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Case Report

Behavioral Disorders and Celiac Disease: Coincidence or Casualty?

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Abstract

This paper presents the case of a child diagnosed with both celiac disease and Asperger's syndrome. The literature does not report this association to date, and the authors believe it to be a coincidence rather than a casualty.

Keywords

Celiac disease; child; Asperger's syndrome; autism spectrum disorder

1. Introduction

The earliest descriptions of gluten-related neurological disorders date back to the 1960s. Gluten ataxia is the most widely known and studied disorder, although other highly specific neurological manifestations such as peripheral neuropathy, celiac disease, epilepsy, or cerebral calcifications syndrome have also been described. These particular manifestations are infrequent in children and,

contrary to that in adults, other less specific associations such as headaches, behavioral disorders, or autism have been described [1, 2].

Celiac disease (CD) is one of the most common chronic digestive disorders. Clinical features of CD differ significantly depending on the age of presentation. Infantile CD usually appears as a classic form and is characterized by a predominance of digestive symptoms (typical malabsorption syndrome with weight loss, profuse diarrhea, and signs of nutritional and vitamin deficiencies). On the other hand, CD in older children, adolescents, and young adults tends to appear in a silent form, with fewer digestive symptoms and frequent extraintestinal manifestations, along with many associated diseases, thus making it extremely difficult to diagnose. Neurological and psychiatric symptoms are probably the least popular clinical conditions of all [3].

Hadjivassiliou et al. [5] established that gluten-related neurological disorders that appear in childhood (headaches, hypotonia, learning, and behavioral disorders, delayed psychomotor development, epilepsy) tend to respond better to a gluten-free diet (GFD); the earlier this approach is initiated, the more efficient are the results. Some symptoms disappeared entirely with the commencement of GFD, while at times, the symptoms worsened after food ingestion [5]. These circumstances are, however, less frequent in adults. Once CD has been diagnosed, and dietary treatment with GFD has been initiated, the risk of developing neurological or psychiatric disorders is low in children, which is approximately 2.6%, compared to 26% in adults [6]. This discrepancy may be due to the early elimination of gluten in child patients (children are exposed to gluten for lesser time) compared to adults with considerably delayed diagnosis and hence, a prolonged active-CD [1].

Psychiatric and psychological disorders in CD have been described for years [7] and are evident in up to one-third of all celiac patients [8]. Daynes et al. [9] in the 1950s introduced the term ‘pre-celiac syndrome’ to refer to personality, cognitive, and behavioral disorders in children with celiac diseases presenting as irritable, indifferent, inappropriate behavior, and apathy [5]. Other manifestations, including depression in association with CD, is more frequently described in adults [10, 11]. The association of CD with attention-deficit hyperactivity disorder (ADHD), autism, and other neurodevelopment disorders have also been described [6]. Asperger's syndrome (AS), a neurodevelopment disorder, forms a part of the autism spectrum disorders. Patients with AS face difficulties in social interactions, verbal and non-verbal communication, and may display behavioral oddities, with stereotypes and limited interests. Nevertheless, such patients do not demonstrate language delay and their cognitive development is not marked by an overall delay, but by specific impairments in certain areas. The differing clinical presentations vary according to the age and psychiatric comorbidities of patients [12].

2. Case Report

An eight year old boy presenting with behavioral disorders from an early age (12 months) reported to the author’s clinic. The disobedient patient did not respond to scolding, warnings, threats, rewards, or punishments. The parents reported these outbursts as tantrums that had only increased since the birth of a sister two years ago.

Family History: The patient’s mother was 36 years old and was undergoing levothyroxine treatment for hypothyroidism. She reported an uneventful gestation, birth, and breastfeeding period. The father of the patient was 34 years old and was insulin-dependent.

Diet History: The patient's mother reported mixed breastfeeding from birth to five months, followed by milk formula exclusively. Gluten was introduced at six months. The patient received all immunizations as per the schedule.

At the age of 30 months, the patient's behavioral disorders exacerbated with frequent nocturnal awakenings for no apparent reason, persistent mouth sores with constant anorexia, and severely marked eye bags. The symptoms were deliberated to be the consequence of an oppositional defiant disorder, and pathological jealousy attributed to a possibly decreased attention on the child after the birth of the younger sibling. The growth curve was normal (p75-p90) for weight and height according to standards by Fernandez et al., 2011 (WHO 2006/2007).

Chronic diarrhea was considered after noticing changes in the stools (increased number of feces, reduced consistency, and intense smell). The laboratory results indicated very high levels of IgA anti-gliadin antibodies (>80 IU/mL, normal <10) and IgA anti-transglutaminase antibodies (>80 IU/mL, normal <10). The liver profile was found to be normal. The blood biochemistry demonstrated ferritin 6 mcg/L (30-400), Hb 97 g/L (130-160), Hematocrit 0.39 (0.39-0.49), while peripheral blood smear confirmed microcytic-hypochromic anemia compatible with iron deficiency anemia. The remaining blood biochemistry appeared normal, specific IgE to food antigens, stool culture, and parasite study in feces (in 3 different samples) were identified to be negative. Oral iron supplementations were initiated. Celiac disease was suspected, and the patient was referred to the Pediatric Gastroenterology Unit.

The previous analysis was repeated in the Pediatric Gastroenterology Unit for confirmation of the results (Table 1), which highlighted strongly positive anti-endomysium antibodies and positive HLA-DQ2 and HLA-DQ8. Confirmatory diagnosis of celiac disease was established without the need for an intestinal biopsy as per the ESPGHAN 2012 criteria [13].

Table 1 Initial lab analysis at diagnosis.

BLOOD COUNT:	
Coagulation study	Normal values
White series and platelets.	Normal values
Hemoglobin	97 g/L (130-160)
Hematocrit	0.39 (0.39-0.49)
MCV	63.1 fl (70-86)
MHC	17.2 pg (23-31)
MCHC	273 g/L (315-360)
RDW	17.2% (11.5-14.5)
BLOOD BIOCHEMISTRY:	
Glucose	Normal values
Ions profile	Normal values
Liver and kidney profile	Normal values
Lipid profile	Normal values
Proteinogram and immunoglobulins	Normal values
24-HOUR URINE:	
Creatinine	Normal values
Calcium, phosphorus	Normal values
Calcium/creatinine ratio	Normal values
Phosphorus/creatinine ratio	Normal values

STOOLS:	
Stool culture	Negative
Parasite study	Negative
SPECIFIC ANALYTICS:	
Glycated Hb	Normal values
Intact PTH	Normal values
Vitamin D-25 hydroxy	Normal values
Alkaline bone phosphatase	Normal values
Vitamin B-12	Normal values
Folic Ac	Normal values
Thyroid-stimulating hormone	Normal values
Free thyroxine	Normal values
Anti-TG, Anti-TPO	Normal values
Specific IgE to food antigens	Normal values
Ferritin	6 mcg/L (30-400)
MARKERS OF CELIAC DISEASE	
Antigliadin IgA	>80 IU/mL (<10)
Antitransglutaminase IgA	> 80 IU/mL (<10)
Antiendomysium Ab	++++/++++
High resolution HLA type	DQA1 (O1), DQA1 (05:01) DQB1 (02:01) DQB1 (05:01)

The evolution of the celiac disease in the patient was favorable; the patient was monitored every 4-6 months during the first year. The analytical parameters normalized after ten months of follow-up (Figure 1) and persisted in the subsequent annual checkups.

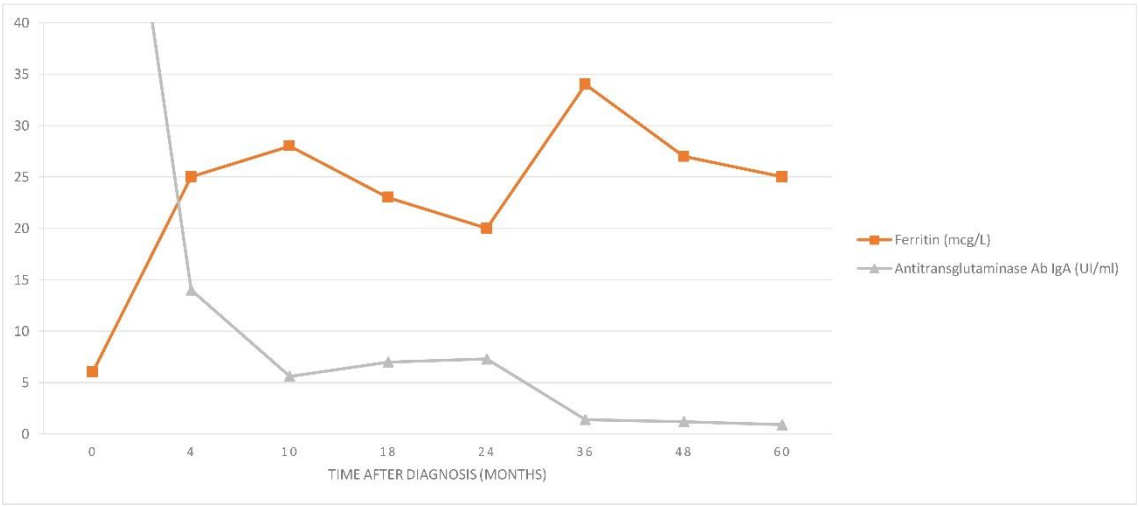

Figure 1 Transglutaminase and Serum Ferritin Levels.

IgA transglutaminase levels in the patient's parents and sister (at age six years) were studied and were found to be normal.

Due to persistent behavioral disorders, the child was referred to a psychiatrist at the age of six. The patient met the criteria of hyperactivity (without attention-deficit) at school and home. He was very restless and disobedient as compared to his peers. High ability traits were also identified in the patient: he could read and write, identify numbers, and perform calculations well ahead of

his peers. The patient disobeyed his teacher and parents. The child presented with language skills and behaved more maturely than his peers. He had a fixation on various subjects, one of which was stickers.

The Children's Mental Health Unit diagnosed the patient with AS. Though the patient was exceptionally gifted, he did not control his emotions well and did not grasp irony or double meanings. He probably violated orders at school and those by parents, mainly because he could not accept a change to rules, as he did not understand sudden changes in his routine. The child lacked empathy for his peers and was unaware of any botheration or hurt he caused to them since he was emotionally immature.

At present, the patient is undergoing treatment for tantrum control, and parents have been asked to ignore his issues. He is increasing his autonomy for daily activities like bathing and eating, and the parents are gradually expanding his responsibility in those aspects as scheduled. The patient and family members are helped to accept the disorder, to avoid behavioral problems while recognizing that the child is immature for his age. It is essential to expose the child to situations that he can understand and discuss. The patient adheres to GFD at home but not in social events, and therefore the family is limiting his social life.

The current diagnoses include hyperactivity disorder without attention-deficit, high cognitive abilities simulating Asperger syndrome, and celiac disease.

The patient is currently being followed up at the Pediatric Gastroenterology Unit and a child psychologist. Although there is a significant improvement, the child continues to display the same psychological characteristics.

3. Discussion

CD shows a classical presentation in children with digestive symptoms, and rarely, with extra-digestive symptoms of a neurological or psychological nature. The most frequently reported traits of these children include a change in character, sadness, and indifference to stimuli, or irritation. However, the only accepted criteria for an established diagnosis of CD are the morphological alterations of the mucosa of the small intestine, the presence of antibodies characteristic of the disease, and the disappearance of these alterations with the withdrawal of gluten from diet [7, 13].

Extraintestinal manifestations are often not considered in the pediatric diagnosis of CD, especially if these manifestations are psychological or psychiatric. On the contrary, in adult patients, specific neurological diseases can be diagnosed and associated with CD.

The etiopathogenesis of these neurological and psychiatric disorders is largely unknown. Different potential mechanisms have been described: a particular way of reacting to infection, the presence of toxin-induced alterations in a more permeable intestinal mucosa, the direct effect of autoimmunity on the nervous system (it is known that anti-gliadin and anti-transglutaminase antibodies can be directly or indirectly neurotoxic), the existence of vasculitis associated with the presence of vitamin deficiencies (folic acid, thiamine, pyridoxine, vitamin B12, vitamin E, biopterin deficiency), to name a few [14-16].

The scarce data, both, for and against each of these arguments, could not yet make a clarification on the origin of the neurological and psychiatric variations [17]. The vital role of serotonin or other neurotransmitters in the development of this disorder has also not been ruled out. Altered production of certain neurotransmitters is well-known in CD and several other

pathologies with psychiatric or psychological manifestations [7]. The changed production can perhaps explain the alteration of the neuronal networks involved in mood and support fact that the use of pyridoxine supplements may lessen the depressive symptoms or mood changes seen in some CD patients [17].

Episodes of increased anxiety, easy irritability, and greater asthenia have been described more frequently in celiac patients, similar to the findings in depressed individuals [18]. This symptomatology generally disappears completely after the establishment of GFD in children and adolescents, whereas adults usually require associated pharmacological treatment such as antidepressants, antipsychotics, or anxiolytics. The recurrence of symptoms, including tension, irritability, dysthymia, and even loss of concentration, has been described after the accidental or voluntary consumption of gluten [18].

From a psychopathological reference, psychiatric and personality disorders like depression or obsessive neurosis have frequently been described in both adults and children exhibiting CD [7]. Kozlowska et al. [19] described the presence of psychiatric symptoms in half of the 41 celiac children, of which 22% were free of symptoms after dietary treatment.

In the present case, the two significant diagnoses that arise are ADHD and AS, considering the lesser specific manifestations.

The association between CD and ADHD is not clear. In a review article by Martínez-Bermejo et al. on patients with CD and ADHD, it was reported the presence of ADHD symptoms in 6.8% of patients in a cohort of celiac patients [8]. This reported prevalence is similar to that of other population groups. This study established that hyperkinesia symptoms were seen in all patients by the age of one, and all of them presented attention-deficit, hyperactivity, low tolerance to frustration, impulsivity, and emotional liability [8].

Although it is assumed that the etiopathogenesis of ADHD and CD, links genetic and biological factors [7], the association between both the entities is not yet clear [4]. Most patients (up to 74%) with previously unrecognized and untreated CD, noted a considerable relief in their ADHD symptoms after six months of GFD in two recent studies by San Mauro Martín et al. [20] and Jackson et al. [21].

To date, no studies have explained the relationship between AS and CD. Though, the association between autism and CD has been mentioned previously; there is some controversy about the exact correlation between both these entities. Pavone et al. [22] studied 120 celiac patients, and none of them was autistic. Ludvigsson et al. [20] did not find any association between CD or intestinal inflammation and autism, although a marked increase in the risk of autism was observed in patients with positive serological tests but normal mucosa [23]. On the other hand, Lau et al. [24] found elevated anti-gliadin antibodies in autistic children with gastrointestinal symptoms, without any other data suggestive of CD. More studies are, therefore, warranted to establish the exact relationship between both entities [7].

Since there is no scientific basis confirming the association between autism and CD, it is not justifiable to start with a GFD in every child with autism. However, a thorough examination and clinical study must be carried out in the search for specific antibodies or enteropathy, since, in the event of a definite diagnosis, GFD will be essential and will probably improve some of the symptoms [25]. In cases with negative histological findings and high suspicion, an investigation for HLA-DQ2 and HLA-DQ8 haplotypes can be carried out, since their negativity excludes the diagnosis [13].

Concerning the association of AS and ADHD, both entities are usually diagnosed between four and eleven years of age and require a comprehensive evaluation that includes a multidisciplinary clinical team for an accurate diagnosis. The similarity in the age of presentation of both these entities leads to a misdiagnosis of AS for ADHD in many children.

In the present case, it is deliberated that the presence of CD and AS is more a result of coincidence and not a matter of chance since it is an association that has never been described earlier. Only extremely isolated cases within a broader study group have been described [26], and the behavioral improvements that would be expected after the initiation of GFD have not yet been proven.

The results of a systematic review and meta-analysis performed by Clappison et al. [27] support the idea that CD is associated with an increased risk for specific psychiatric disorders and has been linked with other developmental disorders like depression, anxiety, eating disorders, and ADHD [27]. These data hint at the importance of regular screening for CD in young patients with these types of mental illnesses [28]. However, more research is needed to investigate the pathophysiology of such associations, and the effects that the gluten-free diet could have on these conditions.

Author Contributions

C.C. conceived the original idea. C.C. took the lead in writing the manuscript. Both C.C. and A.R. authors provided critical feedback and helped shape the review, analysis and manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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