Quill & Scope

Volume 1 *Volume I* Article 9

2008

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Introductory Remarks and Objectives

Over the past two decades, the medical community's understanding of celiac disease, also known as gluten sensitivity, has evolved significantly. No longer just a GI problem, celiac disease is now recognized as a multisystem autoimmune disorder. A growing body of distinct neurological conditions such as cerebellar ataxia, epilepsy, myoclonic ataxia, chronic neuropathies, migraine headache and dementia has been reported, mainly in middle-aged adults. However, while much is known regarding the neuropsychiatric manifestations of celiac disease in the adult population, less is understood about its presentation in the pediatric population. This is especially true of the "soft" neurological conditions, such as headache, learning disorders, attention-deficit/hyperactivity disorder (ADHD), and depression.

The aim of this paper is to briefly discuss the pathophysiology of celiac disease, describe what is currently known about the neuro-psychiatric manifestations of celiac disease in children, and discuss the potential benefits of more aggressive serologic testing.

Pathophysiology of Celiac Disease

Celiac disease is a unique autoimmune disorder most notably because the environmental precipitants (gluten, hordein, secalin) are known (1). The symptoms of the disease manifest not directly from the ingestion of gluten, but rather from the complex interaction between the gastrointestinal system, enzymatically degraded components of gluten, and the immune system of the individual.

The term "prolamins" technically refers to the protein component of certain kinds of grain. These prolamins have a high content of the amino acids proline and glutamine. When referring to the prolamins relevant to those with celiac disease, the term gluten is used loosely to describe the protein fraction of wheat, rye and barley. This is technically incorrect because the prolamins of barley and rye are known as hordein and secalin, respectively. This technical oversite can be made because of the immunologic cross reactivity between the prolamins of wheat, barley and rye (2).

The alcohol-soluble fraction of gluten is known as gliadin, while the alcohol insoluble fraction is known as glutenin. It is the enzymatically modified gliadin fraction, which triggers the immune response in individuals with celiac disease. This immune response ensues because the gliadin fraction is resistant to degradation by gastric, pancreatic and intestinal brush-border membrane proteases in the human intestine and thus remains in the intestinal lumen after gluten ingestion. Gliadin peptides pass through the epithelial barrier of the intestine and are engulfed by antigen-presenting cells (APCs) in the lamina propria. It is possible that passage of gliadin is facilitated by intestinal infection, which would increase gastrointestinal permeability (1).

The inflammatory response which ensues causes the loss of villous architecture, which is the hallmark histologic manifestation of celiac disease on intestinal biopsy as well as the characteristic malabsorption, which cause many of the clinical findings of individuals with celiac disease (e.g. anemia, low protein, nutrient deficiency). This inflammatory cascade is caused by

both the innate and adaptive immune systems and results in the generation of antibodies against gliadin and endomysial components, specifically transglutaminase (1).

A key to understanding celiac disease is that the elimination of gluten from the diet is usually sufficient to terminate the inflammatory cascade, with eventual healing of the gastrointestinal tract and decreased concentrations of antibodies characteristic of celiac disease. This is in stark contrast to other environmentally induced pathologies, in which the process of destruction is not reversible (e.g. radiation induced malignancy). That having been said, there are certain sequelae of celiac disease, which may not be reversible, inclusive of certain psychiatric manifestations to be more fully described later on.

Diagnosis of Disease

Diagnostic criteria for celiac disease vary from country to country, but the most frequently used criteria for diagnosis include endoscopy, serologic investigation and improvement of symptoms on initiation of a gluten-free diet. The term "silent or subclinical celiac disease" refers to individuals who deny symptoms of celiac disease but whose serology point to an immune response against gluten and have evidence of disease on biopsy. It is important to note that many of these "silent" patients often do report feeling better on a gluten-free diet. The term "potential" celiac disease refers to those with positive serologies but benign histologic biopsies (3). Treatment of those with "potential" celiac disease is controversial; see recommendations further on in this article.

Epidemiology of Celiac Disease

Celiac disease is present not only in countries populated by persons of European ancestry but also in the Middle East, Asia, South America and North Africa. It is most prevalent among Caucasians and is most frequently diagnosed between the ages of 10-40. Occurrence of disease is estimated to be 1% of the general population and it is believed that the majority of cases remain undiagnosed. In the United States prevalence estimates range from 1:80 to 1:300 in children. Of those individuals with no risk factors or perceived symptoms, estimates of disease prevalence are suggested to be approximately 1:133. The ratio of asymptomatic to symptomatic cases has been estimated by some investigators to be as high as 7:1 (3).

Between 8 and 10 percent of children with apparent "idiopathic" short stature have serological evidence of celiac disease and patients with patient with gastrointestinal symptoms have slightly attenuated adult height unless treated prior to puberty. Delay in linear growth may occur even when weight for height ratios are fairly normal, and in the absence of significant gastrointestinal symptoms. Thus it is likely that under nutrition cannot be completely to blame (3).

Boys with untreated celiac disease are noted to have decreased levels of dihydrotestosterone (DHT) in their serum, in a trend suggestive of androgen resistance. Adolescent girls may have an increased frequency of menstrual abnormalities (e.g. delayed menarche) and later may have problems with infertility and experience an early menopause. Gluten-free diets appears to prevent these problems (3).

High Risk Populations

Populations particularly at high risk for celiac disease include first and second degree relatives of patients with celiac disease, patients with Down syndrome, patients with Turner syndrome, IgA deficiency, Williams syndrome, and autoimmune thyroiditis. Individuals with Down syndrome have the highest risk of disease, with up to 16% of the population being affected, a 20-fold increase over the general population. Other groups may have 2-7% affected, still a substantially higher incidence. Evidence and theories as to why these associations might be are beyond the scope of this paper. Suffice it to say that many children with chronic care needs will be at high risk for being diagnosed with celiac disease (3). It is worth noting however that there is no evidence that individuals afflicted with autism are at increased risk for celiac disease (4); this is despite the high popularity of gluten and casein free diets among parents caring for children with autism.

Range of Neuropsychiatric Symptoms

Celiac disease may have as its primary manifestation neuropsychiatric symptoms (3). Adults with celiac disease can present with symptoms such as ataxia, depression, anxiety, epilepsy, and headache. Children also can manifest with neuropsychiatric manifestations but in contrast with adults can also present with developmental delay, hypotonia, learning disorders.
Some of these symptoms such as developmental delay and hypotonia can be attributed to malabsorption of specific nutrient deficiencies. These symptoms are likely the result of the damaged gastrointestinal mucosa and it is not surprising that such symptoms should be reversible upon initiation of a gluten-free diet and correction of the deficiencies (3).

However there is evidence for other mechanisms by which the inflammatory response of the immune system might lead to neuropsychiatric manifestations of celiac disease. Hadjivassiliou et al have published extensively on the neurologic manifestations of celiac disease in adults and documented the existence of autoantibodies targeting transglutaminases (TG2) in the brain and intestinal mucosa in patients with gluten ataxia (5). These autoantibodies were most prevalent in the cerebellum, medulla and pons. IgA deposition and vasculitis in the cerebellum can explain the ataxia in many patients with celiac disease and could potentially shed light on other neuropsychiatric manifestations as well.

De Santis et al first described an individual with schizophrenic symptoms who had evidence of cerebral hypoperfusion and celiac disease in 1997 (6). This prompted Addolorato et al to further investigate perfusion in patients with untreated celiac disease, treated celiac disease (gluten-free diet) and case controls and found those with untreated celiac disease were significantly more likely to have areas of cerebral hypoperfusion. He found that brain hypoperfusion was reversible with initiation of a gluten-free diet (7).

While these studies looked at adult patients, the mechanisms behind the cerebral hypoperfusion could potentially extend to the pediatric population and explain many of the neuropsychiatric manifestations of celiac disease in children inclusive of depression.
Zelnik et al found that the range of neuropsychiatric manifestations of celiac disease in the pediatric population was quite broad and included chronic headache, developmental delay, hypotonia and learning disorders or ADHD (4). In contrast with other findings, Zelnik concluded that only migraine headache and transient infantile hypotonia could be corrected by institution of a gluten-free diet.

Speculations Regarding the Neuropsychiatric Manifestations of Celiac Disease

In looking through the rapidly growing body of evidence regarding the neuropsychiatric manifestations of celiac disease it is clear the much remains to be learned regarding the exact mechanisms by which individuals with celiac disease develop symptoms. Some symptoms can be explained simply by nutrient deficiency, while others are perhaps the result of a vasculitis. Other symptoms are perhaps the result of hypoperfusion. However, while there is still much we do not know, it is clear that celiac disease is not simply a disease isolated to the gastrointestinal system. Extra-intestinal symptoms are present in as many as 10% of those with celiac disease (3). Furthermore it is not known how correctable all of these manifestations will be. Therefore it behooves the practicing clinician to be vigilant to suspect celiac disease in patients presenting with neuropsychiatric symptoms, even if GI symptoms are absent or minimized by the patient.

Relevance to the Pediatrician

The majority of research looking into the neuropsychiatric manifestations of celiac disease involves adults. One should never assume that the trends in the pediatric population mimic that of adults. The popular slogan that children are NOT little adults rings true in regards to celiac disease as well. As previously stated, Zelnik et al did find many children with neuropsychiatric symptoms who were afflicted with celiac disease. However, a recent publication by Ruggieri et al found that the prevalence of neurologic/psychiatric manifestation in children with celiac disease was only slightly higher than that in controls (8). In their discussion the authors speculate that children may perhaps be protected against nervous system involvement either by shorter duration of illness, strict adherence to a diet free of gluten or even a changing antigen spectrum during normal growth and development.

Recommendations

In reviewing the literature in preparation for this paper it seems clear to this writer that many with positive serologies suggestive of celiac disease may not be aware of any gastrointestinal symptoms (indeed there may be none). It is also evident that those with celiac disease on a gluten-free diet may not be as adherent as their caregivers would wish. It is also clear that while endoscopy is an excellent tool for diagnosing celiac disease, serologic testing is clearly easier, safer and very effective in its predictive value (3); while also useful in monitoring the adherence to dietary restrictions.

It is my hope that more clinicians will consider serologic testing of asymptomatic individuals who are at high risk for developing celiac disease (e.g. family history, Down syndrome, Turner syndrome) as well as individuals who present with neuropsychiatric symptoms such as ADHD, depression or migraine when there is any evidence of GI comorbidity in the hopes of preventing the more dangerous complications of celiac disease (e.g. malignancy) and more accurately treating the cause of their symptoms. As there is evidence that many of the symptoms (inclusive of some neuropsychiatric symptoms) of celiac disease are reversible with the initiation of a gluten free diet hopefully the earlier diagnosis of celiac disease will provide a higher quality of life for those individuals afflicted with this fascinating autoimmune entity.

The pediatrician should be aware that the exact prevalence and range of neuropsychiatric manifestations in the pediatric population is not clearly established. However because of the fair reliability of serologic testing, initial screening can be done without the need of GI referral or the risks of endoscopy.

Many clinicians would argue against treating through diet those individuals with "potential" celiac disease (serologic evidence but no histologic evidence of disease) but I would consider it. Firstly, the neuropsychiatric symptoms experienced by those with celiac disease are most likely not from antibodies damaging the gut but from those same antibodies doing damage to the nervous system. Decreasing those antibody levels could potentially save the "potential" celiac patient from becoming an active celiac patient and spare the nervous system from the possible ravages of humoral immune deposition and/or hypoperfusion.

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