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2013-03-14

Castaneda , A E , Tuulio-Henriksson , A , Aronen , E T , Marttunen , M & Kolho , K-L 2013 , ' Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease ' , World Journal of Gastroenterology , vol. 19 , no. 10 , pp. 1611-1617 . <https://doi.org/10.3748/wjg.v19.i10.1611>

<http://hdl.handle.net/10138/163826>

<https://doi.org/10.3748/wjg.v19.i10.1611>

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Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease

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Supported by Foundation of Päivikki and Sakari Sohlberg, the Emil Aaltonen Foundation, the Foundation for Pediatric Research, the Helsinki University Central Hospital Research Fund, and the Academy of Finland

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Received: October 15, 2012 Revised: December 12, 2012

Accepted: December 15, 2012

Published online: March 14, 2013

sive symptoms in adolescents with inflammatory bowel disease (IBD).

METHODS: A neuropsychological test battery, including subtests of the Wechsler Adult Intelligence Scale-Revised and III, Wechsler Memory Scale-Revised, California Verbal Learning Test (CVLT), Stroop Color-Word Test, and Trail Making Test, which assessed verbal and visual short- and long-term memory, processing speed, logical reasoning, verbal intelligence, attention, and executive functioning, was administered to 13- to 19-year-old patients with IBD ($n = 34$; active disease $n = 20$). Depressive symptoms were measured with the Beck Depression Inventory. The findings were compared with peers with non-acute juvenile idiopathic arthritis (JIA; $n = 23$). Patients with coexisting psychiatric disorders were excluded.

RESULTS: The IBD group, especially patients in the acute phase, made more perseverative errors in the CVLT test that assessed verbal memory than the JIA group (6.0 ± 4.3 vs 3.3 ± 2.9 , $P < 0.01$), but no other differences between the IBD and JIA groups were observed in the neuropsychological tests. The difference was close to statistical significance, even when glucocorticoid medication was controlled for ($P < 0.052$). The IBD group had more depressive symptoms than the JIA group (7.9 ± 7.6 vs 4.0 ± 4.0 , $P < 0.05$). Approximately one third of the IBD group had at least mild depressive symptoms, and those with acute illness had the highest scores. However, depressive symptoms were not related to the difference in the verbal memory test (perseverative errors in the CVLT) between the IBD and JIA groups.

CONCLUSION: Adolescents with acute IBD may have mild verbal memory problems but no major cognitive deficits compared to peers with JIA.

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Key words: Cognitive impairment; Inflammatory bowel

Abstract

AIM: To investigate cognitive functioning and depres-

disease; Crohn's disease; Depressive symptoms; Ulcerative colitis; Adolescents

Castaneda AE, Tuulio-Henriksson A, Aronen ET, Marttunen M, Kolho KL. Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease. *World J Gastroenterol* 2013; 19(10): 1611-1617 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i10/1611.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i10.1611>

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic life-long disease comprising Crohn's disease, ulcerative colitis and unclassified colitis that may appear at any age. The incidence of IBD among adolescents is increasing^[1-3], and thus, it is important to study the possible burden of the disease on the everyday life of the patients. According to parent reports, adolescents with IBD have more emotional, social, and thought problems and lower competence than their healthy peers^[4]. The disease affects the quality of life of adolescents^[5-7], may have negative consequences on education and school functioning^[8,9], and may cause higher unemployment later in life^[10-13]. Furthermore, adolescents with severe IBD have disturbed sleep and are overtired more often than their healthy peers^[14]. However, research on cognitive dysfunction, which refers to deficits in cognitive information processing, is scarce in patients suffering from IBD.

Two prior studies^[15,16] on adults found some cognitive difficulties among patients with IBD. Attree and co-authors^[15] reported poorer performance in a test measuring verbal functioning in adults with IBD compared to healthy controls. There were, however, no differences in tests assessing attention and mental speed. The other study^[16] also showed that adults with IBD had a decrease in verbal functioning compared with healthy controls and that this was unlikely to be due to premorbid levels of intellectual functioning. Thus, like many other chronic illnesses, IBD seems to be accompanied by some cognitive deficits among adults. However, there are no studies on cognitive functioning among adolescent patients with IBD. In addition, it is not known whether the phase of the illness is associated with cognitive functioning. Given that this disorder often begins in adolescence, it is important to examine whether the illness has an impact on cognitive development and, consequently, the performance of young patients at school.

Depressive symptoms are common among adults^[17] and adolescents with IBD^[18-20]. Depression may also be associated with cognitive impairments^[21,22]. In particular, early-onset depression may be related to deficits in attention, memory, and executive functioning^[23,24]. Depressive symptoms in adolescence might be associated with serious and long-lasting psychosocial difficulties, such as problems in education and work^[25], and cognitive impairments in adolescence and early adulthood may also

complicate school performance and affect successful psychosocial development. Therefore, adolescence is a key period for both the recognition and treatment of mental health and cognitive problems associated with somatic illnesses to avoid long-term sequelae in several areas of psychosocial functioning. Taken together, more studies are needed on illness-related psychosocial and cognitive correlates to improve the care and assessment of young IBD patients.

The main aim of the present study was to examine cognitive functioning among adolescent patients with IBD and investigate whether disease activity or depressive symptoms were associated with cognitive functioning. As a clinical comparison group, an adolescent patient group with minor symptoms of a chronic disease, juvenile idiopathic arthritis (JIA) in the non-acute phase, was included. It was hypothesized that IBD would be related to difficulties in cognitive functioning, especially in verbal functions and that these difficulties would be more pronounced in the acute phase of the disorder.

MATERIALS AND METHODS

Participants

The study groups were enrolled during May 2008-March 2009 at the Hospital for Children and Adolescents, Helsinki, Finland. Consecutive IBD patients aged 13 years or older were invited to participate in the study along with their routine outpatient visits. Likewise, consecutive non-acute JIA patients of the same age group, followed-up at the same outpatient facilities, were invited to participate to represent a control group with non-acute chronic illness (identical recruitment procedure). Patients with coexisting psychiatric, neurological, or developmental disorders (based on hospital case records and information from the patients and their parents) were excluded. All patients were native Finnish speakers and attended regular school, and none had particularly poor school performance (based on self-reports). There were 17 decliners (IBD $n = 8$, JIA $n = 9$). The decliners did not differ from those who participated in age, gender, or severity of the disorder, and the reason for refusal was mainly lack of time. One participant underwent the procedure but was excluded later because of previously diagnosed neuropsychological difficulties and special education at school. None of the included patients had major learning disabilities, but one patient with IBD self-reported as being diagnosed with minor dyslexia in secondary school, with the problems overcome. The final study sample consisted of 34 IBD patients aged 13 to 19 years (ulcerative colitis $n = 16$, Crohn's disease $n = 17$, and unclassified colitis $n = 1$) and 23 JIA patients aged 14-19 years (Table 1). Most patients were full-time students, and only two persons were employees. Current medication included 5-aminosalicylic acid ($n = 26$), azathioprine ($n = 11$), glucocorticoids ($n = 17$), and antibiotics ($n = 3$) in the IBD group and methotrexate ($n = 11$), anti-tumor necrosis factor- α agent ($n = 4$), chloroquine ($n = 4$), and hydroxychloroquine ($n = 4$) in the JIA group.

Table 1 Background data of the study groups

	IBD (<i>n</i> = 34)		JIA (<i>n</i> = 23)	
Age (yr)	16.3 ± 1.7	13.6-19.7	15.5 ± 1.2	14.0-18.6
Age at receiving the diagnosis (yr)	12.7 ± 3.5	2.0-16.7	9.0 ± 4.6	1.3-15.0
Gender (female)	15 (44)		14 (61)	
Socioeconomic status ¹				
Class I	10 (32)		11 (50)	
Class II	9 (29)		3 (14)	
Class III	12 (39)		7 (32)	
Class IV	0 (0)		1 (5)	
State (acute)	20 (59)		0 (0)	
Disease duration				
Less than one year	6 (18)		2 (9)	
One to two years	10 (29)		1 (4)	
More than two years	18 (53)		20 (87)	

¹Data missing for three inflammatory bowel disease (IBD) and one juvenile idiopathic arthritis (JIA) patients. Data are expressed as absolute *n* (%) or mean ± SD.

= 1), leflunomide (*n* = 1), and sulfasalazine (*n* = 1) in the JIA group. Three patients with Crohn's disease had undergone surgery more than six months prior to the neuropsychological examination. None of the patients had current psychotropic medication or ongoing psychiatric treatments. The study was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa, and it conformed to the provisions of the Declaration of Helsinki and its amendments. Written informed consent was obtained after a complete description of the study from each examined patient or a parent when the examinee was under 18 years of age.

Socioeconomic status

The socioeconomic status of the adolescent's family was classified according to Helsinki City socioeconomic statistics: class I included persons with an academic degree, business managers, and professionals (*e.g.*, engineers); class II included administrative personnel, owners of small businesses, and minor professionals (*e.g.*, graduate nurse); class III included skilled manual employees (*e.g.*, laboratory assistant); and class IV included unskilled employees (*e.g.*, domestic maid). This grading is adapted nationally and comparable to international classification^[26]. The higher socioeconomic class of the parents was considered to be the socioeconomic class of the family (Table 1).

Clinical evaluation

The activity of IBD was based on the clinical evaluation of experienced clinicians (Physician's Global Assessment) and inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein, and fecal calprotectin, with values < 100 µg/g of stool considered normal and values >1000 µg/g considered exceedingly high]^[27]. The disease activity in JIA was based on the child health assessment questionnaire and clinical evaluation by a pediatric rheumatologist.

On the day of the neuropsychological assessment,

patients also completed a questionnaire in the Finnish language gathering information on depressive symptoms and background factors. Depressive symptoms were measured with the Beck Depression Inventory (BDI)^[28]. The BDI is a 21-item questionnaire in which the items are answered using a 4-point rating scale ranging from 0 to 3. High scores indicate a high level of depressive symptoms. The total score was calculated and used in the statistical analyses. Additionally, the BDI total score was categorized into four classes by classifying scores from 0 to 9 as no symptoms, 10 to 18 as mild symptoms, 19 to 29 as moderate symptoms, and 30 to 63 as severe symptoms. Five patients had one missing value in the BDI, which was replaced by their individual item mean scores of the BDI. The patients also completed an in-house questionnaire with questions on school performance, subjective view of learning difficulties, sick leave, employment, and parental professions.

Neuropsychological examination

The neuropsychological examination was conducted individually by a psychologist blinded to the presence of diagnosis or disease activity prior to the examination. The examination took place in one session of approximately one hour. The neuropsychological test battery, including Finnish versions of internationally used, validated test methods administered in a fixed order, was selected to allow for the comparison of verbal and visual short-term memory, verbal long-term memory and learning, attention, logical reasoning and social insight, psychomotor processing speed, and executive functioning between the study samples. Because the cognitive functioning of adolescents with IBD has not been previously investigated, the tests were chosen to evaluate a wide range of neuropsychological functions instead of focusing on only some specific functions. Tests were scored according to standardized procedures by the examiner.

Auditory attention and verbal working memory were assessed with the Digit Span Forward and Backward subtests, respectively, of the Wechsler Memory Scale, Revised^[29] (WMS-R). Visual attention and working memory were measured with the Visual Span Forward and Backward subtests, respectively, of the WMS-R^[29]. Visuo-motor performance and processing speed were assessed with the Digit Symbol subtest of the Wechsler Adult Intelligence Scale, Revised^[30] (WAIS-R). General verbal intelligence was estimated with the Vocabulary subtest of the WAIS-R^[30], and logical reasoning and social insight were assessed with the Picture Arrangement subtest of the WAIS-III^[31]. The Stroop Color-Word Test^[32] (Golden), given in three parts, was administered to evaluate executive functioning, and the interference score was calculated and used in the analysis. The Trail Making Test^[33] (TMT), given in two parts, was administered to evaluate attentive and executive functioning. Part A measures visuo-spatial attention and performance speed, whereas Part B requires mental flexibility, ability to shift attention,

and strategy. Possible errors made by the examinee were not corrected by the examiner. The time to complete Parts A and B and the difference in score between B and A (the executive aspect of the task when the speed component is removed) were used in the statistical analysis. The California Verbal Learning Test^[34] (CVLT), in which the examinee is required to learn a 16-item word list over five trials and recall and/or recognize it after short and long delays, was used to measure various aspects of verbal learning and memory. The following variables of the CVLT were included in the statistical analyses: Total Recall from trials 1-5 (learning performance), Short-Delay Free Recall (short delay memory performance), Long-Delay Free Recall (long delay memory performance), Discriminability (recognition memory taking into account both hits and false positives), Perseverative Repetition Errors, Intrusion Errors, Semantic Clustering (the use of an active learning strategy of reorganizing target words into categorical groups), and Learning Slope (the increase in recalled words per trial over trials 1-5). Higher scores indicate better performance in all tests, except in the Stroop test, TMT and Perseverative and Intrusive Errors of the CVLT.

Three IBD patients had missing values in neuropsychological tests: the Stroop test performance of two patients was excluded due to red-green color blindness. One patient had distractions during the testing situation, and therefore, the results of the Picture Arrangement and the Stroop test were considered invalid in this case.

Statistical analysis

Pearson's χ^2 test was used to compare differences in gender, a one-way analysis of variance (ANOVA) was used to compare differences in age, and a two-tailed Mann-Whitney test was used to compare differences in the socioeconomic status of the adolescent's family between the study groups.

Neuropsychological test scores were compared between the IBD and JIA groups with a univariate ANOVA. The main group comparisons were performed separately for each test score as a dependent variable, with group membership as an independent variable and gender as an additional independent variable to adjust for gender effects. Neuropsychological test performance was also compared between subgroups of active and non-active IBD groups and the JIA group with Bonferroni's *post hoc* test. To adjust for the effects of glucocorticoids, group comparisons of neuropsychological functioning were conducted when this medication (yes *vs* no) was treated as an additional independent variable.

Depressive symptoms were compared between the groups with ANOVA. ANOVAs with *post hoc* tests, corrected for multiple testing with the Bonferroni correction, were also used to compare depressive symptoms between the subgroups of active and non-active IBD patients and the JIA group. Linear regression models were used to predict depression score by age or gender. In addition, to adjust for the effects of depressive symptoms

on neuropsychological test performance, these group comparisons were also conducted with the continuous BDI score as an additional covariate factor.

All analyses were conducted with SPSS 16.0 software, and a *P* value < 0.05 was defined as indicating a statistically significant result throughout the study. Raw test scores were used. Scores that were not normally distributed were log (TMT: A, B, B-A; CVLT: Perseverations, Intrusions) or cube (CVLT: Discriminability) transformed.

RESULTS

The IBD and JIA groups did not differ in age ($F = 3.210$, $\nu = 1, 55$, $P = 0.079$), gender ($\chi^2 = 1.540$, $\nu = 1$, $P = 0.215$), or socioeconomic status of the family ($U = 304.500$, $P = 0.483$). Among IBD patients with the acute state ($n = 20$), the median ESR was 19 mm/h (range from 3 to 53 mm/h), fecal calprotectin was 870 $\mu\text{g/g}$ (range from 101 to 3130 $\mu\text{g/g}$), and 14 of the 20 patients were on glucocorticoids. The respective figures for IBD patients with quiescent disease ($n = 14$) were 4 mm/h for ESR (from 1 to 28 mm/h), 183 $\mu\text{g/g}$ for fecal calprotectin (from 150 to 505 $\mu\text{g/g}$) and three on low-dose glucocorticoids.

The only statistically significant difference in the neuropsychological test performance between the groups appeared in Perseverative Repetition Errors of the CVLT, with the IBD group performing poorer than the JIA group (Table 2). When the subgroups of active and non-active IBD patients were compared with each other and the JIA group, the only difference was again in Perseveration Errors ($F = 5.150$, $\nu = 2, 51$, $P = 0.009$), with the acute IBD group performing poorer than the JIA group ($P = 0.027$; other data not shown). When glucocorticoid medication was treated as an additional independent variable, the difference in Perseveration Errors was close to the level of statistical significance ($F = 3.948$, $\nu = 1, 51$, $P = 0.052$; other data not shown).

The IBD group had scores suggesting more depressive symptoms than the JIA group (mean \pm SD, IBD: 7.9 ± 7.6 , JIA: 4.0 ± 4.0 ; $F = 5.046$, $\nu = 1, 55$, $P = 0.029$), especially IBD patients in the active disease phase ($F = 3.966$, $\nu = 2, 54$, $P = 0.025$; active IBD *vs* JIA $P = 0.022$). In the IBD group, 24% had scores suggesting mild depressive symptoms (half of the patients were in the active and half in the non-active state), and 9% had scores suggesting moderate or severe depressive symptoms (all in the active state). In the JIA group, 9% had scores for mild depressive symptoms, while none had moderate or severe symptoms. None of the patients reported suicidal ideation or suicidal behavior in the BDI. The depression score was not predicted by age ($\beta = 0.247$, $\nu = 1, 55$, $P = 0.064$) or gender ($F = 2.766$, $\nu = 1, 55$, $P = 0.102$).

When the BDI score was set as a covariate in the group comparisons of the neuropsychological data, the difference in Perseveration Errors remained significant between the study groups ($F = 4.591$, $\nu = 1, 52$, $P = 0.004$), and no other differences between the groups emerged (data not shown).

Table 2 Neuropsychological test results (row scores) in the study groups

	IBD (<i>n</i> = 34)	JIA (<i>n</i> = 23)	IBD vs JIA		
			<i>F</i> ¹	<i>ν</i>	<i>P</i> value
Attention					
WMS-R: Digit span forward	7.3 ± 1.4	7.0 ± 1.8	0.866	1, 53	0.356
WMS-R: Visual span forward	8.3 ± 1.6	8.5 ± 2.0	0.054	1, 53	0.817
TMT: A (time)	31.2 ± 8.6	31.0 ± 8.6	0.000	1, 53	0.989
Executive functioning					
TMT: B (time)	74.7 ± 25.3	66.4 ± 15.0	0.812	1, 53	0.372
TMT: B-A (time)	43.6 ± 22.1	35.3 ± 14.0	0.986	1, 53	0.325
Stroop: Interference score (time)	56.5 ± 13.9	57.9 ± 19.5	0.190	1, 50	0.665
Working memory					
WMS-R: Digit span backward	6.3 ± 1.7	6.1 ± 1.5	0.596	1, 53	0.444
WMS-R: Visual span backward	8.7 ± 1.3	8.3 ± 1.3	1.218	1, 53	0.275
Processing speed					
WAIS-R: Digit symbol	55.3 ± 10.0	56.7 ± 9.7	0.001	1, 53	0.970
Basic ability					
WAIS-R: Vocabulary	39.7 ± 9.7	40.6 ± 10.4	0.049 ²	1, 53	0.826
Logical reasoning/social insight					
WAIS-III: Picture arrangement	13.4 ± 4.0	12.9 ± 4.2	0.277	1, 52	0.601
Verbal learning and memory					
CVLT: Total recall of trials 1-5	55.3 ± 8.7	56.8 ± 8.3	0.009	1, 53	0.925
CVLT: Short-delay free recall	11.7 ± 2.9	11.4 ± 3.1	0.250 ²	1, 53	0.619
CVLT: Long-delay free recall	12.3 ± 2.5	12.5 ± 2.3	0.010	1, 53	0.920
CVLT: Discriminability	1.0 ± 0.0	1.0 ± 0.0	0.280	1, 53	0.599
CVLT: Perseverative errors	6.0 ± 4.3	3.3 ± 2.9	8.249	1, 53	0.006
CVLT: Intrusion errors	2.8 ± 3.4	2.0 ± 2.8	0.527	1, 53	0.471
CVLT: Semantic clustering	1.8 ± 0.7	1.7 ± 0.7	0.168	1, 53	0.683
CVLT: Learning slope	1.3 ± 0.3	1.2 ± 0.5	0.346 ²	1, 53	0.559

¹A one-way analysis of variance (group and gender as independent factors); ²Levene's test of equality of error variances $P < 0.05$. IBD: Inflammatory bowel disease; JIA: Juvenile idiopathic arthritis; WMS-R: Wechsler Memory Scale-Revised; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WAIS-R: Wechsler Adult Intelligence Scale-Revised; TMT: Trail Making Test; CVLT: California Verbal Learning Test.

DISCUSSION

To our knowledge, this is the first study that describes cognitive functioning in adolescent patients with IBD. We found only minor impairments in the verbal memory test, in which IBD patients, particularly in the acute phase, produced more perseverative errors than patients with non-acute JIA. Perseveration in the CVLT test may be related to a momentary loss of alertness in the tiresome and long verbal memory test. However, no other differences in cognitive functioning between the study groups were detected. These findings indicate that adolescents with active IBD may have some mild problems in verbal memory but no major cognitive deficits. The two prior studies in adults with IBD found deficits, particularly in verbal functioning^[15,16], suggesting that in the clinical evaluation of young patients with IBD, it may be relevant to pay attention to even minor cognitive problems that may be aggravated in the process of growing up.

Depressive symptoms were measured using the BDI on the same day as the neuropsychological examination. Adolescents with IBD, especially those in the acute phase of the illness, may more commonly have depressive symptoms compared with peers with mild disease or non-acute JIA. Approximately one third of the IBD patients had scores indicative of at least mild depres-

sive symptoms, and some of those with acute illness scored for moderate or severe symptoms. This finding is noteworthy, as in non-acute JIA, no patients reported moderate or severe depressive symptoms, and less than one out of ten reported mild symptoms. In line with our results, previous studies have described depressive symptoms among young patients with IBD^[18-20]. Although the minor impairment in the verbal memory test in IBD patients was not explained by the severity of depressive symptoms, depressed mood may have other severe and long-lasting consequences for the psychosocial functioning of these patients.

One limitation of the present study is the lack of a healthy control group, which potentially weakens the generalization of the findings. The patient control group was chosen to represent adolescents with similar life surroundings (chronic disorder with inflammatory pathology) but with less severe health problems that have not been found to be related to cognitive deficits^[35]. The strength of the present study is that the JIA patients underwent exactly the same procedure as the IBD group in the outpatient clinic of the same hospital during the same time period and with the same examiners, who were blinded to patient data. Furthermore, the patient groups did not differ in age or gender. There was no major attrition of participants that could limit the interpretation of the results; however, the sample

sizes were still relatively small. Another limitation is that there may be some potential confounders, such as sleep disturbances or acute stressful life events, *e.g.*, divorce of parents, that should be taken into account. In the IBD group, the majority (70%) of the patients in the acute state were on glucocorticoids, which may affect cognitive functioning^[36]. Unfortunately, the total exposure time of glucocorticoids was not available. However, it is unlikely that the only reason for the minor problem in the verbal memory test was glucocorticoids because the group difference between the IBD and JIA patients remained close to the level of statistical significance when glucocorticoid medication was adjusted for in the statistical analyses. Furthermore, in active IBD, patients need either glucocorticoids or other immunosuppressive therapy, and it would be unethical to decline these medications for study purposes. Thus, studying treatment-naïve patients with active IBD is challenging.

Taken together, this is the first study that investigates cognitive functioning in adolescents with IBD. The results indicate that young patients with IBD, especially in the acute state of the disease, may have some problems in verbal memory, particularly when assessed with a test requiring alertness in a tiresome context. However, no major cognitive deficits among young patients with IBD were found compared to peers with JIA. The clinical significance of this finding and its possible impact on school performance, is unclear, warranting further studies. Likewise, the relation of cognitive functioning to medication and disease-related factors, such as sleep disturbances or depression, needs to be assessed in larger study samples. In particular, longitudinal studies on disease activity and cognitive functioning related to psychosocial functioning are warranted in adolescents with IBD.

ACKNOWLEDGMENTS

The authors thank all study participants, Anne Nikkonen RN for recruiting the patients, and MPsych Hannamari Heino for assisting in the neuropsychological data collection.

COMMENTS

Background

The incidence of inflammatory bowel disease (IBD) among adolescents is increasing, and therefore, it is important to study its possible burden on patients' everyday life. However, research on cognitive functioning has been scarce in IBD, especially among adolescents.

Research frontiers

It is important to examine whether IBD has an impact on cognitive development and possibly consequently on the performance of young patients at school and everyday life.

Innovations and breakthroughs

Cognitive functioning in IBD has previously been investigated in only two studies, which both found some cognitive deficits relating to IBD, but both studies were conducted in adults. There are no studies investigating cognitive functioning in adolescents with IBD. This study shows that adolescents with acute IBD may have mild verbal memory problems but no major cognitive deficits.

Applications

In the clinical evaluation of young patients with IBD, it may be relevant to pay attention to even minor cognitive problems that may be aggravated in the process of growing up and affect school performance.

Terminology

Cognitive functioning refers to functions of cognitive information processing, such as memory, attention, concentration, processing speed, and executive functions.

Peer review

The present study includes an interesting research question with an original design. The authors utilize numerous neuropsychological tests to assess cognition from various perspectives.

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