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Mini Review

Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder in Children with Inflammatory Bowel Disease

Hasret Ayyıldız Civan[1]* and Gonca Bektaş[2]

[1]Department of Gastroenterology, Hepatology and Nutrition, Turkey

[2]Department of Pediatric Neurology, Training and Research Hospital, Turkey

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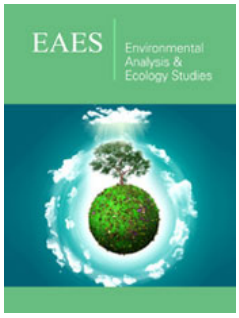

***Corresponding author:** Hasret Ayyildiz Civan, Department of Gastroenterology, Hepatology and Nutrition, Bakırköy, Turkey

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Abstract

Objective: Inflammatory Bowel Diseases (IBD) are accompanied by some psychiatric disturbances some of which are suggested to have a common pathophysiological pathway related to the intestinal malfunction, The goal of the study was to evaluate the presence of symptoms associated with Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD) in children with IBD and to investigate the relation of symptoms to their clinical features.

Methods: A total of 42 children with IBD, either ulcerative colitis or Crohn disease and 45 healthy controls were included. Demographic features, the duration of the IBD and currently used medications were recorded. The Social Communication Questionnaire (SCQ) and Turgay DSM-IV Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S) were employed for ASD and ADHD related symptoms.

Result: The mean total SCQ score, the SCQ reciprocal social interaction score, and the SCQ communication score were significantly higher in children with IBD indicating an increased likelihood for ASD whereas total T-DSM-IV-S and subscale scores for hyperactivity- impulsivity and inattention were not statistically different between groups. However, 4 patients with IBD (10%) presented an increased likelihood for ADHD with more positive items whereas none of the healthy controls presented an increased likelihood for ADHD. Conclusion: Children with IBD may have a higher risk of having ASD and ADHD without regard to the age, age at disease onset and the duration of IBD. Young patients with IBD should be assessed in terms of neurodevelopmental disorders.

Keywords: Inflammatory bowel diseases; Autism spectrum disorder; Attention deficit/hyperactivity disorder; ADHD

Introduction

Inflammatory Bowel Diseases (IBD) are a group of immune-mediated disorders involving Crohn disease, ulcerative colitis and indeterminate colitis. Although not particularly an etiology of mortality, IBD are associated with significant morbidity and impact on the quality of life. Thromboembolism, malignancies, hepatobiliary disorders, decrease or increase in the diversity of bacteria in the gut, arthropathies and high levels of psychological stress are among those morbidities and related complications. Considering the extra-intestinal manifestations of IBD, those involving the psychiatric pathologies are relatively rare.

Attention-Deficit/Hyperactivity Disorder (ADHD), on the other hand, is a clinical entity marked by a continuous pattern of inattention and/or hyperactivity-impulsivity that restrains functioning or development, whereas Autism Spectrum Disorder (ASD) is a developmental issue that disrupt communication and behavior. Both ADHD and ASD may

be associated by gastrointestinal symptoms or complications. Evidence from the current literature suggests a combination of changes in gut microflora, intestinal permeability, inappropriate immune response, activation of specific metabolic pathways, and behavioral changes in genetically predisposed individuals, which notes multiple intersection points of IBD and psychiatric issues [1].

The aims of this study were to evaluate the presence of symptoms associated with ASD and ADHD in children with IBD, and to investigate whether there is an association of these symptoms to the clinical features of the children with IBD.

Methods

This was a single-center prospective case-control study including children with IBD followed-up by the pediatric gastroenterology outpatient clinic at the Bakirkoy Dr. Sadi Konuk Research and Training Hospital from February 1st, 2019 to August 1st, 2019.

Participants

The inclusion criteria were as follows; children with IBD, either ulcerative colitis or Crohn disease, and aged 6-18 years. The IBD was diagnosed according to ESPGHAN revised Porto criteria [1]. Children with a preexisting neurological or psychiatric disorder were excluded from the study. Healthy subjects matched by age, sex, and socioeconomic status constituted the control group.

The study was reviewed and approved by the Institutional Ethics Committee at the Bakirkoy Dr. Sadi Konuk Research and Training Hospital. All participants were asked for assent and their legal representatives provided written informed consent.

Clinical data and neuropsychological assessment

Demographic features, the duration of the IBD, and the currently used medications were abstracted from medical records. All participants were evaluated by standardized assessment batteries completed by parents or caregivers. The Social Communication Questionnaire (SCQ) and Turgay DSM-IV Disruptive Behavior Disorders Rating Scale (T- DSM-IV-S) were the used instruments to assess ASD and ADHD related symptoms.

The features of ASD were screened utilizing SCQ based on 3 subscales; reciprocal social interaction, communication, and restricted, repetitive, stereotyped patterns of behavior. SCQ, a 40-item questionnaire, was reported as a reliable and valid tool for children aged 4 to 18 years [2-4]. The score of each item ranges 0 to 1 and the total scores range between from 0 to 39. The total score above the threshold of 15 represents a likelihood of ASD. T-DSM-IV-S is an instrument that evaluates the ADHD symptoms. It has four subscales including hyperactivity/impulsivity, inattention, opposition-defiance, and conduct disorder. T-DSM-IV-S is a reliable and valid tool to measure ADHD related symptoms [5,6]. Hyperactivity-impulsivity (9 items), inattention (9 items) and total ADHD (18 items) scores were examined in our analyses. Each item was scored based on the severity of symptom from 0 to 3 points, in which higher scores representing more psychopathology. Also, each item was defined as positive if scored as 2 or 3, and negative if scored as 0 or 1. ADHD type was classified based on the number of positive items of hyperactivity-impulsivity or inattention, which requires more than 5 positive items.

Statistical analysis

All statistical analyses were applied using SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). The distribution of variables was determined by Kolmogorov-Smirnov test. Demographic features and the scores of instruments were assessed using independent samples t-tests in case of normality and homogeneity of variances, or Mann-Whitney U-tests otherwise. The value of $p < 0.05$ was accepted as statistically significant.

Result

Demographic and clinical characteristics

A total of 87 children, 42 children with IBD and 45 healthy controls, were evaluated. The patient group included 26boys and 16girls with a ratio of 1:1.6, indicating slightly male predominance. The mean age of patients was 14.1±3.1 (range 7.2-17.2 years) with an age at disease onset of 12.5±3.8 years (range 3-17 years). The mean duration of disease was 19.9±22.3 months (range 2-120 months).

The overall 42 patients with IBD consisted of 31 (18 males) patients with ulcerative colitis and 11 (8 males) patients with Crohn disease. The currently used medications of children with IBD were amino-salicylates in 41 patients (97,6 %); corticosteroids in 4 (9,5%),immune modifying agents in 14(33,3%), and biologic agents (adalimumab, infliximab) in 2(4,8%). The demographic and clinical characteristics of participants are provided in Table 1.

Table 1: Demographic and clinical features of children with inflammatory bowel disease.

Patients with Inflammatory Bowel Disease		
n		42
Sex (male to female)		26/16
Age (years)	Mean	14.1 ± 3.1
	Range	7.2-17.2

Age at diagnosis (years)	Mean	12.5 ± 3.8
	Range	3 to 17
Duration of disease (months)	Mean	19.9 ± 22.3
	Range	2-120
Current Medications		
Amino-salicylates, n (%)		41 (97,6)
Corticosteroids, n (%)		4(9,5)
Immune modifying agents, n (%)		14(33,3)
Biologic agents, n (%)		2(4,8)

Neuropsychological assessment

All participants were evaluated using both the SCQ and T-DSM-IV-S. The mean total SCQ score, the SCQ reciprocal social interaction score, and the SCQ communication score were significantly higher in children with IBD compared to healthy controls (p=0.002, p=0.001, p<0.001, respectively) (Figure 1). There was no significant difference observed between two groups in terms of the SCQ restricted interests score (p=0.57). Eight patients (19%) among patients with IBD versus 1 child (2%) in the control group exhibited a score above the cut-off value, indicating an increased likelihood for ASD.

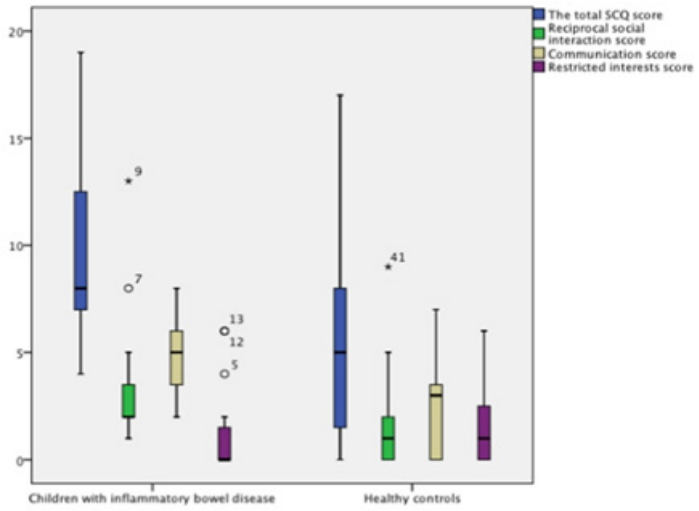

Figure 1: Box plots for reciprocal social interaction, communication score, restricted interests score, and total SCQ score in children with inflammatory bowel disease and healthy controls.

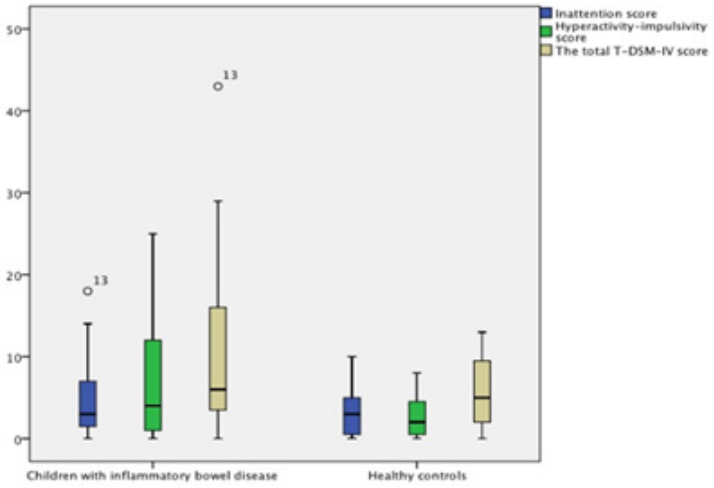

Figure 2: Box plots for inattention, hyperactivity-impulsivity scores and total T-DSM-IV score in children with inflammatory bowel disease and healthy controls.

The total T-DSM-IV-S score and subscale scores for hyperactivity-impulsivity and inattention were not statistically different between patients with IBD and healthy controls (p=0.097, p=0.17, p=0.91, respectively) (Figure 2). The number of positive items for hyperactivity-impulsivity and inattention were significantly different between patients with IBD and healthy controls (p=0.018, p=0.04, respectively). A total of 4 patients with IBD (10%) presented an increased likelihood for ADHD (1 patient for the hyperactivity- impulsivity type and the remaining for the mixed type), whereas none of the healthy controls presented an increased likelihood for ADHD.

We observed no correlation between the SDQ and T-DSM-IV-S scores and clinical variables including the age, the age at disease onset, disease duration (p>0.05).

Discussion

In our study, children with IBD presented an increased likelihood of ASD and ADHD related symptoms compared to healthy controls. In terms of ASD, the reciprocal social interaction and communication more likely impaired in children with IBD than healthy children, whereas restricted interests were similar between both groups. Also, children with IBD were more prone to exhibit symptoms of hyperactivity-impulsivity and inattention than healthy children.

The prevalence of ADHD ranges from 1.4% to 3.4% in the general population, depending on the diagnostic approach [7,8]. Overall, among children with IBD, the risk of having ADHD was 10%, which was more than the general population and healthy controls. The relationship between ADHD and IBD has been previously defined in a study with a large sample size, which indicates a 1.2-fold increase in the risk of ADHD in children with IBD [9]. ADHD has been related to multifactorial pathogenic mechanisms including genetics and environmental factors [10]. It has been suggested that the increase in dopamine precursors related to altered gut microbiome functions may lead to the core symptoms of ADHD [11]. This observation may clarify the increased likelihood of ADHD in children with IBD.

In our study, ASD related symptoms were more common in children with IBD than healthy children, in line with previous studies showing a 1.4-fold increased risk [12]. The underlying pathogenic mechanism for ASD is defined as multifactorial. Besides genetic factors, it has been suggested that inflammation and immunity, triggered by the impaired intestinal barrier, may play a role in the pathogenesis of the disease [13]. On the other side, it has been notified the epithelial barrier genes showed altered functions in the active state of IBD [14]. Therefore, the proposed brain-gut-microbiome axis may be responsible for the association between IBD and ASD.

The pediatric IBD population was reported to have a higher frequency of poor adherence to oral drugs, namely immunomodulators and mesalamine [15]. Additionally, in case of ASD, where children may have challenging attitudes and noncompliance to therapies, adalimumab or certolizumab may have been preferred as they are administered with subcutaneous injections and thus more effective in terms of compliance and feasibility, and not necessarily associated with inherent severity. In our study, however, two of the cases were taking biologic agents which had been initiated for juvenile idiopathic arthritis. Thus, oral medications were well tolerated with good compliance in our study population.

Our study has some limitations. Firstly, the small sample size and the lack of confirmatory evaluation to diagnose ASD and ADHD are significant. Secondly, the correlation of the IBD activity index to the scores of screening tools for ASD and ADHD may help to improve the understanding of the association of these disorders. It has been reported that uninflamed mucosa represents normal intestinal barrier gene levels [14]. Therefore, to compare the presence of ASD and ADHD related symptoms between the active state of disease and following disease control may be valuable.

In conclusion, our results showed that children with IBD may have an increased risk of having ASD and ADHD irrespective of the age, age at disease onset and the duration of IBD. All children with IBD should be monitored for the neuro-developmental disorders.

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