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Association of Attention-Deficit/Hyperactivity Disorder and Celiac Disease: A Brief Report

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Abstract

Objective:

A possible association of celiac disease with psychiatric and psychological disturbances such as attention-deficit/hyperactivity disorder (ADHD) has been reported repeatedly. The objective of this study was to observe whether a gluten-free diet could alleviate the behavioral symptoms in patients with celiac disease and ADHD.

Method:

Sixty-seven subjects aged 7 to 42 years (mean = 11.4 years) with ADHD were enrolled in the study in South Tyrol, Italy, from 2004 to 2008. Hypescheme, an operational criteria checklist that incorporates *DSM-IV* and *ICD-10* criteria, was used to assess ADHD-like symptomatology. Additionally, blood serum levels of all subjects were assessed for possible celiac disease by examining antigliadine and antiendomysium antibodies. A gluten-free diet was initiated for at least 6 months in celiac disease–positive patients with ADHD.

Results:

Of the 67 patients with ADHD, 10 were positive for celiac disease. After initiation of the gluten-free diet, patients or their parents reported a significant improvement in their behavior and functioning compared to the period before celiac diagnosis and treatment, which was evident in the overall mean score on the Hypescheme questionnaire ($t = 4.22$, $P = .023$).

Conclusions:

Celiac disease is markedly overrepresented among patients presenting with ADHD. A gluten-free diet significantly improved ADHD symptoms in patients with celiac disease in this study. The results further suggest that celiac disease should be included in the ADHD symptom checklist.

The diagnosis of celiac disease, a destructive inflammatory disease of the mucosa of the upper small intestine resulting from gluten ingestion in genetically susceptible individuals, is based on demonstration of a more or less pronounced villus atrophy in a jejunal biopsy.[1,2] Therapy for celiac disease consists of permanently excluding gluten from the diet and allows for total healing of the mucosal lesion.

Since the early 1980s, it has become evident that celiac disease is underdiagnosed.[1–5] In young Italians aged 6–15 years, the overall prevalence of celiac disease was 1 in 184, as screened by combined

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determination of serum immunoglobulin G (IgG) and IgA antigliadine antibody test.[3] Among healthy Finnish adults, the prevalence was as high as 1 in 130 using IgA antiendomysium antibody determination.[4] Presentation with minor symptoms, such as irritable bowel syndrome, anemia, slight weight loss, and fatigue, has become increasingly common, and, in many cases, the disease may be clinically silent despite manifest small bowel mucosal lesions. If undetected or neglected, celiac disease may cause considerable late complications from malabsorption or secondary autoimmune diseases.[1,2,5]

Psychiatric symptoms[5–7] as well as neurologic dysfunctions[5,8,9] are common in patients with celiac disease. Depressive symptoms are often present in adults with the disease, regardless of treatment and age at diagnosis.[6] In some cases, depressive symptoms have reportedly improved soon after starting a gluten-free diet.[10] The prevalence of severe mental and behavioral disorders in untreated celiac disease is unknown, but a history of psychiatric treatment before the diagnosis of celiac disease has been reported in 21% (9/42) of adult patients with the disease compared with 5% (2/42) of a medical control group.[7] The objective of this study was to observe whether a gluten-free diet could alleviate those behavioral symptoms.

METHOD

Seventy-seven subjects with a diagnosis of ADHD were asked to participate in the study, which was conducted in South Tyrol, Italy, from 2004 to 2008. Ten patients were not interested in participating; therefore, the study included 67 participants (52 male and 15 female) ranging in age from 7 to 42 years (mean = 11.4 years). Severe mental disorders like psychosis, major depression, and drug dependency were exclusion criteria. Further exclusion criteria included the diagnosis of autoimmune disorders, such as diabetes mellitus and thyroiditis, and neurologic diseases, such as epilepsy,[1,8] because they are known to trigger ADHD-like symptomatology. The participants were motivated, cooperative, and of a socioeconomic status level of II to IV (Hollingshead criteria[11]). All adult patients and parents of included children provided written informed consent.

Clinical Points

- ♦There is evidence that ADHD is not only a separate disorder, but also a symptom of various other diseases.
- ♦Current evidence supports checking antiendomysium and antigliadine antibodies in patients with ADHD.
- ♦Clinicians can help patients with ADHD avoid drug treatment by adding new diagnostic tools.

Subjects were assessed for possible ADHD-like symptomatology using Hypescheme, an operational criteria checklist for ADHD.[12] Hypescheme includes the following areas: demographic data, symptoms of *DSM-IV* ADHD and *ICD-10* hyperkinesis (at home and school), symptoms of oppositional and conduct disorders, summary symptoms of specific anxiety disorders, summary symptoms of other psychiatric disorders, summary symptoms of developmental (language and learning) disorders, IQ (verbal, performance, and full scale), associated neurologic conditions, and questions regarding medication use and efficacy. The main value of Hypescheme is that it captures the key constructs relevant to the genetics of ADHD. There is 1 key assessment issue: the use of multiple informants (a symptom is only scored if it appears in 2 or more of 3 situations [at home/at school or work/peer group]). The diagnosis of ADHD-like symptomatology should include the concept of pervasiveness as incorporated by either *DSM-IV* or *ICD-10* criteria.

The blood serum levels of all included patients were checked for endomysium antibodies demonstrated by immunohistology using the human umbilical cord as substrate. Similarly, all patients carried elevated tissue transglutaminase antibodies using the human recombinant antigen as substrate (Pharmacia Diagnostics, Uppsala, Sweden). Patients with ADHD and celiac disease were asked about their symptoms using the Hypescheme questionnaire before and 6 months after the initiation of a gluten-free diet for celiac disease.

Specific item differences were measured since patterns of change from dietetic treatment were anticipated

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that would not be identified by the specific item clusters defined by factor analysis. The goal was to clarify the most specific patterns of change induced by this treatment.

Statistical analysis utilized Bonferroni-corrected paired-sample *t* tests. As this analysis may demand a more stringent assessment of significance, note that the results maintain significance even at the $\alpha = .05$ level.

RESULTS

Of the 67 patients with ADHD, 10 were positive for celiac disease (7 male, 13.5%, and 3 female, 20.0%). After initiation of a gluten-free diet, which lasted for at least 6 months, celiac disease–positive patients with ADHD or their parents reported a significant improvement in their behavior and functioning compared to the immediate period before diagnosis and dietetic treatment, which was evident in the overall mean score on the Hypescheme questionnaire ($t = 4.22$; $P = .023$; Table 1).

Hypescheme items showed a significant decrease in mean symptoms of ADHD (no close attention to details, easily distracted, and often blurts out answer before the question is completed) (Table 1). For the other items, no significant differences were observed. Since there was no interfering medication or nutritional rehabilitation (only iron supplementation was given in most instances), the scores of individual behavioral items may show specific effects of the gluten-free diet. Therefore, nearly all overactive and distractible patients (n = 7, 74%) expressed the desire to continue the gluten-free nutritional treatment because they experienced a remarkable enhancement of their attention and behavioral control.

DISCUSSION

Knivsberg[13] and Ghezzi and Zaffaroni[14] reported a close association of celiac disease, sensory deficits, hyperkinesia (as described by Guevara and Stein[15]), and dyslexia. Bruzelius et al[16] found a significantly increased frequency of epilepsy and dementia in patients suffering from celiac disease. Ricca et al[17] noticed an association of anorexia nervosa and celiac disease and hypothesized that the gastrointestinal malabsorption may trigger the eating disorder. De Santis et al[18] suggested that even subtypes of schizophrenia may be caused by celiac disease. Furthermore, a close connection of anxiety disorders and celiac disease has been reported by Addolorato et al,[19] Dohan et al,[20] and Hallert and Derefeldt.[7] Niederhofer and Pittschieler[21] found a significant number of patients in a celiac disease sample suffering from additional ADHD-like symptomatology who showed some improvement after initiation of a gluten-free diet lasting for at least 6 months.

In a study by Hernanz and Polanco,[22] 9 of 15 untreated children with celiac disease showed signs of behavioral disturbances and were irritable or apathetic. However, after starting a gluten-free diet, there was improvement in mood and behavioral disturbances in some of the patients, possibly with concomitant elevations in plasma concentrations of tryptophan (a precursor of serotonin). Impaired availability of tryptophan in the central nervous system predisposes to disturbances in central serotonergic function associated with depressive disorders and aggression dysregulation.[23,24] Significantly lower levels of whole blood tryptophan have been found in prepubertal children with a recent history of a suicide attempt compared with normal controls.[25]

Clinical Implications

The results of this study suggest that a gluten-free diet improves ADHD symptoms significantly and that untreated celiac disease may predispose patients to mental and behavioral disorders such as ADHD.

The results also indicate that celiac disease, which has a prevalence rate of 4%,[26] should be included in the list of symptoms of ADHD. Barbaresi et al[27] reported an incidence of 10% for ADHD, as well as a prevalence of stimulant treatment of 86.5% for definite ADHD and 50% for probable and questionable ADHD, which indicates that stimulant treatment is often administered even if diagnosis is not proven.

A limitation of the study is that the sample size was quite small. Nevertheless, the results strongly suggest that a diagnosis of celiac disease should be included in the ADHD symptom checklist to avoid unnecessary stimulant treatment. Further research is urgently required.

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Figures and Tables

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Table 1

Improvement of ADHD-Like Symptomatology in Patients With Celiac Disease Before and After Initiation of a Gluten-Free Diet

Variable	Before Diet	After Diet	*t*	*P*
No close attention to details, mean (SD)	1.16 (0.73)	0.75 (0.51)	3.18	.012*
Easily distracted, mean (SD)	1.12 (0.21)	0.57 (0.18)	4.33	.014*
Often blurts out answer, mean (SD)	1.23 (0.31)	1.19 (0.77)	2.62	.014*
Overall score, mean ± SD	21.24 ± 6.93	14.18 ± 4.20	4.22	.023*

*Indicates statistical significance.

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

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