moderate (10–18 points), or severe (≤ 9 points) cognitive impairment.

Trail Making Test (TMT) was used for assessment of executive function [14] (Appendix B)

- *TMT part A*: (Measured attention and performance speed), where the participant was asked to connect circled numbers in a numerical sequence (i.e., 1-2-3) as rapidly in possible.
- *TMT part B*: (Measured mental flexibility and ability to shift attention), where the subject was asked to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence (i.e., 1-A-2-B) as rapidly as possible.

The time taken by the candidate for fulfilling each part was observed and documented. Longer time consumed indicated lower performance.

The average scores of TMT A and B were 29 and 75 s, respectively. Scores over 79 and 273 s were considered deficient [15].

Both of these tests have been previously validated on Arabic-speaking populations [16].

Statistical analysis

Data was collected, revised, coded, and entered into the Statistical Package for Social Science (SPSS) (IBM) version 23. The quantitative data was presented as mean, standard deviations, and ranges when parametric, median, and interquartile range when data was found non-parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was done using the chi-square test and/or Fisher exact test when the expected count in any cell was less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent *t*-test, while comparison between more than two groups was done by using one-way ANOVA test with post hoc analysis. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. *P*-value < 0.05 was considered statistically significant.

Ethical committee approval

The study was approved by Ain Shams University Faculty of Medicine Research Ethics Committee (REC), reference number MS 480/2022.

Results

The mean duration of disease remission among cases was 21 ± 9 months.

Demographic data

The majority of our included patients were males, 60% (n = 42). The mean of their age was 34 ± 8 years. The control group was matched for sex and age (males represented 73.5% (n = 36), and the mean of their age was 33 ± 13 years) (Table 1).

Mini-mental status examination score

IBD patients performed significantly lower than controls (P < 0.001). While the mean score of MMSE in the control group was 30, the mean MMSE score among cases was 28.5 ± 3 (Table 2). Detailed analysis of cases score showed that 42 patients had a score of 30, whereas 22 patients had scores between 24 and 30 (i.e., low normal). Cognitive impairment, denoted by scores less than 24, was recorded in 6 patients, of whom 3 had mild impairment (mean = 21 ± 0.7) and the other 3 had moderate impairment (mean = 17 ± 0.3) (Table 2).

The difference between cases and controls was significant in all five domains of MMSE (orientation, registration, attention, recall, and language) (Table 3). Further analysis revealed that participants with UC, rather than CD, performed significantly worse on MMSE (mean 28.6 ± 2.8, P = < 0.001) as compared to controls (means 30) (Tables 4 and 5). Of the UC patients, 4 had mild and moderate cognitive impairment, where the scores were less than 24.

Table 1 Demographic data and patient characteristics

	Min.	Max.	Mean	SD
Age	19.00	53.00	33.84	8.31
	N	%		
Sex	Male	42	60.0%	
	Female	28	40.0%	
Smoking	Nonsmoker	53	75.7%	
	Smoker	17	24.3%	
Occupation	Working	41	58.6%	
	Not working	27	38.6%	
	Student	2	2.9%	
Marital status	Single	28	40.0%	
	Married	38	54.3%	
	Divorced	2	2.9%	
	Widow	2	2.9%	
Residence	Urban	38	54.3%	
	Rural	32	45.7%	
Education	Elementary	11	15.7%	
	Preparatory	13	18.6%	
	High school	10	14.3%	
	Vocational	17	24.3%	
	College	19	27.1%	
	Min.	Max.	Mean	SD
Period of remission (months)	12.00	48.00	21.13	9.24
	N	%		
Type of disease	UC	50	71.4%	
	CD	20	28.6%	
Type of treatment	Biological	19	27.1%	
	Conventional	51	72.9%	
DM	Yes	20	28.6%	
	No	50	71.4%	
HTN	Yes	19	27.1%	
	No	51	72.9%	
Extraintestinal manifestations	No	61	87.1%	
	Yes	9	12.9%	

Table 2 Mini-mental state examination (MMSE) and Trail Making Test (TMT) of cases and controls

		Group				t	*p*-value
		Cases (*n* = 70)		Controls (*n* = 50)			
		Mean	SD	Mean	SD		
Orientation		9.7	0.8	10.00	.00	2.98	0.004
Registration		3	1	3	0	3.36	0.001
Attention		5	1	5	0	2.73	0.01
Recall		3	1	3	0	3.36	0.001
Language		8	1	8	0	3.22	0.002
MMSE total		28.54	3.04	30.00	.00	4.01	< 0.001
Trail Making Test A (time in seconds)		31.66	19.45	23.28	2.84	3.55	< 0.001
Trail Making Test B (time in seconds)		255.01	47.96	233.94	22.43	2.89	0.01
		N	%	*N*	%	χ^2	*p*-value
Copying	.00	4	5.7%	0	0.0%	2.96 FE	0.14
	1.00	66	94.3%	50	100.0%		
MMSE total	Normal	42	60.0%	50	100.0%	29.63 FE	< 0.001
	Low normal	22	31.4%	0	0.0%		
	Mild CI	3	4.3%	0	0.0%		
	Moderate CI	3	4.3%	0	0.0%		

Table 3 Comparison between ulcerative colitis and Crohn's disease regarding MMSE and TMT testing

		Type of disease				*t*	*p*-value
		UC (*n* = 50)		CD (*n* = 20)			
		Mean	SD	Mean	SD		
MMSE		28.62	2.77	28.35	3.72	0.333	0.740
TMT		283.60	57.86	294.35	71.51	0.656	0.514
		N	%	N	%	χ^2	*p*-value
Level of cognition	Normal	46	92.0%	18	90.0%	1.76 FE	0.71
	Mild CI	2	4.0%	1	5.0%		
	Moderate CI	2	4.0%	1	5.0%		

Table 4 Comparison between ulcerative colitis and controls regarding MMSE and TMT testing

	UC (*n* = 50)		**Controls (*n* = 50)**		***t*[a]**	***p*-value**
	Mean	**SD**	**Mean**	**SD**		
MMSE	28.62	2.77	30.00	.00	3.52	< 0.001
TMT	283.60	57.86	257.22	23.03	2.99	0.003

[a] Student *t*-test

Table 5 Comparison between Crohn's disease and controls regarding MMSE and TMT testing

	Crohn's (*n* = 20)		**Controls (*n* = 50)**		***t*[a]**	***p*-value**
	Mean	**SD**	**Mean**	**SD**		
MMSE	28.35	3.72	30.00	.00	1.99	0.06
TMT	294.35	71.51	257.22	23.03	22.28	0.03

[a] Student *t*-test

TMT

IBD cases significantly recorded longer duration to finish parts A and B, compared to the healthy controls ($P < 0.001$ & 0.01, respectively), with mean values of 32 ± 19.5 and 255 ± 48 s for parts A and B, among cases (Table 2). Meanwhile, both UC and CD patients took significantly longer time to finish TMT (mean 283.6 ± 58 s and 294.4 ± 71.5, respectively), compared to controls (mean 257 ± 23, $P = 0.003$ and 0.03, respectively) (Tables 4 and 5).

Factors affecting MMS

1. Patient-related factors

There was a significant difference in the age of patients with cognitive impairments than those without (41 ± 7.3 versus 33 ± 8, respectively, $P = 0.019$). Divorced patients ($n = 2$) had significantly lower mean MMSE (21 ± 2.8) than other marital statuses ($P < 0.001$) and took longer duration to finish TMT (Tables 6 & 7). Cases living in

Table 6 Relation between patients' data and MMSE results among cases

Parameter		**MMSE total**			
Age	Pearson's correlation	−0.280			
	p-value	0.019			
		MMSE total		**Test value**	***p*-value**
		Mean	**SD**		
Sex	Male	28.57	3.21	0.10*	0.92
	Female	28.50	2.83		
Marital status	Single	29.50	.88	8.13**	< 0.001
	Married	28.45	3.34		
	Divorced	21.00	2.83		
	Widowed	24.50	4.95		
Residence	Urban	29.32	.99	2.21*	0.03
	Rural	27.63	4.23		
Education	Elementary	27.36	5.24	0.98**	0.43
	Preparatory	28.08	3.28		
	High school	29.50	.71		
	Vocational	28.35	3.24		
	College	29.21	1.23		
Occupation	Working	29.10	2.02	1.87**	0.16
	Not working	27.67	4.12		
	Student	29.00	.00		
DM	Yes	27.80	4.11	1.06*	0.30
	No	28.84	2.49		
HTN	Yes	28.68	3.43	0.24*	0.82
	No	28.49	2.92		
Smoking	Nonsmoker	28.34	3.25	0.99*	0.33
	Smoker	29.18	2.24		
Type of disease	UC	28.62	2.77	0.33*	0.74
	CD	28.35	3.72		
Type of treatment	Biological	28.37	3.17	0.29*	0.77
	Conventional	28.61	3.03		
Extraintestinal manifestations	No	29.08	2.49	3.03*	0.01
	Yes	24.89	4.04		
		MMSE total			
Period of remission (months)	Pearson's correlation	0.065			
	P-value	0.593			
Duration of disease (months)	Pearson's correlation	-0.158			
	P-value	0.191			

*Student *t*-test. **One-way ANOVA test

Table 7 Relation between patients' data and TMT results among cases

Parameter		**MMSE total**			
Age	Pearson's correlation	0.308			
	p-value	0.009			
		MMSE total		**Test value**	***p*-value**
		Mean	**SD**		
Sex	Male	284.21	64.57	0.41*	0.69
	Female	290.36	58.15		
Marital status	Single	265.18	21.32	11.29**	< 0.001
	Married	291.39	65.63		
	Divorced	480.00	29.70		
	Widowed	304.50	34.65		
Residence	Urban	274.58	21.41	1.68*	0.10
	Rural	301.03	86.84		
Education	Elementary	302.09	89.35	0.52**	0.72
	Preparatory	296.69	75.54		
	High school	269.30	20.80		
	Vocational	288.12	77.67		
	College	278.74	18.21		
Occupation	Working	274.83	43.57	2.40**	0.10
	Not working	306.48	80.71		
	Student	262.00	2.83		
DM	Yes	293.45	73.67	0.58*	0.57
	No	283.96	56.87		
HTN	Yes	278.37	47.43	0.68*	0.50
	No	289.76	66.42		
Smoking	Nonsmoker	287.45	59.95	0.19*	0.85
	Smoker	284.24	68.86		
Type of disease	UC	283.60	57.86	0.66*	0.51
	CD	294.35	71.51		
Type of treatment	Biological	296.37	80.88	0.80*	0.43
	Conventional	283.06	53.42		
Extraintestinal manifestations	No	277.05	43.93	1.96*	0.09
	Yes	351.89	113.57		
		TMT total			
Period of remission (months)	Pearson's correlation	−0.040			
	P-value	0.745			
Duration of disease (months)	Pearson's correlation	0.188			
	P-value	0.119			

*Student *t*-test. **One-way ANOVA test

rural areas had significantly lower MMSE score than those in urban areas (27.6 ± 4) vs (29 ± 1) ($P < 0.03$) (Table 6).

2. Disease-related factors

The presence of extraintestinal manifestations was associated with significantly lower MMSE score with a mean of 24.8 ± 4 versus 29.1 ± 2.5 in those without manifestations ($P = 0.01$). A total of 9 of patients had one or more extraintestinal disease, of whom 5 (55.6%) had arthritis (Table 6).

Discussion

Our results revealed the potential effect of IBD on global cognitive functions. In this study, the 70 IBD patients (50 UC and 20 CD) recorded significantly lower than the healthy controls on the MMSE, where 6 patients (8.6%) had scores less than 24 (denoting mild to moderate cognitive impairment). Also, significantly longer time

was taken to fulfill the TMT test by these cases as compared to healthy controls (32 ± 19.5 versus 23 ± 2.8 for TMT part A and 255 ± 48 versus 234 ± 22.4 s for part B, respectively).

Our results agree with *Rasmus et al. (2016)* whose cohort of 30 IBD patients recorded a mean score of 27 on MMSE, which was lower than that of the healthy controls [17]. Similarly, *Sharma et al.* reported significantly lower cognitive performance in 20 ulcerative colitis patients, on applying MMSE, with a mean of 21.8 ± 3.1, in comparison to healthy controls (mean = 26.9 ± 0.5) (p-value < 0.01) [18]. When *Castaneda et al.* (2013) [19] applied TMT among 34 adolescents with IBD, they found that the time taken was 31.2 ± 8.6 for part A and 74.7 ± 25.3 for part B. Our results were, in part, similar to the aforementioned observations; however, our patient cohort took much longer time to finish part B (255 ± 48). *Castaneda et al.* also concluded that no major cognitive deficits existed in IBD patients which agrees with our findings as none of our patients recorded severe dysfunction measured by MMSE. In our study, the MMSE score of UC cases was 28.6 ± 2.8which was significantly lower than healthy controls (30). CD patients, however, had insignificantly lower MMSE score (28.3 ± 3.7) than the controls ($P = 0.06$). This goes in accordance to *Van Erp et al.*, who compared the cognitive functions of 20 cases with quiescent CD versus healthy controls. They demonstrated an insignificantly lower difference (28.9 ± 1.62 versus 29.65, respectively, $P = 0.87$). Additionally, CD patients did not significantly perform worse on neither part of TMT as compared to controls ($P > 0.05$) [20].

Comparison of cognitive performance between UC and CD patients, similar to our findings, *Tadin Hadjina et al. (2019)* [21] found no significant difference. The aforementioned findings are largely consistent with a recent 16-year longitudinal analysis of the Taiwanese National Health Insurance Research Database, where IBD patients were found to have over 2.5-fold increased risk of developing dementia over 16-year follow-up [22].

In attempt to identify the affected domains in cognitive dysfunction among IBD patients, a meta-analysis concluded that "attention," particularly alertness, and "executive" function, particularly the working memory, were affected the most, suggesting that cognitive impairment could be a potential extraintestinal manifestation of IBD [23]. This was emphasized by studies, which applied different and more complex tests [24].

According to our results, cognitive dysfunction was not related to disease type, duration of illness, or period of remission. This agrees with *Berrill et al.* [25], who, despite not restricting his analysis to IBD patients in remissions, concluded that neither disease type, duration, nor activity affects cognitive function in those patients.

This also goes in accordance with *Golan et al.* [26], who derived that cognitive scores were correlated with the intensity of intestinal disease (activity index), but not with disease duration or past complications. Also, a significant correlation was found between their global cognitive scores and nutritional risk index, independent of depression. They also observed the negative association between serum CRP of patients with CD and memory. This was rationalized by the hypothesis that cognitive dysfunction in CD may be driven and mediated by inflammation-associated cytokines, gaining access to the brain through breaches in the blood brain barrier, which may impede brain function in a potentially reversible way [27].

In our patient cohort, patients with extraintestinal manifestations had lower scores on MMSE and more modest TMT results. On the other hand, it is controversial among studies whether hemoglobin level affects cognitive function in IBD patients. While *Golan et al.* [26] found a significant correlation between Hb levels and better cognitive performance, *Wells et al.*, like our study findings, disagree [28].

As for the patient-related factors, older age, being divorced, and living in rural areas seemed to negatively impact cognitive performance among IBD patients in the current study. Aging generally is associated with deterioration of cognitive function especially tasks responsible for speed of processing, working memory, and executive cognitive function [29]. In our study, patients with cognitive impairment were significantly older than those without; this agrees with *Tadin Hadjina et al.* who found a strong correlation between age and poor cognitive performance in IBD [21].

Previous studies have frequently reported that IBD patients are vulnerable to depression and anxiety disorders, which inherently and independently contribute to cognitive impairments [6, 30, 31], and being divorced might be an additional psychological contributor to the observed cognitive compromise.

Conclusion

Quiescent IBD patients potentially suffer from cognitive impairment, which could be mild to subclinical. IBD patients with subjective cognitive complaints might benefit from brief cognitive screening tools such as MMSE and TMT to provide preliminary discrimination of cognitive deficits. Extraintestinal complications, age, marital status, and living in rural areas might be contributing factors to the observed cognitive impairment. Further studies are needed to assess the effect of other modifiable risk factors, such as anxiety, depression, and nutritional compromise on cognitive impairment in IBD patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43162-024-00304-w.

Supplementary Material 1.

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Authors' contributions
Dr. AAB, Dr. HM, Dr. SA, Dr. RMN, and Dr. SA were responsible for the organization and coordination of the study. Dr. AAB, HM, and Dr. SA were the chief investigators responsible for the data collection, analysis, and interpretation. Dr. AAB, Dr. SA, RMN, and Dr. HM developed the study rationale and design. All authors contributed to the writing of the final manuscript. All members of the study team contributed to the management or administration of the trial.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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