

A Preliminary Investigation of ADHD Symptoms in Persons With Celiac Disease

Helmut Niederhofer

Klaus Pittschieler

Regional Hospital of Bolzano, Italy

Objective: Several studies report a possible association of celiac disease (CD) with psychiatric and psychological disturbances, such as ADHD. **Method:** The authors assess 132 participants from 3 to 57 years of age ($M = 19.3$ years) affected by CD for the possibility of an associated ADHD-like symptomatology, using the Conner Scale Hypescheme, a behavioral scale similar to the Conners Rating Scales, before their gluten-free diet was started and 6 months later. **Results:** The overall score improves significantly as well as most of the ADHD-like symptomatology specific features (Bonferroni-corrected, paired-sample t tests). **Conclusion:** The data indicate that ADHD-like symptomatology is markedly overrepresented among untreated CD patients and that a gluten-free diet may improve symptoms significantly within a short period of time. The results of this study also suggest that CD should be included in the list of diseases associated with ADHD-like symptomatology.

Keywords: ADHD; celiac disease

Celiac disease (CD) is a destructive inflammatory disease of the mucosa of the upper small intestine resulting from gluten ingestion in genetically susceptible individuals. The diagnosis is based on demonstration of a more or less pronounced villus atrophy in a jejunal biopsy (Feigbery, 1999; Maki & CoHin, 1997). The therapy consists of excluding gluten permanently from the diet and allows a total healing of the mucosal lesion. Since the early 1980s, it has become evident that CD is underdiagnosed (Catassi et al., 1996; Feigbery, 1999; Kolho, Farkkila, & Savilahti, 1998; Maki & CoHin, 1997; Rolmes, 1996). In young Italians ages 6 to 15, the overall prevalence of CD was 1 in 184, screened by combined determination of serum immunoglobulin G (IgG) and IgA antigliadin antibody test (Catassi et al., 1996). Among healthy Finnish adults, the prevalence was as high as 1 in 130 using IgA antiendomysium antibody determination (Kolho et al., 1998). 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 manifesting small-bowel mucosal lesions. If undetected or neglected, CD may cause considerable late complications from malabsorption or secondary autoimmune diseases (Feigbery, 1999; Maki & CoHin, 1997; Rolmes, 1996).

Neurological dysfunction (Hadjivassilou et al., 1996; Hadjivassilou et al., 1998; Rolmes, 1996) and psychiatric symptoms are common in CD (Ciacci, Lavarone, Mazzacca, & De Rosa, 1998; Hallert & Astrom, 1982; Hallert & Derefeldt, 1982; Rolmes, 1996). Depressive symptoms often feature in CD of adults, regardless of treatment and age at diagnosis (Ciacci et al., 1998). In some cases, depressive symptoms have reportedly improved soon after starting a gluten-free diet (Corvaglia, Catamo, Pepe, Lazzarri, & Corvaglia, 1999). The prevalence of severe mental and behavioral disorders in untreated CD is unknown, but a history of psychiatric treatment before the diagnosis of CD has been reported in 21% (9 out of 42) of adult CD patients compared with 5% (2 out of 42) of a medical control group (Hallert & Astrom, 1982; Hallert & Derefeldt, 1982). We observed that many patients affected by a more or less overt CD showed

Authors' Note: Address correspondence to Susan G. Crawford, Behavioural Research Unit, Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta, Canada T3B 6A8; phone: (403) 943-7365; e-mail: susan.crawford@calgary-healthregion.ca. The authors thank Alberta Mental Health Research Fund and the Alberta Children's Hospital Foundation for financial support and Brenda Wilson, M.S., O.T.(C), for helping organize and conduct the motor skills assessments.

signs of ADHD-like symptomatology before initiating a dietetic treatment, and therefore, we were interested in observing whether a gluten-free diet could alleviate those behavioral symptoms.

Method

One hundred and thirty-two participants ranging in age from 3 to 57 ($M = 19.3$ years) affected by CD and diagnosed according to the modified ESPGHAN criteria were asked to participate. The serum of all investigated patients was positive 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). The histological examination of jejunal or duodenal mucosa showed in all patients a total a partial villous atrophy and for the CD specific inflammatory features.

Fifty-four patients were not interested in participating. Thirty-six of the remaining 78 were males, and 42 were females. No significant differences between participants and nonparticipants were found in gastro-intestinal or malabsorption symptoms and mental disorders. Severe mental disorders, such as psychosis, major depression, and drug dependency, were exclusion criteria. The concomitant diagnosis of autoimmune disorders associated with CD, such as diabetes mellitus and thyroiditis but also neurological diseases such as epilepsy (Feigbery, 1999; Hadjivassilou et al., 1996), were further exclusion criteria because they are known to trigger ADHD-similar symptomatology. The participants were motivated, cooperative, and of a socioeconomic status Level 2 to 4 (Hollingshead & Redlich, 1958). All adult patients and parents of included children gave a written informed consent.

Participants were checked for possible ADHD-like symptomatology using Hypescheme, which is an operational criteria checklist for ADHD, oppositional defiant disorder, and conduct disorder and is proposed as a minimum data set for those engaged in molecular genetic studies of ADHD. Hypescheme consists of a computerized data checklist system that includes all the operational criteria required for both Diagnostic and Statistical Manual of Mental Disorders (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) and International Classification of Diseases–Version 10 (ICD-10) diagnostic criteria and a systematic record of information about comorbid psychiatric, developmental, and neurological disorders. Using these data, an algorithm applies both *DSM-IV* and ICD-10 criteria to generate operational diagnostics under both these systems. Hypescheme is not

designed to replace current assessment protocols but to be a final common checklist that can be completed by experienced researchers using all available data (Curran, Newman, Taylor, & Asherson, 2000). This method uses a coding form to summarize sample characteristics, aspects of the ADHD-like symptomatology phenotype, and other key data. The Hypescheme does not require investigators to use a specific instrument to collect data. Instead, it specifies and summarizes the information to be collected, regardless of source, into a common format. It includes the following areas: demographic data, symptoms of *DSM-IV* ADHD and ICD-10 hyperkinesia (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 a learning) disorders, IQ (verbal, performance, and full scale), associated neurological conditions, and questions regarding medication use and efficacy. Only in absence of comorbidities, ADHD can be diagnosed. Each site can transfer data into the Hypescheme format from whatever instruments were currently used for data collection. This allows the creation of a common data set to promote cross-site comparisons and to facilitate meta-analyses. The main value of the Hypescheme is that it captures the key constructs relevant to the genetics of ADHD. Hypescheme includes all the operational criteria required for both *DSM-IV* and ICD-10 diagnostic criteria and a systematic record of information about comorbid psychiatric, developmental, and neurological disorders and was for this reason used instead of the ADHD directed Conner Scale. This facilitates subtyping across sites at the symptom level. Using the Hypescheme does not require a significant amount of extra work. Rather, it provides a set of organizing principles and common data structure for data that have already been collected by most sites.

There is one Hypescheme key assessment issue: the use of multiple informants (a symptom is only scored if it appears in two or more of three situations [at home/at school or work/peer group]). The diagnosis evaluation of ADHD-like symptomatology should incorporate the concept of pervasiveness as incorporated by either *DSM-IV* (American Psychiatric Association, 1994) or ICD-10 (World Health Organization, 1998). These require either that symptoms of ADHD-like symptomatology cause impairment in more than one setting (*DSM-IV*) or that the symptoms are evident in two or more settings (ICD-10).

Using Hypescheme, patients were retrospectively asked about their ADHD-like symptomatology symptoms before and 6 months after the diagnosis and dietetic treatment of CD.

Table 1
Improvement of ADHD-Like Symptomatology of CD Patients Before and Under Gluten-Free Diet

Score	Before Diet		After Diet		<i>t</i>	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
No close attention to details	1.14	.87	0.73	.55	3.49	.014*
Difficulty sustaining attention	1.27	.44	1.12	.38	2.45	.035*
Fails to finish work	1.11	.57	0.78	.57	4.29	.023*
Easily distracted	1.17	.28	0.63	.13	4.89	.018*
Often fidgets with hands	1.33	.59	0.88	.37	3.92	.021*
Leaves seat	1.28	.35	1.10	.22	2.19	.036*
Unduly noisy	1.19	.14	1.03	.33	2.55	.018*
Often blurts out answer	1.26	.28	1.14	.56	2.68	.018*
No organization	1.33	.37	1.25	.46	2.61	.467
Looses things	1.46	.35	1.38	.37	2.44	.357
Generally restless	1.23	.39	1.10	.39	2.00	.392
Interrupts frequently	1.38	.33	1.28	.37	1.99	.593
Overall average score	22	-6	16	-4	4.20	.024*

Note: CD = celiac disease.

To maintain the closest correlation with actual clinical practice, the initial investigation was conducted using a within-subjects design. Dependent measures consisted of the Hypescheme ADHD-like symptomatology factor scores. We measured specific item differences, as we anticipated patterns of change from diet that would not be identified by the specific item clusters defined by factor analysis. We wanted to clarify the most specific patterns of change induced by this treatment. Statistical analysis used Bonferroni-corrected paired-sample *t* tests. As this analysis may demand a more stringent assessment of significance, note that our results maintain significance even at the alpha .01 level.

Results

After at least 6 months of a gluten-free diet, patients or their parents reported a significant improvement in their behavior and functioning compared to the immediate period before diagnosis and dietetic treatment, evident in the overall average score on the Hypescheme Questionnaire ($t = 4.20, p < .001$).

Assessment of improvement within the Hypescheme items showed a significant decrease in mean symptoms of ADHD-like symptomatology (no close attention to details, difficulty sustaining attention, fails to finish work, easily distracted, often fidgets with hands, leaves where remaining seated is required, unduly noisy, and often blurts out answer before the question is completed). For the other items, we observed no significant differences (Table 1). Because there was no interfering medication or nutritional rehabilitation (only iron supplementation was

given in most of them), the scores of individual behavioral items may show specific effects of the gluten-free diet. Therefore, nearly all overactive and distractible patients (74%) expressed the desire to continue the gluten-free nutritional treatment because they experienced a remarkable enhancement of their attention and behavioral control. The level of pain reduction in each patient correlated with the level of improved attention symptoms.

Discussion

Ghezzi and Zaffaroni (2001) and Knivsberg (1997) reported a close association of CD, sensory deficits, hyperkinesia (as described by Guevara & Stein, 2001), and dyslexia. Bruzelius, Liedholm, and Hellblom (2001) found a significantly increased frequency of epilepsy and dementia in patients suffering from CD. Ricca et al. (2000) noticed an association of anorexia nervosa and CD and hypothesized that the gastrointestinal malabsorption may trigger the eating disorder. DeSantis et al. (1997) suggested that even subtypes of schizophrenia may be caused by CD. Furthermore, a close connection of anxiety disorders and CD has been reported by Addolorato et al. (1996), Dohan, Martin, Grasberger, Boehme, and Cottrell (1972), Hallert and Astrom (1982), and Hallert and Derefeldt (1982).

The mechanisms involved in the a etiology and pathogenesis of psychiatric symptoms related to CD remain unclear. In a study by Hernanz and Polanco (1991), 9 of 15 untreated celiac children 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 (e.g., Smith, Fairburn, & Cowen, 1997; van Praag, 1998). Compared with normal controls, significantly lower levels of whole blood tryptophan have been found in prepubertal children with a recent history of a suicide attempt (Pfeffer et al., 1998).

Limitations

Our sample size was small, and we used a retrospective design. We also did not use a control group of untreated celiac patients during the course of the assessment. Nevertheless, this preliminary investigation provides supportive data that ADHD symptoms occur beyond a chance level in patients with CD. If further, better controlled research using larger samples replicates the present findings, clinicians are urged to actively seek out information about the potential presence or past diagnosis of CD during the course of assessments for ADHD.

Clinical Implications

Our results indicate that ADHD-like symptomatology is markedly overrepresented among untreated CD outpatients, and a gluten-free diet improves these symptoms significantly (before diet overall average Hypescheme score of 22, after diet overall average Hypescheme score of 16). Confusing data are seen in the literature, as Pynnonen, Isomets, Aalberg, Verkasab, and Savilahti (2002) found that CD is not more frequently present among psychiatric patients than in the general population. Instead, Kozłowska (1991) observed a significantly higher incidence of psychiatric disorders in treated CD patients, but he did not check untreated ones. For that reason, all ADHD-like symptomatology patients should be tested for CD with serum screening tests such as EMA or tTGA, as CD could be one of the causes of these neuropsychiatric symptoms. We are convinced that untreated CD may predispose to important mental and behavioral disorders.

Our results suggest that ADHD-like symptomatology should be included in the list of symptoms of CD, which has a prevalence rate of 4% (Not et al., 1998). ADHD-like symptomatology is a frequently diagnosed disease. Barbaresi et al. (2002) report an incidence of 10% 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 also administered even if diagnosis is not proven.

We found a CD prevalence rate of also 4% (121 of 300,000 inhabitants in South Tyrol). Assuming that the ADHD prevalence corresponds to that reported by Barbaresi et al. (2002), we suppose that 0.4% (12 patients) suffer from definite CD and definite ADHD, and 2% (60 patients) suffer from definite CD and probable or questionable ADHD, which are treated with stimulants.

References

- Addolorato, G., Stefanini, G. F., Capristo, E., Caputo, F., Gasbarrini, A., & Gasbarrini, G. (1996). Anxiety and depression in adult untreated celiac subjects and in patients affected by inflammatory bowel disease: A personality "trait" or a reactive illness? *Hepatology*, *43*, 1513-1517.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Barbaresi, W. J., Katusic, S. K., Colligan, R. C., Pankratz, V. S., Weaver, A. L., Weber, K. J., et al. (2002). How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. *Archives of Pediatrics & Adolescent Medicine*, *156*, 217-224.
- Bruzelius, M., Liedholm, L. J., & Hellblom, M. (2001). Celiac disease can be associated with severe neurological symptoms. Analysis of gliadin antibodies should be considered in suspected cases. *Lakartidningen*, *98*, 3538-3542.
- Catassi, C., Fabiani, E., Ratsch, I., Coppa, G., Giorgi, P., & Pierdomenico, R. (1996). The coeliac iceberg in Italy. A multi-centre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatrica Supplement*, *412*, 29-35.
- Ciacci, C., Lavarone, A., Mazzacca, G., & De Rosa, A. (1998). Depressive symptoms in adult coeliac disease. *Scandinavian Journal of Gastroenterology*, *33*, 247-250.
- Corvaglia, L., Catamo, R., Pepe, O., Lazzarri, R., & Corvaglia, E. (1999). Depression in adult untreated celiac subjects: Diagnosis by the pediatrician. *American Journal of Gastroenterology*, *94*, 839-843.
- Curran, S., Newman, S., Taylor, E., & Asherson, P. (2000). Hypescheme: An operational criteria checklist and minimum data set for molecular genetic studies of attention deficit and hyperactivity disorders. *American Journal of Medical Genetics*, *96*, 244-250.
- DeSantis, A., Addolorato, G., Romito, A., Caputo, S., Giordano, A., Gambassi, G., et al. (1997). Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: Regression after gluten-free diet. *Journal of Internal Medicine*, *242*, 421-423.
- Dohan, F. C., Martin, L., Grasberger, J. C., Boehme, D., & Cottrell, J. C. (1972). Antibodies to wheat gliadin in blood of psychiatric patients possible role of emotional factors. *Biological Psychiatry*, *5*, 127-137.
- Feigbery, C. (1999). Celiac disease: Clinical review. *British Medical Journal*, *319*, 23-29.
- Ghezzi, A., & Zaffaroni, M. (2001). Neurological manifestations of gastrointestinal disorders, with particular reference to the differential diagnosis of multiple sclerosis. *Neurological Sciences*, *22*(suppl. 2), S117-S122.
- Guevara, J. P., & Stein, M. T. (2001). Evidence based management of attention deficit hyperactivity disorder. *British Medical Journal*, *323*, 1322-1325.

- Hadjivassiliou, M., Gibson, A., Davies-Jones, G., Lobo, A., Stephenson, T., & Milford-Ward, A. (1996). Does cryptic gluten sensitivity play part in neurological illness? *Lancet*, *347*, 369-371.
- Hadjivassiliou, M., Grunewald, R., Cbattopadhya, A., Davies-Jones, S., Gibson, A., Jarrat, J., et al. (1998). Clinical, radiological, and neuropathological characteristics of gluten ataxia. *Lancet*, *352*, 1582-1585.
- Hallert, C., & Astrom, J. (1982). Psychic disturbances in adult coeliac disease. 2. Psychological findings. *Scandinavian Journal of Gastroenterology*, *17*, 21-24.
- Hallert, C., & Derefeltd, T. (1982). Psychic disturbance s in adult celiac disease. 1. Clinical observations. *Scandinavian Journal of Gastroenterology*, *17*, 17-19.
- Hollingshead, A., & Redlich, R. C. (1958). *Social class and mental illness*. New York: John Wiley.
- Hernanz, A., & Polanco, I. (1991). Plasma precursor amino acids of central nervous system monoamines in children with coeliac disease. *Gut*, *32*, 1478-1481.
- Knivsberg, A. M. (1997). Urine patterns, peptide levels and IgA/IgG antibodies to food proteins in children with dyslexia. *Pediatric Rehabilitation*, *1*, 25-33.
- Kolho, K. I., Farkkila, M. A., & Savilahti, E. (1998). Undiagnosed coeliac disease is common in Finnish adults. *Scandinavian Journal of Gastroenterology*, *33*, 1280-1283.
- Kozłowska, Z. E. (1991). Evaluation of mental status of children with malabsorption syndrome after long-term treatment with gluten-free diet (preliminary report). *Psychiatria Polska*, *25*, 130-134.
- Maki, M., & CoHin, P. (1997). Celiac disease. *Lancet*, *349*, 1755-1759.
- Not, T., Horvath, K., Hill, I. D., Partanen, J., Hamed, A., Magazzu, G., et al. (1998). Celiac disease risk in the USA: High prevalence of antiendomysium antibodies in healthy blood donors. *Scandinavian Journal of Gastroenterology*, *33*, 494-498.
- Pfeffer, C., McBride, A., Anderson, G., Kakuma, T., Fensterheim, L., & Klialt, V. (1998). Peripheral serotonin measures in prepubertal psychiatric inpatients and normal children: Association with suicidal behavior and its risk factors. *Biological Psychiatry*, *44*, 568-577.
- Pynnonen, P., Isomets, E., Aalberg, V., Verkasab, M., & Savilahti, E. (2002). Is coeliac disease prevalent among adolescent psychiatric patients? *Acta Paediatrica*, *91*, 657-659.
- Ricca, V., Mannucci, E., Calabro, A., Bernardo, M. D., Cabras, P. L., & Rotell, C. M. (2000). Anorexia nervosa and celiac disease: Two case reports. *International Journal of Eating Disorders*, *27*, 119-122.
- Rolmes, O. K. T. (1996). Non-malignant complication s of celiac disease. *Acta Paediatrica*, *412*, 68-75.
- Smith, K., Fairburn, C., & Cowen, P. (1997). Relapse of depression after rapid depletion of tryptophan. *Lancet*, *349*, 915-919.
- van Praag, H. M. (1998). Anxiety and increased aggression as pace-makers of depression. *Acta Psychiatrica Scandanavica*, *98* (Suppl. 393), 81-88.
- World Health Organization. (1998). *International classification of diseases* (Version 10). Seattle, WA: Author.

PLS PROVIDE BIOS