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Current Evidence in the Diagnosis and Treatment of Children With Celiac Disease

ABSTRACT

Recent statistics report that 3 million people, or 1% of the population in the United States (U.S.), are affected by celiac disease (CD). In addition, in the U.S., as many as 1 in 80 children is affected with CD. However, CD can be challenging to diagnose and many children are not correctly diagnosed or live without a diagnosis for several years. Symptoms, if present, are often nonspecific and may be common manifestations of many pediatric illnesses. The purpose of this review is to examine the current evidence regarding incidence, pathophysiology, diagnosis, and treatment of a child with CD. Clinical implications for nurses caring for children and families are discussed.

Celiac disease (CD) is rapidly becoming one of the most common chronic diseases affecting children (Fasano, Berti, & Gerarduzzi, 2003). It is estimated that approximately 1 in 140 Americans have been diagnosed with CD; however, it is also believed that nearly 85% of people with CD remain undiagnosed or misdiagnosed (Rubio-Tapia, Ludvigsson, Brantner, Murray, & Everhart, 2012). If CD is so common, why does it continue to be so difficult to correctly diagnose in children? Vague symptoms, such as irritability, diarrhea, and stomach aches, are common manifestations of CD that often mimic common childhood illnesses causing many children with CD to remain undiagnosed for an extended period of time (Amerine, 2006; Madani & Kamat, 2006). In addition, the presentation of CD is changing and more often children present with atypical or silent CD (Hill et al., 2016). Appropriate diagnosis of CD is essential to ensure appropriate physical and cognitive growth as well as to avoid the negative sequelae of the disease (Reilly, Dixit, Simpson, & Green, 2012). The purpose of this article is to review the current evidence on pediatric CD, including the prevalence and incidence, pathophysiology, clinical manifestation, disease process, diagnosis, and treatment and management.

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Search of Literature

The aim of this this review was to examine the current evidence on pediatric CD, including the pathophysiology, diagnosis, and management. The databases EBSCOHOST, CINAHL, MEDLINE, and Web of Science were searched (2010 to present) using the following key words: pediatric, children, celiac disease, coeliac disease, diagnosis, treatment, and screening. An ancestry search was also used to find relevant articles.

Pathophysiology

Celiac disease is a multifactorial immune-mediated enteropathy of the small intestine caused by a response to ingested gluten (Jericho et al., 2017; Silano, Agostoni, Sanz, & Guandalini, 2016; Tully, 2008). The pathogenesis of CD is a complex interaction between environmental, genetic, and immunologic factors (Martin, 2008; Reilly et al., 2012). Gluten is a protein complex that is found in wheat, barley, and rye (Jericho et al., 2017). The gluten fractions that are toxic are called gliadins, which are a component of gluten. In the presence of gliadins, the number of immunoglobulins (IgM, IgG, and IgA) increase and cause damage to the small intestine. A

normal small intestine will have abundant villi; however, one with CD will have damage to the small intestinal mucosa leading to villous atrophy, hyperplasia of the crypts, and infiltration of the epithelial cells with lymphocytes (Kwon & Farrell, 2006). The damage to the tissue lining is the result of an autoimmune dysfunction when the villi are introduced to the protein gliadin. This damage causes malabsorption and worsens signs and symptoms (Amerine, 2006). Genetics also have a strong role in the pathogenesis of CD. Celiac disease occurs in 90%–95% of those who have the human leukocyte antigen (HLA) DQ2 genotype and the remaining 5%–10% exhibit the HLA-DQ8 genotype. Finally, immunologically, an increase in intraepithelial lymphocyte count has been recognized in CD (Martin, 2008).

Prevalence and Incidence

Celiac disease is considered one of the most common causes of chronic malabsorption (Di Sabatino & Corazza, 2009). Recent research suggests that the overall prevalence in the United States (U.S.) ranges from 1:300 to 1:80 (Hill et al., 2016). In at-risk groups, the prevalence increases to 1:22 in first-degree relatives, 1:39 in second-degree relatives, and 1:56 in symptomatic patients (Fasano et al., 2003), making it one of the most common chronic pediatric disorders (Rashid et al., 2005). Celiac disease continues to remain underdiagnosed in the U.S. (Rubio-Tapia & Murray, 2010a), and many researchers believe that a significant number of CD cases are atypical, silent, or present later in adulthood, resulting in what is known as the "celiac iceberg" (Fansano & Catassi, 2001; Lionetti & Catassi, 2011). In fact, Leonard, Fogle, Asch, and Katz (2016) studied the prevalence of CD in a pediatric practice and found that 60% of newly diagnosed patients were asymptomatic. Certain genetic and autoimmune disorders are associated with an increased risk for developing CD as shown in Table 1 (Hill et al., 2005; Westerberg et al., 2006).

Clinical Manifestations

Symptoms of CD in children are vague or nonspecific and vary by age and extent of disease, thus, making diagnosis challenging (Fasano & Catassi, 2001; Lionetti & Catassi, 2011). Symptoms may appear between 4 and 24 months of age after solid foods containing gluten are introduced into the child's diet; however, a delay or latent period can occur between the introduction of gluten and the onset of symptoms (Daigneau, 2007). Symptoms in infants and toddlers are different than those experienced by older children. Infants and younger children may present with diarrhea, anorexia, abdominal distention and pain, failure to thrive, and irritability, and severe malnutrition and muscle wasting can occur if diagnosis is delayed (Hill et al., 2005). Older children may present with

TABLE 1. Conditions and Symptoms Related to Celiac Disease[a]

Conditions	Classic Symptoms	Atypical Symptoms
Addison's disease	Abdominal pain/gas/bloating	Fatigue, weakness, ataxia, seizures
Autoimmune hepatitis and thyroid disease	Weight loss or poor growth	Anemia, easy bruising
Bone disease, collagen vascular disorders	Constipation	Mood swings/depression, Attention deficit hyperactivity disorder
Dermatitis herpetiformis	Nausea/vomiting	Mouth ulcers, eczema, patchy hair loss
Down syndrome	Steatorrhea	Osteopenia, osteoporosis, bone/joint pain
Epilepsy	Diarrhea	Abnormal liver function, Hypertransaminasemia
Idiopathic dilated cardiomyopathy		Muscle cramps
IgA deficiency/nephropathy		Dermatitis herpetiformis
Lupus erythematosus		
Lymphomas		
Rheumatoid arthritis		
Sjögren syndrome		
Turner syndrome		
Type 1 diabetes mellitus		

[a]Based on information from Allen (2004); Hill et al. (2005); and Megiorni and Pizzuti (2012).

gastrointestinal (GI) symptoms depending on the amount of gluten ingested and their symptoms include diarrhea, nausea and vomiting, abdominal pain, bloating, weight loss, and constipation (Hill et al., 2005).

The symptoms of CD can be divided into three subcategories: typical, atypical, and silent (Fansano & Catassi, 2001; Lionetti & Catassi, 2011). Gastrointestinal presentations including chronic diarrhea, vomiting, poor appetite, abdominal distension, abdominal pain, irritability, and failure to thrive were once considered to be "classic" symptoms of CD. Older children often present with atypical symptoms including subtle GI symptoms (e.g., constipation) as well as non-GI symptoms such as growth failure, short stature, crankiness, extreme weakness, anemia, mood swings, depression, delayed puberty, dermatitis, and sleep disturbance (Lionetti & Catassi, 2011; Megiorni & Pizzuti, 2012) (Table 1). Silent CD refers to children who have no symptoms of CD and is diagnosed through serological testing of a child who has an associated autoimmune or genetic disorder or a relative with CD (Lionetti & Catassi, 2011).

Diagnosis

Early diagnosis and treatment can drastically reduce and prevent serious complications (Fasano & Catassi, 2001). However, diagnosis of CD can be challenging and it is estimated that approximately 83% of Americans are undiagnosed or misdiagnosed. Rashid et al. (2005) found that one-third of families consulted more than two pediatricians before confirmation and that prior to diagnosis, these children received other diagnoses including anemia (15%), irritable bowel syndrome (11%), gastroesophageal reflux (8%), stress (8%), and peptic ulcer disease (4%). Testing for CD is dependent on the consumption of gluten and starting a gluten-free diet (GFD) before testing can result in a false negative as mucosal tissue heals and serological markers return to normal leading the patient and the family to believe that the patient does not have CD (Allen, 2015; Hill et al., 2016). The national North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, 2005) provides two algorithms for celiac testing in symptomatic and asymptomatic children (Figures 1 and 2). According to the American College of Gastroenterology Clinical Guidelines (Rubio-Tapia, Hill, Kelly, Calderwood, & Murray, 2013), testing for CD should occur in the following circumstances:

1. A child experiences symptoms, signs, or laboratory evidence suggestive of malabsorption (i.e., chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating).

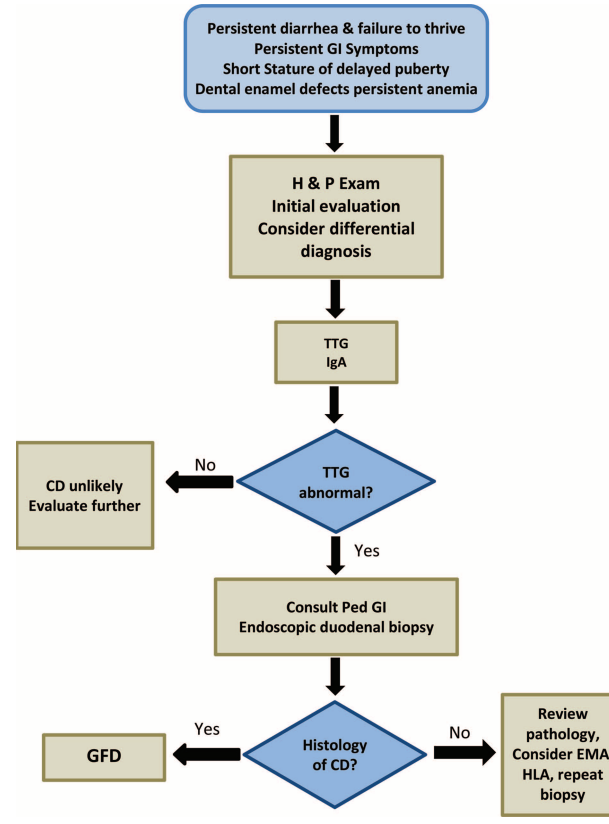

FIGURE 1. Algorithm of a child with symptoms. CD = celiac disease; EMA = endomysium; GFD = gluten-free diet; GI = gastrointestinal; HLA = human leukocyte antigen; IgA = immunoglobulin A; tTG = tissue transglutaminase. Reproduced with permission from NASPGHAN (2005).

2. A child with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD.
3. A child who experiences possible signs or symptoms of CD and whose first-degree family member has a confirmed diagnosis of CD.
4. Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD.

Several tests such as serologic tests, genetic testing, and histology are used to diagnose and monitor CD (Snyder et al., 2016). If CD is suspected, the first step is to perform a serologic test. Routine initial testing should be done with the tissue transglutaminase (tTG)-IgA antibody that has demonstrated high specificity and sensitivity (Hill et al., 2013; Hill et al., 2016; Holmes, 2010; Snyder et al., 2016). However, it is important to note that in approximately 10% of cases, a false-negative serologic evaluation can occur.

Although the accuracy of serologic tests is high, the accuracy may vary by the age of the child. Lagerqvist et al. (2008) found that in children older than

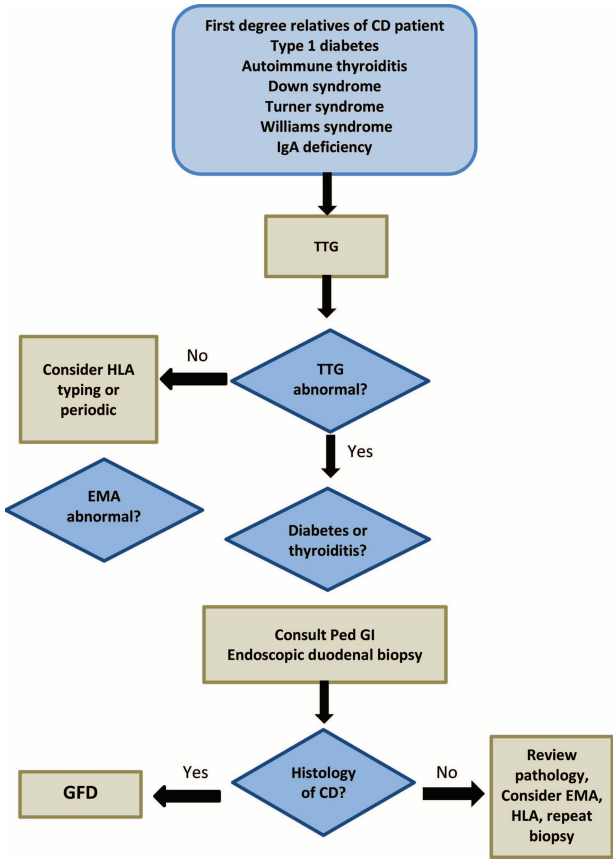

FIGURE 2. Algorithm of a child with no symptoms. CD = celiac disease; EMA = endomysium; GFD = gluten-free diet; GI = gastrointestinal; HLA = human leukocyte antigen; IgA = immunoglobulin A; tTG = tissue transglutaminase. Reproduced with permission from NASPGHAN (2005).

18 months, both tTG-IgA and endomysium (EMA)-IgA tests may not be accurate because a large proportion of younger children with CD lack these antibodies. Therefore, in children younger than 2 years, the tTg-IgA test should be combined with define DGP-IGA (first use) DGP-IgG to improve the accuracy of testing (Hill et al., 2016; Husby et al., 2012).

Children with positive serological tests should undergo a tissue biopsy because other medical conditions, such as diabetes, can cause a positive serum test (Newton, Kagnoff, & McNally, 2010). Furthermore, if a child is experiencing symptoms of CD and has a negative serological test, a biopsy is still recommended (Hill et al., 2005; Rubio-Tapia et al., 2013). However, new guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (2012) recommend that symptomatic children with serum anti-tTG antibody levels greater than 10 times the upper limit of normal are no longer required to undergo an upper endoscopy with duodenal biopsies to confirm diagnosis. Trovato et al. (2015) examined whether asymptomatic patients with serum anti-tTG antibody levels greater than 10 times the upper limit of normal should also be spared an upper endoscopy. They found that symptomatic and asymptomatic patients showed no difference in histological damage, thus concluding that asymptomatic children may also be spared the upper endoscopy.

Currently, in the U.S., formal diagnosis of CD must be done by biopsy as the results of serological tests suggest only the presence of CD (Hill et al., 2016; Newton et al., 2010). The gold standard of CD diagnosis is intestinal biopsy of the proximal duodenum. Positive biopsies show hypertrophy of the intestinal crypts and villous atrophy and are graded on a scale (Marsh) depending on the amount of hypertrophy, atrophy, and presence of antibody cells (Mangiavillano et al., 2010). Multiple biopsies should be taken in children as multiple sections of the intestine may be affected and a positive diagnosis of CD can lead to treatment and possible correction of weight gain problems (Mangiavillano et al., 2010).

Finally, genetic testing, HLA, can be an additional screening strategy; however, they should not be used as an initial diagnostic test. The two HLA genetic markers for CD, DQ2 and DQ8, are not specific to CD and occur in 40% of the population (Hill et al., 2016; Rubio-Tapia et al., 2013). Human leukocyte antigen testing should be used for children at risk for CD and have negative serology and for those patients who are in diagnostic dilemmas (Hill et al., 2016; Snyder et al., 2016). In addition, HLA testing can be useful in children who have been placed on a GFD without a positive serologic evaluation (Fasano & Catassi, 2012; Snyder et al., 2016).

Management

Significant advances have been made in the identification and diagnosis of CD; however, effective management of CD continues to remain problematic (Snyder et al., 2016). Currently, the only treatment for CD is to completely remove gluten from the diet and adopt a GFD. The diet must be maintained for the entire life of the person with CD and ingestion of gluten can cause a recurrence of abdominal symptoms and damage to the intestinal mucosa (Allen, 2015; Rubio-Tapia et al., 2013). Adherence to a GFD is difficult and compliance varies from 42% to 91% of patients complying with the diet (Black & Orfila, 2011). The American College of Gastroenterology (2013) recommends the following:

1. Children with CD should be monitored regularly for normal growth and development, new symptoms, adherence to GFD, and assessment of complications.
2. Periodic medical follow-up and consultation with a dietician.

3. Monitoring of adherence to GFD should be based on a history and serology.
4. Upper endoscopy with intestinal biopsies is recommended in children with a lack of clinical response.
5. Monitoring of normalization of laboratory values.

In addition to the aforementioned recommendations, Snyder et al. (2016) performed a critical review of 600 articles to develop recommendations for the treatment and monitoring of CD. The expert panel developed recommendations surrounding six key categories: bone health, hematologic issues, endocrine problems, liver disease, nutritional issues, and testing. Because of increased serological testing, children typically present with milder symptoms of osteoporosis and osteopenia (Snyder et al., 2016). The evidence clearly supports that a GFD diet with adequate nutrition reverses bone mineral density loss. In addition, supplementation of vitamin D is indicated (Snyder et al., 2016). However, there is disagreement and a lack of evidence regarding the use of diagnostic tests to monitor bone health. Routine screening for bone health is not supported by evidence; however, if the child does not adhere to a GFD, there is evidence that routine bone density studies should be performed to evaluate bone health. In addition, there is an agreement that screening for vitamin D and calcium is indicated.

Anemia is reported in up to 70% of patients with CD. Because of the prevalence of anemia in children with CD, there is strong evidence to support screening for anemia at the time of diagnosis. In addition, although the evidence is weak, Snyder et al. (2016) agree that routine screening for anemia should be performed. Children with CD should be screened for thyroid disease with thyrotropin. Mild elevation of serum liver enzymes is also common in children with CD; however, the majority of affected patients will have normal transaminase levels 4–8 months after adopting a GFD (Vajro, Paolella, Maggiore, & Giuseppe, 2013).

Finally, long-term management should involve a team of pediatric specialists (e.g., gastroenterologist, pediatrician, dietician, psychologist) who have experience in CD (Hill et al., 2016). Children with CD should be serologically tested after 3–6 months of treatment with a GFD and routinely serologically tested and monitored for the assessment of returning or new symptoms, growth, and adherence to GFD (Rubio-Tapia et al., 2013). If the serology is positive, the child may not be adhering to the GFD or unknown gluten contamination may be occurring. The child's diet should be evaluated to determine etiology and provide additional education and support regarding dietary compliance. If the serological testing is normal, but the child is having CD symptoms, further evaluation needs to be performed (Hill et al., 2005). After stabilization of symptoms, children with CD should be monitored yearly.

Delayed diagnosis and treatment noncompliance can result in serious long-term effects and complications resulting in increased mortality and decreased quality of life (Fasano & Catassi, 2012; Snyder et al., 2016). Serious complications are related to severe nutritional deficiencies and include growth failure, delayed puberty, iron deficiency anemia, and impaired bone health (Fasano & Catassi, 2001; Hill et al., 2005). Furthermore, vitamin and mineral deficiencies may cause osteoporosis, anemia, clubbing, and cutaneous bleeding (Amerine, 2006; Tully, 2008). There is also an increased risk in developing non-Hodgkin lymphoma, esophageal and pharyngeal carcinoma, primary liver cancer (Catassi, Bearzi, & Holmes, 2005), bowel adenocarcinoma (Nelsen, 2002), dental enamel defects, alopecia, infertility (Farrell & Kelly, 2002; Hill et al., 2005), and depression (Green, 2005).

Nursing Implications

Nurses play an important role in the identification and treatment of CD. Evidence demonstrates that the GI signs and symptoms of CD are no longer the classical presentation. Regardless of the practice setting, the registered nurse may be the first healthcare provider to identify children who are at risk for CD. Nurses can educate parents regarding both GI and non-GI symptoms and appropriate testing resulting in earlier diagnosis and treatment. As an advocate for the child and the family, nurses can encourage testing while the child is still on a diet containing gluten, thus reducing false negatives. Nurses should have basic knowledge about the GFD to help provide education to parents and children regarding dietary adherence along with referrals to a registered dietician and social worker (Ludvigsson et al., 2016; Roma et al., 2010).

In addition to education and proper referrals, parents should be encouraged to join and participate in CD support groups (Roma et al., 2010; Sharrett & Cureton, 2007), which can be of particular importance in learning valuable tips from those experienced in dealing with the day-to-day trials of GF dietary management. If no local support group exists, additional resources are often available to parents via online celiac Web sites (Table 2) that offer national support groups. Knowledge of necessary dietary modifications, access to GF foods, and social support are common components that factor into compliance with the GFD (Roma et al., 2010; Sharrett & Cureton, 2007).

Parents also need to be informed of the risk of exposure to gluten in sources other than food. Gluten can be present in non–food products such as hygiene products, lip gloss/lipstick, moisturizers, cosmetics,

TABLE 2. Online Resources[a]

American Celiac Society	www.americanceliacsociety.org
Academy of Nutrition and Dietetics	www.eatright.org
Beyond Celiac	www.beyondceliac.org/
Canadian Celiac Association[a]	www.celiac.ca
Catholic Celiac Society	www.catholicceliacs.org
Celiac Disease Awareness Campaign (National Institutes of Health)	www.celiac.nih.gov
Celiac Disease and Gluten-Free Resource	www.celiac.com
Celiac Disease Center at Columbia University	www.celiacdiseasecenter.columbia.edu/
Celiac Disease Foundation[a]	www.celiac.org
Celiac Sprue Association USA[a]	www.csaceliacs.info/
Gluten Intolerance Group of North America[a]	www.gluten.net/
Gluten-Free Living	www.glutenfreeliving.com
National Foundation for Celiac Awareness	www.celiaccentral.org
North American Society for Pediatric Gastroenterology,	www.naspghan.org
Hepatology and Nutrition, University of Maryland Center for Celiac Research	www.celiaccenter.org

[a]Celiac Support Group Available.

over-the-counter medications, children's vitamins, some prescriptions, and arts and craft supplies (Kids with Food Allergies, 2013). Currently, the Food and Drug Administration does not require the labeling of prescription or over-the-counter medications. In addition, no regulation exists in the labeling of cosmetics or beauty products. However, multiple Web sites are available as resources for health providers and parents (Table 2) to provide guidance in identifying high-risk products.

Developmental stages of the child should also be considered when screening for the risk of exposure to nonfood gluten-containing products. For example, preschoolers and school-aged children's use of arts and crafts may place them at risk when using these products and then putting their hands near the face or the mouth. Day care providers and teachers should be educated on the risks of gluten in art and craft products and should be observant for items containing gluten. Parents should be advised that contents in personal hygiene products, cosmetics, vitamins, and prescriptions can change frequently and should be monitored on a regular basis. Nurses can direct parents to online resources that provide up-to-date information on available products to help families implement necessary dietary and lifestyle changes (Zawahir, Safta, & Fasano, 2009).

Nurses are in the ideal position to provide education to families regarding diagnosis and treatment of CD, assess family coping, adhere to the GFD, and increase awareness of the developmental challenges of children and adolescents. It is important that nurses have current and relevant information. For example, there is disagreement in the literature regarding exclusive breastfeeding and gluten introduction. However, a recent systematic review by Silano et al. (2016) found no evidence that supported exclusive breastfeeding as a protective factor. In addition, Silano et al. (2016) found no evidence to support the avoidance of early or late gluten introduction in the majority of children at risk for CD. The one exception noted was DQ2 homozygous girls where early introduction of gluten may be associated with a greater risk of developing CD (Lionetti et al., 2014).

Adhering to a GFD can be especially challenging, because it requires daily lifestyle adjustments by both the child and the parents (Gelfond & Fasano, 2006; Van Doorn, Winkler, Zwinderman, Mearin, & Koopman, 2008). However, these challenges can also increase as children grow older and develop more independence from parents. New social situations, school trips, and extracurricular activities with peers can increase risk on nonadherence to the GFD in adolescents (Roma et al., 2010). Adherence to the GFD during adolescence can be additionally linked to social inconvenience and lack of knowledge and understanding by others (Olsson, Lyon, Hornell, Ivarsson, & Sydner, 2009), with eating out at restaurants with friends, partaking in social activities, and having to educate others on CD being identified issues (Olsson et al., 2009; Rubio-Tapia & Murray, 2010b).

Adolescents with minimal immediate symptoms related to gluten ingestion are also more likely to be noncompliant with the GFD (Olsson et al., 2009) as it is felt that there is less consequence to health as a result. However, dietary nonadherence is also associated with decreased quality of life (QoL), eventual increased physical symptoms, and long-term health risks such as osteoporosis (Lebwohl, Mechaëlsson, & Green, 2014). It is recommended that the importance of dietary adherence and the consequences of not adhering to the GFD be discussed regularly with adolescents as they transition to increased levels of CD self-management (Ludvigsson et al., 2016).

Conclusion

Not all children who have CD present with classical signs and symptoms and healthcare providers must be aware of the variety of presentations in pediatrics. In fact, many children present with atypical or silent CD and live undiagnosed for several years before finally obtaining a correct diagnosis. New guidelines recommend increased testing using newer, more reliable and valid method of serological testing. In addition, genetic tests are becoming increasingly more common to diagnose CD in children with challenging or atypical clinical presentation. Nurses can educate parents on early recognition of symptoms, particularly in high-risk children, leading to proper screening and earlier diagnosis of CD. The only known treatment to date is modification to a GFD. However, adherence to a GFD is challenging and long-term physical and emotional responses can occur for children with CD. Further consideration of QOL issues for these children and their families is important in long-term management of CD. ✪

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