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Celiac disease in children: an old disease with new features

N. RIZKALLA REILLY [1], R. DIXIT [2], S. SIMPSON [2], P. H. GREEN [2]

[1]Division of Pediatric Gastroenterology
Columbia University Medical Center
New York, NY, USA
[2]Department of Medicine
The Celiac Disease Center, Columbia University
Medical Center, New York, NY, USA

Celiac disease is an underdiagnosed condition in children with variable manifestations. Presenting symptoms in children are changing over time, are impacted by age and geography, and are distinct from those of adults with this disease. Prompt diagnosis of celiac disease in affected children may avoid growth and nutritional deficits in addition to preventing long term disease complications such as infertility and malignancy. Diagnosis and management of celiac disease in children requires expert medical and nutritional care to maximize positive outcomes.

Key words: **Celiac disease - Diet, gluten-free - Pediatrics.**

Celiac disease (CD) is an enteropathy induced by gluten in genetically-susceptible individuals. Although historically known as a disease of childhood, CD is now known to affect both adults and children, with a range of manifestations and associated comorbidities. The manifestations, diagnosis, and management of CD in children are distinct from the clinical picture and treatment of adults. Appropriately diagnosing children suffering from CD is critical to ensure appropriate nutrition, growth, physical and cognitive development, as well as to avoid long term sequelae of the disease such as osteoporosis, infertility, and malignancy.

Pathogenesis

Development of CD is induced by a combination of factors (Figure 1). Each of these constitutes a necessary, though unilaterally insufficient, component in disease pathogenesis.

Immunology of celiac disease

Gluten is the major storage protein of wheat and related grains, such as rye and barley. In its normal metabolism, gluten is degraded by gastric, pancreatic and intestinal brush border enzymes into peptides, including gliadin. Gliadin is resistant to enzymatic degradation, conferring its antigenicity in genetically susceptible individuals.[1, 2]

Conflicts of interest.—The authors have no conflicts of interest to declare.

Corresponding author: P. H. Green, MD, Celiac Disease Center, Columbia University College of Physicians and Surgeons, 180 Fort Washington Ave., Rm. 956, New York, NY 10032, USA. E-mail: pg11@columbia.edu

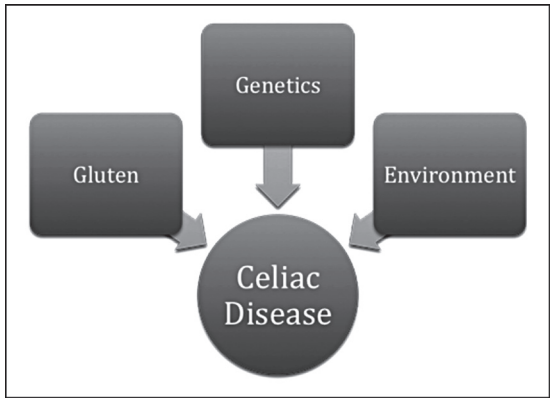

Figure 1.—Factors contributing to celiac disease pathogenesis.

Both adaptive and innate immune responses provide the basis for the onset and evolution of CD in the individual. In terms of adaptive immunity, gliadin may gain access to the lamina propria through infection, inflammation or other moderators of epithelial damage and mucosal permeability. Once in the lamina propria, gliadin encounters tissue transglutaminase-2 (TG2), an enzyme produced in association with elements of the extracellular matrix and which may both deamidate as well as crosslink gliadin. The amino acid composition of gliadin, including the high proportion of proline residues, makes it a preferred substrate for deamidation by TG2.[3] With rare exception, individuals with CD possess the HLA Class II genes DQ2 and/or DQ8, expressed on antigen presenting cells. Negatively-charged deamidated gliadin binds to HLA-DQ2 and DQ8 cell surface receptors with high affinity, inducing a gliadin-specific $CD4^+$ Th1 T cell response and triggering chemokine release, including interferon-γ.[4, 5] The resulting cytokine cascade produces destructive intermediates, including metalloproteinases, causing tissue damage marked by intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy.[6]

Release of interleukin-15 (IL-15), as part of the innate immune response, induces tissue damage and serves a key role in the pathogenesis of CD.[7, 8] While this mechanism has not been well-described at this point, IL-15 may impede the regulatory and suppressive T cell activity which is ordinarily upregulated in the intestinal mucosa of patients with untreated CD.[9]

Genetics

Predisposition for CD is determined by the presence of HLA-DQ2 and HLA-DQ8. Among individuals with CD, 95% express DQ2, with the remaining 5% expressing DQ8. HLA-DQ2, however, is relatively common among healthy individuals, with a prevalence in the order of 30%.[10] Approximately 2-5% of individuals with the HLA-DQ2 or DQ8 heterodimers go on to develop CD. Absence of HLA-DQ2 and HLA-DQ8 has a negative predictive value approaching 100%.[10] Monozygotic twins demonstrate greater CD concordance than dizygotic twins, and far greater than the general population, but this concordance rate does not reach 100%,[11] indicating that genetic potential alone does not completely control disease pathogenesis. Environment clearly plays an integral role.

Environment and CD

Factors including physical environment, diet, and intestinal microbiome, among others, are potential influences of the pathogenesis of CD. Swedish children born in the summer had an increased risk of developing CD in one study, which may reflect differences in dietary behaviors or seasonal infectious causes, among other potential explanations.[12] Socioeconomic status and geographic distribution may also impact disease presentation, though the reasons for this are unclear.[13] Rotavirus infection is associated with an increased risk of CD autoimmunity in children possessing HLA risk alleles, with increasing risk in children sustaining multiple infections,[14] though simple gastroenteritis occurring during gluten introduction does not seem to confer the same risk.[15]

The Swedish epidemic of CD from 1973 to 1997, during which a dramatic increase in the incidence of CD was noted among

children below 2 years of age in concert with alterations in breastfeeding behavior and in the timing of gluten introduction, illustrates the influence of infant feeding practices upon CD risk.[16] Longer duration of breastfeeding and overlap of gluten introduction into the infant diet with breastfeeding is protective against the development of CD, though it remains unclear whether these practices reduce the incidence or delay disease onset.[17, 18] There appears to be a protective window of time in infancy during which genetically predisposed children may begin consuming gluten with a lower risk of developing CD. Children with genetic susceptibility for CD were shown to be at increased risk of manifesting serologic evidence of CD if introduced to gluten prior to age 4 months or after age 6 months — in infants consuming gluten early in infancy, a 5-fold risk was noted.[19]

Method of delivery at birth also appears to play a role in disease onset. There is an association between cesarean delivery and development of CD,[20] and method of delivery had been shown to affect the composition of intestinal microflora in the infant gut.[21] Additionally, the composition of bacteria in the human intestine has been shown to affect the development of the mucosal immune system, including Th1 and Th2 responses.[22, 23] Alterations in these responses in children delivered by cesarean section may contribute to the development of conditions marked by aberrant immune responses, such as CD.

Prevalence

The prevalence of CD among the general population is approximately 0.75-1.5%.[24-26] The highest prevalence described is in the Saharawi community of western Africa, with CD found in 5.6% of the general pediatric population.[27]

CD remains an underdiagnosed condition, though the rate of detection of CD is increasing.[28-30] While greater disease awareness may be responsible for some of this increase, the prevalence of CD has been increasing over the past several decades.[26, 31] The increase in disease prevalence may be attributable, at least in part, to improved serological screening assays, which are now highly sensitive and specific.[24, 32, 33] However, as important a role as detection may play in rising disease prevalence, this cannot account for the increase in seroprevalence reported using stored sera.[24, 27, 32, 33] Other environmental factors are likely involved, including alterations in the processing of grains and patterns of gluten ingestion.[24, 33, 34]

Presentation

CD has a varied presentation, impacted by factors such as age at presentation and duration of disease. Young children present more often with "classical" CD, marked by diarrhea, abdominal distension, and failure to thrive.[35, 36] Older children and adolescents are more likely to present with atypical gastrointestinal complaints such as pain, vomiting, or constipation; extraintestinal symptoms such as arthritis, neurologic symptoms, and anemia; or may have silent disease without any apparent symptoms.[37, 38] Our experience shows that currently, the bulk of children present with abdominal pain or via serological screening while only 9% of children presented with diarrhea. In fact, diarrhea and the malabsorption syndrome were mainly evident in the very young, less than 2 years of age, with pain becoming a frequent presenting complaint among older children (Figure 2).

In addition to the diverse spectrum of disease presentations and age-related variability of the manifestations of CD, the shifting presentation of the disease over time should be recognized. An overall decrease in the prevalence of diarrheal presentations over the past two decades, accompanied by an increase in atypical manifestations of the disease, has been well-described in both adults and children.[30, 39, 40] More widespread use of serologic markers has facilitated diagnosis of CD in children,[40] but this alone does not

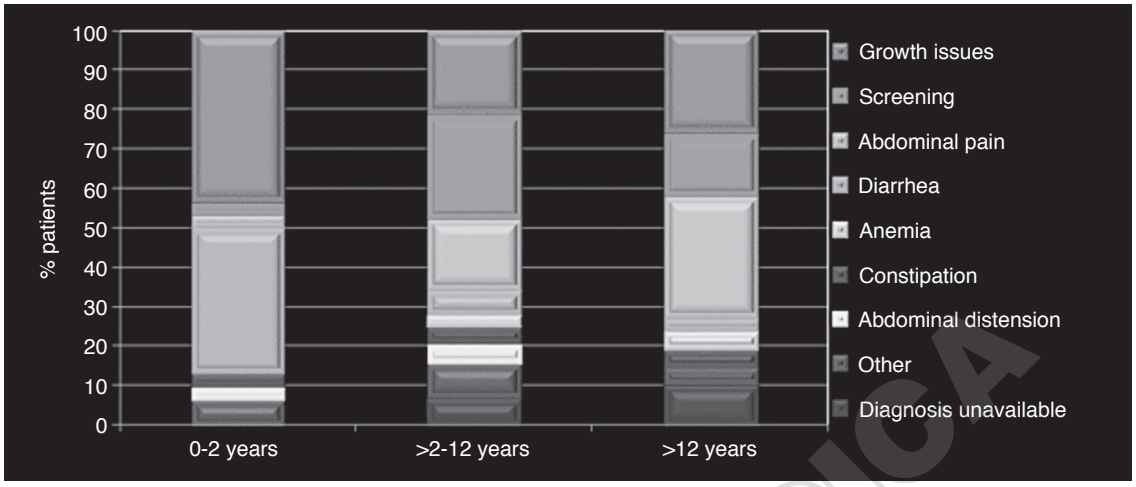

Figure 2.—Presentation of pediatric celiac disease patients by age. For ≤2 years, n=30; for >2-12 years, N.=200; for >12 years, N.=88.

entirely explain the decrease in diarrheal manifestations, as many long-term studies of adult and pediatric patients predating the use of these markers have documented this shift in clinical presentation.[39, 41] Of note, since the initial availability of sensitive and specific serological assays over the past two decades, the gap between initial presentation and diagnosis in symptomatic children has been gradually fading.[35, 37]

Serological screening of at-risk groups is undoubtedly responsible for increased detection of CD in asymptomatic children. Improved serological techniques has led to a dramatic increase in the prevalence of asymptomatic disease identified due to serological screening of first-degree relatives, those with associated autoimmune conditions, and atypical extraintestinal manifestations of the disease.[40, 42]

Associated conditions

The association between CD and type 1 diabetes in children is well-described.[43, 44] The presentation of diabetes generally precedes that of CD in children. There are conflicting data as to whether treatment of CD with a gluten-free diet may improve glucose control in those with type 1 diabetes. Some studies report increased insulin requirements among these patients after treatment [45] and lower hemoglobin A1C levels at diagnosis which, following treatment with a gluten-free diet, rise to the level of controls with diabetes but without CD.[46] Other investigators have found that treatment of CD with a gluten-free diet does not impact glycemic control of diabetic children though, treatment with a gluten-free diet in the setting of diabetes may improve pediatric growth outcomes.[47] While an increased prevalence of CD has been described among adults with autoimmune thyroid disease, this association has not been well-described in children.[48]

IgA-deficient patients have a 10-30% prevalence of CD [49, 50] and should be screened for development of CD. Children and adolescents with autoimmune liver disease, including biliary disease, have a high prevalence of CD as well.[51, 52] The association between CD and autoimmune hepatitis (AIH) has been limited to type 1 AIM. An increased prevalence of CD has additionally been identified in children with Down Syndrome (7%).[53, 55] Screening should be considered in patients with such conditions associated with a comparatively high prevalence of CD.

Diagnosis

A diagnosis of CD may be rendered in a patient who demonstrates characteristic

lesions on duodenal biopsy (increased intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy) as well as response to treatment with exclusion of dietary gluten. Serology is useful in identifying patients in need of biopsy. In complicated cases, HLA typing may be necessary to support a suspected diagnosis.

Serology

Serological tools available to screen patients for CD include IgA and IgG class anti-gliadin antibodies (AGA-IgA, AGA-IgG); more recently developed IgA and IgG class deamidated gliadin peptide antibodies (DGP-IgA, DGP-IgG); IgA class anti-endomysium antibodies (EMA); and anti-tissue transglutaminase IgA (TG-2). AGA — IgA and IgG are directed against dietary gliadin, DGP antibodies against deamidated synthetic gliadin peptide molecules, EMA against connective tissue elements (mainly tissue transglutaminase), and TG-2 against tissue transglutaminase — the enzyme responsible for the deamidation of gliadin in the lamina propria.

Which of these antibodies should be selected to test a particular child for CD, either singularly or in combination, is a matter of some debate. The performance of DGP in detecting CD has been shown to be equal in sensitivity and specificity to EMA and TG-2 testing in adults. When combined with other testing methods, DGP appears to be useful as an adjunctive method in establishing a diagnosis of CD as well as monitoring therapy. A combined conjugate of IgA and IgG DGP and TG-2 was 100% specific in diagnosing CD in 119 children with biopsy-proven disease.[56] DGP was recently shown to be superior to EMA and TG-2 in monitoring dietary compliance in a group of Italian children after diagnosis, though did not outperform these serologies in screening.[57] However, in a group of young children, DGP alone showed poor specificity relative to EMA and TG-2, though good sensitivity.[58] A combination of TG-2 and DGP has excellent sensitivity and specificity in identifying children requiring duodenal biopsy to evaluate for CD, though there may be other combinations with equal yield.

Both IgA and IgG-class AGA have poor accuracy, both for screening and monitoring compliance, and should be avoided.[59] An exception to this exists in children less than 24 months of age, in whom AGA may be useful in diagnosis, although authors of recent Italian and Swedish studies on the subject recommended a combination of AGA, TG-2, and EMA for these patients.[60, 61] For young children in whom only AGA is elevated, DGP may differentiate between those with true CD and those with other causes of their symptoms and duodenal pathology.[62]

Another special circumstance exists in the case of IgA-deficient children. In these patients, IgA-based serological methods are unreliable and IgG-class testing should be utilized. DGP-IgG or TG-2 IgG should be used in these cases.[63, 64]

Biopsy

A duodenal biopsy should be collected in any patient suspected to have CD prior to initiation of dietary treatment. This enables the diagnosis of this lifelong condition to be established with certainty, and for the patient's risk for comorbidities to be fully stratified. Additionally, patients diagnosed based on serological assays alone who fail to respond to dietary treatment may eventually undergo biopsy, the results of which pose a diagnostic dilemma if normal at that point. However, recent ESPGHAN guidelines on the subject state that in cases in which a child manifests clear symptoms of CD, demonstrates very high levels of TG-2, and has confirmatory HLA testing, the physician may consider omitting a duodenal biopsy.[65]

The number of duodenal biopsies taken and the location of these biopsies are critical factors in attaining the appropriate confidence level that a diagnosis is made where one exists. The current recommendation from adult literature is that a minimum of 4 duodenal biopsies should be taken.[66, 67] These studies have not been replicated in

children. Additionally, both adult and pediatric studies have shown that at least one biopsy should be taken from the duodenal bulb, due to the patchy nature of the disease and the potential that findings consistent with CD may only be found here in some patients.[68, 69]

The typical histological lesion of CD demonstrates villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. However, there is a wide range of histopathology which may be consistent with CD, ranging from intraepithelial lymphocytosis alone to total villous atrophy.[70] In addition, many other childhood conditions may cause small bowel villous atrophy, including autoimmune enteropathy; immune deficiency; dietary protein-induced enteropathy; viral, bacterial, and parasitic infections; eosinophilic gastroenteritis, and Crohns disease. Distinguishing CD among these other possible etiologies requires a skilled pathologist, additional evidence provided by serology and HLA-typing, and response to treatment with a gluten-free diet.

Some children with elevated serologies may not demonstrate the expected lesions on small bowel biopsy. Such patients are often said to have potential CD. The outcome of children with potential CD is not well-known, though up to one-third may manifest histological findings of CD after 3 years.[71] These patients should be followed, and may require additional serologic and histologic evaluation to confirm or rule out the diagnosis.

Genetic testing

Which pediatric patients should undergo HLA gene testing must be assessed on an individual basis. For children with biopsy and serology findings consistent with CD, as well as a positive response to a gluten-free diet, HLA testing is not necessary. At the time of presentation to the gastroenterologist, some children may have already undergone testing for the HLA-DQ2 or DQ8 alleles if this was requested by another provider following diagnosis of a sibling or parent with CD. In counseling patients for whom HLA typing has been done or is being considered, families should be advised as to the poor specificity associated with carrying one of these haplotypes.[72] However, children lacking both alleles are highly unlikely to have CD,[72] and in such patients this diagnosis may be excluded with no further serological testing necessary. For children with the presence of one or both haplotypes, clinical concern for CD, or a first-degree relative diagnosed with CD, serological screening should be performed and the patient should then undergo endoscopic biopsy if indicated. Knowledge of the presence of HLA-DQ2 or DQ8 may also be of use in cases of equivocal biopsy findings and low-titer or negative serological testing results.

Wireless capsule endoscopy

In children for whom there is a high index of suspicion for CD but lack of endoscopic findings, or who are not suitable candidates for endoscopic biopsy (such as poor anesthesia candidates or those with bleeding disorders) wireless capsule endoscopy (WCE) may aid in diagnosis.[73] WCE is generally well-tolerated in children, but in those too young or unable to swallow the capsule, anesthesia is required for endoscopic placement. In adult patients, WCE was 70-93% sensitive and 100% specific in detection lesions of villous atrophy.[74, 75] Such data is not yet available in children. Quantified image analysis may reduce elements of bias in WCE interpretation and may improve the sensitivity of this technology in CD diagnosis.[76] Patients without marked symptoms or highly elevated serologies should be diagnosed with care by WCE, however, and additional measures such as HLA testing and gluten challenge following withdrawal should be considered to solidify a diagnosis of CD.

Treatment and surveillance

The only treatment for CD is a lifelong gluten-free diet. Gluten-free foods may not

be widely available and, in countries in which such specialized foods do not qualify for government subsidies, can be costly as well.[77, 78] For treatment to be successful, a dietitian with expertise in CD should be consulted if possible. An initial dietary consultation for a child with CD should include a thorough nutrition assessment; inventory of typical eating habits and usual intake, food preferences, and restrictions; budget constraints; social supports; and baseline adequacy of macronutrient and micronutrient intake. Anthropometrics and laboratory values should be evaluated, and medication intake as well as other chronic illnesses must be considered.

The major concerns for children prescribed a gluten-free diet include compliance with the diet, adequate macronutrient and micronutrient intake, and appropriate growth. Gluten-free foods are not consistently fortified and may not provide sufficient amounts of certain nutrients, particularly fiber, iron, calcium and the B vitamins,[79] though children with CD have been shown to be mainly deficient in vitamin D and several other micronutrients, with sufficient calcium and iron intake, relative to their peers without CD.[80] We generally recommend a daily gluten-free multivitamin for children with CD.

Most children with newly diagnosed CD tolerate lactose and do not require a lactose-free diet.[81] However, some patients with significant symptoms may benefit from an empiric trial of temporary lactose restriction or lactase supplementation.[82] Care should be taken, however, to ensure adequate vitamin D and calcium intake, particularly if dairy intake is low, since children with CD demonstrate low bone mineral density at diagnosis and have the potential to reverse these findings with adequate dietary treatment.[83]

While children with growth deficits should clearly be followed for improvement following initiation of dietary treatment, children with a normal Body Mass Index (BMI) at diagnosis warrant surveillance to monitor for and prevent unwanted weight loss or progression to overweight. Children with CD may be at risk of becoming overweight due to high fat consumption while adhering to a gluten-free diet.[84] Growth patterns of the overweight child should also be monitored to ensure that this does not worsen. Overweight and obesity are more common among children with CD than has traditionally been recognized.[85, 86] Studies indicate that a gluten-free diet may have a beneficial effect upon the BMI of overweight adults and children with CD.[86, 87]

Ensuring that purchased foods are gluten-free requires education in label reading, particularly in countries in which foods are not routinely labeled with their gluten content. Purchased foods should be free of wheat, rye, barley, malt and certain oats. Although pure oats have been shown to be safe in adults and children with CD,[88, 89] oats may become contaminated during processing and must be guaranteed to be pure prior to being recommended to a child with CD.

Cross-contamination is an issue of particular importance for children with CD. Generally speaking, all food preparation areas, utensils, pots, pans, plates, cutlery and cooking appliances must be well-cleaned after use, particularly if used for gluten-containing foods. We recommend use of separate toasters, colanders and condiments such as peanut butter, butter, and mayonnaise, which can become contaminated by repeated accessing with utensils. Buffets and bulk bins should be avoided. Foods that have been deep fried in the same oil as breaded products (such as French fries and corn chips) should be avoided, as well as foods cooked on contaminated grills. Young children must be monitored carefully, especially in group settings with other children, to ensure that food is not shared and that hands are cleaned well and frequently to avoid contamination from hand-to-mouth behaviors.

There is no universally agreed upon panel of laboratory studies which should be monitored in children with CD. Certainly, celiac-specific autoantibodies should be reassessed after diagnosis. These may be measured approximately 6 months after adherence to a gluten-free diet and repeated every 3-6

months until normalization has been documented. Following that point, if the child is doing well clinically, he or she should be assessed annually. In terms of other laboratory surveillance, one should document correction of previously-recognized deficiencies, such as anemia, hepatic transaminitis, or vitamin deficiencies. Iron, zinc, and vitamin D may be measured, as these have been shown to be depleted in patients with CD, however few studies have specifically addressed this in children.[90-92] Patients should undergo regular surveillance for type 1 diabetes and autoimmune thyroid disease.

Children with CD may not seroconvert in response to hepatitis B immunization if the vaccine is administered prior to treatment with a gluten-free diet.[93] Providers should consider assessing immunity to hepatitis B as revaccination may be necessary in some children with CD following dietary treatment.

The future of CD treatment: alternatives to dietary therapy

Although the safety of a gluten-free diet is clear, many patients with CD are eager for non-dietary treatments.[94] There is potential for selection of wheat varieties lacking T-cell stimulating sequences which may be safe for individuals with CD.[95, 96] Luminal therapies are undergoing investigation, such as use of prolyl endoproteases to digest gluten,[97] or binding agents [98] to neutralize gluten and prevent toxicity. Drugs that may decrease intestinal permeability, altering the course of CD, are also being studied.[99] Investigation into vaccination and desensitization is underway, and mediators in disease pathogenesis, such as interferon-γ and IL-15, are potential targets for pharmacotherapy.[100] Some of these therapies are currently in clinical trials in adults. The applicability to use in childhood will require specific testing.

Conclusions

CD is a condition with unique characteristics in the pediatric population. Approaches to diagnosis and treatment are evolving, and must be tailored to the individual patient, as differences in age alone can significantly impact disease manifestations, diagnostic an therapeutic approaches. Attention must be paid to the specific needs of children affected with CD to maximize successful treatment.

Riassunto

La malattia celiaca nei bambini: una vecchia patologia con nuove caratteristiche

La malattia celiaca (*celiac disease*, CD) è un'enteropatia indotta dal glutine in individui geneticamente predisposti. Sebbene storicamente sia stata considerata una patologia dell'infanzia, è oggi noto che la CD colpisce sia gli adulti sia i bambini, con una serie di manifestazioni e comorbilità associate. Le manifestazioni, la diagnosi e la gestione della CD nei bambini sono distinte dal quadro clinico e dal trattamento degli adulti. Un'adeguata diagnosi dei bambini che soffrono di CD è essenziale per garantire una nutrizione, una crescita e uno sviluppo fisico e cognitivo adeguati, oltre che per evitare sequele della patologia come l'osteoporosi, la sterilità e i tumori maligni.

Parole chiave: Malattia celiaca – Dieta priva di glutine – Pediatria.

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