Pediatric Celiac Iceberg: An old nosology or a new challenge

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Abstract

Introduction: celiac disease, or gluten-sensitive enteropathy, is an autoimmune disorder characterized by inflammation, villous atrophy, and crypt hyperplasia of the small-bowel mucosa. The mucosal lesion develops in genetically susceptible individuals after ingestion of dietary gluten and recovers when gluten-containing cereals, wheat, rye, and barley, are withdrawn from the diet. Population-based screening studies have shown that at least 0.5% of adults in Western countries suffer from the disease. Patients may present with only subtle, if any, symptoms , which is the main reason why the disease is highly under diagnosed in the United States and elsewhere. This notwithstanding, the disease should be detected as early as possible, because untreated celiac disease is associated with many, even severe, complications such as intestinal lymphoma or cancer and osteoporosis.

Case presentation:A 14 years old female girl(K.A), born second from a twin pregnancy, term delivery, Bw= 2000 gr, was admitted at the Paediatric Endocrinology Department for short stature, loss of appetite, growth failure, puberty delay.

She was admitted several times in hospital for anaemia, she took medication but the sings didn't improve at all. She had abdominal discomfort and learned the attitude of being elective with foods. She preferred cornproducts rather than wheat ones.

After we performed protocol screening, several findings, iron deficiency anaemia, malnutrition, X- ray of the hand showed a growth delay (her radiological age was 7 years), increased IgA and positive antitransglutaminaseauto antibodies.

The patient was then transferred to the Gastroenterology department for further evaluation and treatment. After the gluten-free diet the girl's symptoms improved within weeks with weight gain, better appetite, increased height.

Conclusions: It is obvious that a number of patients with diverse endocrinological disorders suffer from celiac disease, the symptoms of the disease being sometimes, if not mostly, subtle or atypical. For this reason the majority of patients remain undetected. For initial screening purposes, up-to-date serological antitissue transglutaminase antibodies, are highly specific and sensitive enough in cases in which symptoms do not clearly indicate celiac disease. Thereis no doubt that many patients with celiac disease primarily contact specialists other than gastroenterologists. The majority of cases thus remain undetected. A close association between various autoimmune endocrinological disorders and celiac disease has been shown in numerous studies. Symptoms usually disappear on a gluten-free diet within a few weeks, whereas the recovery of the small-bowel mucosa may take much longer, 1 year or even more.

KEYWORDS: Celiac icebearg, nosology, pediatric, albania

I. Introduction

Celiac Disease, Or gluten-sensitive enteropathy, is an autoimmune disorder characterized by inflammation, villous atrophy, and crypt hyperplasia of the small-bowel mucosa. The mucosal lesion develops in genetically susceptible individuals after ingestion of dietary gluten and recovers when gluten-containing cereals, wheat, rye, and barley, are withdrawn from the diet[1] . Population-based screening studies have shown that at least 0.5% of adults in Western countries suffer from the disease[2]. Patients may present with only subtle, if any, symptoms[3] , which is the main reason why the disease is highly underdiagnosed in the United States and elsewhere [4, 5] This notwithstanding, the disease should be detected as early as possible, because untreated celiac disease is associated with many, even severe, complications such as intestinal lymphoma or cancer[6] and osteoporosis [7].

The disease is generally considered to affect mainly the gastrointestinal tract. Recent evidence has shown, however, that the condition may also involve a number of extraintestinal manifestations, and patients may thus be referred initially to specialists other than gastroenterologists. Circulating antibodies against gliadin, endomysium, and tissue transglutaminase are typical for the condition, and the development of sensitive and specific antibody assays [8]makes it easy to screen for celiac disease, especially in cases where typical gastrointestinal symptoms are not obvious.

Endocrinologists should consider celiac disease in different autoimmune conditions where the prevalence of the condition is distinctly higher than in the general population. Symptoms suggestive of celiac disease should be recognized and should signal the need for further examinations.

Presenting history

Present history: A 14 years old female girl(K.A), was admitted at the Paediatric Endocrinology Department for short stature, loss of appetite, growth failure, puberty delay.

Past history: The girl wasborn second from a twinpregnancy, term delivery, Bw= 2000 gr, her Apgar score was 8-9. She cry at birth and her neonatal period was normal. She was breastfed until 5 months laterwith the formula

She was admitted several timesin hospital for anaemia, she took medication but the sings didn't improve at all. She had abdominal discomfort and learned the attitude of being elective with foods. She preferred cornproducts rather than wheat ones.

Physical Examination:

Vitals:

Temp: 36.3 ºC, Pulse: 78 , Resp. Rate: 22 , BP: 90 / 60 mmHgO2 sats: 94% on room air.

General:

Alert, fretful, Height 135cm, weight 33 kg . Noacute distress.

HEENT:

Pupils equal, round, reactive to light and accommodation. Extra-ocularmovements intact. Moist mucous membranes in oropharynx.

Neck:

Supple, without lymphadenopathy or thyromegaly. No carotid bruits.

Lymph:
No axillary, cervical, supraclavicular, pre-auricular, submental, or occipitallymphadenopathy,
Cardiovascular:
Regular rate and rhythm, with normal S1 and S2. No murmurs, rubs, orgallops. No JVD. 2+ pulses bilaterally – dorsalis pedis and radial.
Lungs:
Vesicular breathing throw the two lung fields . No wheezes. No accessorymuscle use or cyanosis. No tenderness to palpation.
Abdomen:
Normative bowel sounds. Distended abdomen , liver and spleen was normal. No lymph node palpable.
Skin:
Warm, dry, well-perfuse. No rashes or other lesions.
Extremities:
2+ pulses in upper and lower extremities. No lower extremity pain or oedema;legs are symmetric in appearance.
Neuro:
Alert and oriented to person, place, and time. Able to communicate well.
Cranial nerves 2-12 grossly intact. 5/5 strength in all extremities bilaterally. Sensation intact in all extremities. Normal gait. 1. No clonus.
Admission labs:
WBC: 9.000, Hgb: 7.0 : Hct: 35.0,
Iron=24, other labs was normal.

After we performed protocol screening, several findings, iron deficiency anaemia, malnutrition, X- ray of the hand showed a growth delay (her radiological age was 7 years), increasedIgA and positive antitransglutaminaseauto antibodies.
The patient was then transferred to the Gastroenterology department for further evaluation and treatment. After the gluten-free diet the girl's symptoms improved within weeks with weight gain, better appetite, increased height.

Iron-deficiency anemia: In several studies, iron-deficiency anemia that is resistant to oral iron supplementation is reportedly the most common extraintestinal manifestation of celiac disease in adults. In children, iron deficiency with or without anemia is very common too, but seldom it is seen as the only presenting sign. Anemia can only be the result of folate, vitamin B-12 deficiency, and it may also coexist with anemia of chronic disease as a result of the chronic intestinal inflammation. In addition to anemia, a number of less common hematologic manifestations can be seen, including hyposplenism, thrombocytosis, and selective IgA deficiency. [9]
Short stature and delayed puberty: Short stature may be the only manifestation of celiac disease. As many as 10% of children with idiopathic short stature may have celiac disease that can be detected on serologic testing. Some patients with short stature also have impaired growth hormone production following provocative stimulation testing; this production returns to normal when the patient is put on a gluten-free diet. Adolescent girls with untreated celiac disease may have delayed onset of menarche.

Laboratory studies used to assess the major causes of short stature in children include the following:

- Measurement of serum levels of insulinlike growth factor-I (IGF-I), formerly named somatomedin C, and IGF binding protein-3 (IGFBP-3)
  - Interpret a low serum IGF-I concentration cautiously because poor nutrition is associated with low serum IGF-I concentration.
  - The serum IGFBP-3 concentration has greater specificity than serum IGF-I concentration in the diagnosis of GHD.
- Karyotype by G-banding
  - The 45,X pattern defines patients with Ullrich-Turner syndrome.
  - Because 10% of patients with Ullrich-Turner syndrome possess a mosaic karyotype (eg, 45,X; 46,XX), counting at least 30 cells reduces the possibility of failing to identify a patient with mosaic Turner syndrome (TS).
- Measuring serum levels of GH
  - Although a random serum GH value of more than 10 mg/dL generally excludes GHD, a random low serum GH concentration does not confirm the diagnosis of GHD.

Other useful tests include the following:

- CBC count for hematologic disease
- Wintrobe sedimentation rate for inflammatory bowel disease
- Antiendomysial immunoglobulin A (IgA) and immunoglobulin G (IgG), transglutaminase IgG, and antigliadin IgG titers for sprue (gluten enteropathy) (Antiendomysial IgA titers are more sensitive, and IgG titers are more specific.)
- Serum total thyroxine (total T4) and thyrotropin (TSH) levels to test for hypothyroidism
- Sweat chloride testing to exclude cystic fibrosis (CF): Consider this test in patients who are short and have a history of meconium ileus or pulmonary symptoms.
- Serum transferrin and prealbumin concentrations for undernutrition

Imaging & other studies:

We perform anteroposterior radiography of left hand and wrist to assess bone age which was delay bone development as a 7- years old gird and not as a 14- years old girl with chronological age.

Also we perform an abdominal ultrasoundwhich was normal with no evidence of genito - urinary tract malformation due to Turner Syndrome which was excluded with kariotype screening.

We perform a mucosal biopsy which resulted as Marsh 3.

Intervention

Mucosal biopsy of the duodenum shows the changes described in Workup. However, changes referred to as Marsh 1 or even Marsh 2 are nonspecific because they can also be found in food-allergic enteropathies, such as cow's milk allergy or soy allergy (especially in infancy). These changes are also observed in giardiasis and in autoimmune enteropathy.

Although also not pathognomonic for celiac disease, changes referred to as Marsh 3 are usually much more specific, especially if they are associated with supportive serology findings.

Evidence suggests that patients with Marsh type 1 changes who have a positive serology findings may develop more severe changes if they continue a gluten-containing diet; this challenges the idea that celiac disease is only observed in those who have more advanced findings.[10]

II. Diagnosis and Serological Screening of Celiac Disease

In untreated celiac disease the characteristic abnormalities in the small-bowel mucosa are villous atrophy, crypt hyperplasia, and an increased density of inflammatory cells in the epithelium and lamina propria. This type of lesion is nowadays uncommon in other conditions [11]The mucosal lesion recovers with a gluten-free diet and deteriorates further if the patient resumes a gluten-containing diet [1]IgA and positive antitransglutaminaseauto antibodies.
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At the present time, a small intestinal biopsy is almost invariably taken with biopsy forceps by upper gastrointestinal endoscopy, but devices are also available by which to obtain biopsies in fluoroscopy.
The current diagnostic criteria comprise the finding of typical mucosal lesion, and the introduction of a gluten-free diet should result in clinical or histological recovery. The occurrence of further mucosal deterioration upon gluten challenge was earlier recommended to distinguish the condition from other diseases causing villous blunting [12]; this is no longer necessary except in cases where the diagnosis has remained inconclusive [13].
The occurrence of circulating antibodies against gliadin or intestinal matrix further supports a diagnosis of celiac disease. Various antibody assays have been developed to select patients for diagnostic small-bowel biopsy. Antireticulin [12]and antigliadin [13] antibodies were the first tests to be employed in screening, the latter still being widely in use. In the context of celiac screening in asymptomatic patients and in various risk groups, however, the benefits of the more recent IgA class antiendomysial antibody test [14, 15] and the latest antitissue-transglutaminase te[16, 17]would now seem obvious.
First, the specificity of these tests is close to 100%, and the sensitivity is high enough for screening purposes. Antiendomysial antibody is a somewhat observer-dependent immunofluorescence test, whereas the antitissue transglutaminase antibody test is based on ELISA and is obviously easier to interpret and more suitable for large screening programs than the antiendomysial antibody. Both tests can well be applied in screening for celiac disease in patients with various endocrinological disorders, and the two can also be combined. A positive test result should always be confirmed by small-intestinal biopsy. However, 2–3% of patients with celiac disease have selective IgA deficiency[17, 18] and hence remain negative for IgA class gliadin and antiendomysial and antitissue transglutaminase antibodies; IgG class gliadin antibodies or serum total IgA can be applied in screening of these cases[19]
The small-bowel lesion develops gradually from mucosal inflammation to crypt hyperplasia and villous atrophy[20]. A body of evidence shows that sometimes in cases

where the first biopsy is normal or nondiagnostic, celiac disease can sometimes be observed subsequently when patients have continued on a gluten-containing diet[21, 22, 23, 24] . Thus, a normal small-bowel biopsy does not necessarily exclude celiac disease for life. Especially antiendomysial antibody-positive patients without villous atrophy, and relatives of celiac disease patients, seem to harbor this latent form of the condition [25, 26].

III. Common Manifestations of Celiac Disease

A. Typical symptoms

The classical features of celiac disease are well recognized. In small children, abnormal stools, steatorrhea, and abdominal distention may occur. Poor growth and failure to thrive are the most typical symptoms, and growth curves may reveal the condition early. In children aged 2 yr or more, symptoms appear to be milder and resemble those observed in adults [27]. Subclinical isolated nutrient deficiencies may occur, and bone mineral density (BMD) may be impaired even in childhood [28]. In adults, celiac disease typically produces diarrhea or steatorrhea, malaise, and weight loss. Abdominal distension after meals is a common, albeit unspecific symptom; only rarely do patients notice a relationship between the abdominal complaints and the ingestion of cereals [9]. Symptoms that suggest the diagnosis of celiac disease are bloating flatulence, chronic diarrhea, and lactose malabsorption. A great variety of malabsorption may exist, including anemia due to deficiency of iron or folic acid, and less commonly of cobalamin; serum calcium and fat-soluble vitamins D [7, 29], and less often K[30] , may be low. Weight loss and fatigue may occur; however, even constipation, overweight, or obesity do not exclude celiac disease [9].

These common modes of presentation have remained, by and large, the same since 1960, but overall there has occurred, both in children and adults, a shift toward milder symptoms[31] . Steatorrhea and profuse diarrhea are relatively rare, whereas patients often suffer only from occasional loose stools. Malabsorption may be subclinical, and severe forms are infrequent. Some celiac patients may experience abdominal discomfort mimicking irritable bowel syndrome [32].

Symptoms usually disappear on a gluten-free diet within a few weeks, whereas the recovery of the small-bowel mucosa may take much longer, 1 yr or even more. Apparently, a gluten-free diet often alleviates abdominal symptoms even in nonceliac patients [33]. Hence, all approaches to detect celiac disease by dietary interventions are to be strongly discouraged: subsequently, the diagnosis may be difficult to establish, because possible mucosal lesions may have recovered as a result of gluten withdrawal.

Since the development of serological screening tests for celiac disease, it has become evident that the symptoms described above constitute only a minor component in the concept of celiac disease[14, 34]. In many, perhaps in the majority of cases, celiac disease remains clinically silent, or symptoms emerge outside the gastrointestinal tract.

B. Extraintestinal and atypical symptoms

The recognition of atypical and clinically silent celiac disease has resulted in a marked increase in the incidence of the condition. Consequently, the overall prevalence of celiac disease in the population seems to be 0.5–1.0%—not less than 0.1% as was thought 20 yr ago[2] . In first-degree relatives of celiac patients the risk is at least 10-fold [35, 36]. The best known extraintestinal manifestation is dermatitis herpetiformis, an itching

papulovesicular skin disease appearing predominantly at the knees, elbows, and buttock. Granular IgA deposition in the papillary dermis of the uninvolved skin is diagnostic for the condition[37] . All untreated patients also evince at least some degree of small-bowel mucosal inflammation or atrophy, and both the skin symptoms and the mucosal lesion resolve on a gluten-free diet[38] . The occurrence of autoimmune disorders in dermatitis herpetiformis is similar, by and large, to that in celiac enteropathy [39]. Dermatitis herpetiformis is today considered one form of the celiac trait rather than an associated disease.

Recurrent oral aphthous ulcerations and enamel defects in the permanent teeth may be the only presenting manifestations of celiac disease[40] . Neurological symptoms include peripheral neuropathy, memory loss, and ataxia[41] (). Sjögren's syndrome, nonspecific arthritis, and arthralgia have been described in connection with celiac disease [40].

Osteoporosis and infertility can be considered complications of celiac disease, because they are at least partially reversible on a gluten-free diet. In addition, a number of endocrinological autoimmune diseases, as reviewed below, belong to the category of celiac disease associations.

The prevalence of the atypical/silent form has increased significantly recently both in adults and children. In atypical/silent CD the most frequent age of diagnosis coincides with school age and adolescence. This increase appears more likely due to a greater diagnostic awareness and to a better use of screening tests than to a higher number of atypical/silent cases. Both in adults and children, iron-deficiency anemia appears to be the most frequent extraintestinal symptom, followed by short stature in children [42)]. Thus, short stature is 1 of the main extraintestinal presentations of CD, and CD should be considered in all children with short stature. In these patients the prevalence of CD varies from 2.9% to 8.3%, and CD is by far the most common causal agent, much more than growth hormone deficiency or any other organic disorder [(43)]

The pathogenesis of CD-associated short stature is still unclear. Growth retardation traditionally has been attributed to generalized or selective malnutrition, but many report a dysfunction of the endocrine growth axis in children with CD. The insulin-like growth factor (IGF) system is crucial for growth because it regulates cell proliferation, differentiation, and apoptosis. Changes in this system have been described in CD at diagnosis; in particular, patients with CD had reduced or normal levels of basal growth hormone (GH), low GH levels during induced hypoglycemia examination, lower IGF-I, lower IGF-II, similar IGF-binding protein (IGFBP)-1, lower IGFBP-3, and higher IGFBP-2 compared with that of controls. In untreated CD, partial GH insensitivity is also present because exogenous administration of human GH does not restore normal IGF-I levels. Patients with CD also had increased concentrations of interleukin (IL)-6, tumor necrosis factor-α, interferon-γ, IL-1β, IL-8, IL-18, IL-4, and IL-10 in serum compared with that of controls, suggesting that inflammation can contribute to the dysregulation of the IGF system in CD. Upon institution of a gluten-free diet (GFD), various parameters of the somatotropic axis change: sensitivity to GH increases and levels of IGF-I, IGF-II, and IGFBP-3 rise, whereas levels of IGFBP-2 decrease [(44)]. At the same time, catch-up growth takes place. Changes reflect the recovery toward a normally functioning somatotropic axis. It is possible that changes were dependent on the reduction in

inflammatory cytokines, as the negative correlation of IL-6 with IGF-I would suggest, or were directly related to improved nutritional conditions on GFD.

The possible autoimmune (AI) involvement of the pituitary gland in patients with CD has been suggested, but demonstrated in only a few patients receiving GFD. The association between CD and AI disorders may be secondary to the linkage disequilibrium of genes predisposing for both CD and other AI diseases or to the existence of shared epitopes between gliadin and antigens of "self" structures. Some studies demonstrated a remarkable prevalence of positive anti-pituitary antibodies (APA) in newly diagnosed patients with CD. High APA titers are associated with height impairment, likely mediated by a reduction of IGF-I, thus suggesting that AI pituitary process could induce a linear growth impairment. In fact, APA are associated with lower levels of IGF-I and their presence may help in identifying subjects with short stature who are prone to develop GH deficiency (GHD) [(45)].

Catch-up growth, a discontinuous process made up of a sequence of bursts of growth followed by a resting phase [(46)], is defined as rapid, compensatory growth during rehabilitation from prior nutritional deficit. During catch-up growth, the child may grow in height at up to 4 times the average rate for his or her chronological age. Velocity decreases as the child approaches his or her genetically predisposed channel growth. Catch-up growth is maximal in the first 6 months on a GFD. In patients with CD, after GFD starts, weight catches up more quickly than height. The increments in height may be influenced by age at the time of diagnosis of CD because children with an early diagnosis demonstrated higher increments in height than children who were diagnosed late [(47)]. However, there are conflicting results concerning final height attained by patients with CD; some authors suggest that growth recovery is not always complete and final height may remain 1.5 SD less than the mean despite early treatment, careful follow-up, and good adhesion to dietary restrictions, whereas others conclude that the final height of patients with CD is similar to that of the general population. Some authors demonstrated that delayed diagnosis of CD had an influence on the final adult height in men, with an inverse correlation between the age at diagnosis and the final attained height [(48)]. Diet compliance seems not to influence the height.

Some patients with CD do not show catch-up growth during GFD, despite reversion of seronegativity for CD markers including anti-endomysial and anti-tTG. The absence of catch-up growth requires evaluation of compliance, endocrinological evaluation, and possible concurrent GH deficiency. In a few cases, incomplete catch-up growth could be caused by persistent nutritional defects or by the marked acceleration in bone maturation that parallels the rapid increase in growth velocity. In patients with CD with no catch-up growth after at least 1 year of GFD, GHD was found in 0.23% of them [(43)]. In these patients, GH replacement therapy should be started to allow complete catch-up growth. Growth rate strikingly increases during the first year of recombinant human GH therapy in patients with CD-GHD and then gradually wanes as height approaches its target. Furthermore, the effect of GH treatment in patients who comply with a GFD seems to be comparable with that observed in children with idiopathic GHD [(49)].

It is important to mention that Turner syndrome (TS) is another important cause of short stature in girls and it is frequently associated with CD (6%–18% of patients). Thus, subjects withtreatment [(50)] TS require screening for CD, which should occur as soon as

possible after the diagnosis of TS and be repeated periodically. It could be advantageous to treat subjects already screened for CD with GH to improve the response to.

In conclusion, short stature is 1 of the most common clinical manifestations of CD and should be considered in all children with short stature. Catch-up growth is observed on GFD, mostly in the first 6 months from diagnosis. The absence of catch-up growth requires the evaluation of compliance and endocrinological evaluation. Patients should be tested for GH reserve, particularly if APA is positive.

Discussion

Time to change clinical practice

It is obvious that a number of patients with diverse endocrinological disorders suffer from celiac disease, the symptoms of the disease being sometimes, if not mostly, subtle or atypical. For this reason the majority of patients remain undetected. The diagnosis of celiac disease is based on intestinal biopsy samples usually taken by upper gastrointestinal endoscopy. Many individuals consider this investigation unpleasant and inconvenient. Fortunately, endoscopy can now be limited to subjects with a great likelihood of celiac disease and those found positive in screening surveys. For initial screening purposes, up-to-date serological tests, IgA class antiendomysial and antitissue transglutaminase antibodies, are highly specific and sensitive enough in cases in which symptoms do not clearly indicate celiac disease.

Future aspects

Cost-benefit analyses of screening for celiac disease in risk groups or in the whole population are warranted, and the importance of measuring health-related quality of life should be recognized. The impact of early diagnosis and gluten-free dietary treatment on the occurrence of autoimmune endocrinological conditions should be further investigated in prospective surveys. These should comprise individuals with silent and developing latent celiac disease. Research into common genetic involvement in endocrine conditions and celiac disease should be carried out. The finding that tissue transglutaminase is the target for celiac antibodies makes it possible to study the role of this enzyme in nonintestinal organ-specific involvements in celiac individuals. This may make possible, in the future, specific treatments of celiac complications, such as osteoporosis or infertility, and perhaps even prevent the development of autoimmune conditions. The development of curative treatment in celiac disease is still far away. It is as difficult to induce oral tolerance as it is to block the T cell response to gluten. Serious side effects prevent the use of immunosuppressive drugs in clinical practice. The development of wheat free of toxic peptides may be possible, but at the risk of losing its baking properties[51].

Conclusion

CD, also known as gluten enteropathy, is an inflammatory autoimmune disease of the small bowel characterized by sensitivity to gluten, a storage protein in wheat, barley and rye. Its etiology is considered to be multifactorial, comprising genetic, immunological and environmental factors. Major histocompatibility complex alleles expressing

HLADQ2 and HLADQ8 are present in more than 90-95% of diagnosed CD patients. The disease prevalence is 8-12% in first-degree relatives of affected individuals. Environmental factors include gluten ingestion. Viral infection, pregnancy, high-dose gluten challenge and gastrointestinal surgery may increase the immunological response and can lead to precipitation of CD symptoms.

There is no doubt that many patients with celiac disease primarily contact specialists other than gastroenterologists. The majority of cases thus remain undetected. A close association between various autoimmune endocrinological disorders and celiac disease has been shown in numerous studies. The diagnosis of celiac disease requires a small-bowel biopsy, usually taken by endoscopy. However, sensitive and specific antibody assays, the antiendomysial and antitissue transglutaminase tests, are helpful in preliminary screening for gluten intolerance in cases where symptoms are atypical, appear outside the gastrointestinal tract, or are totally absent. The need to prevent osteoporosis advocates the early diagnosis and treatment of even asymptomatic celiac disease. The benefits of screening for celiac disease in autoimmune disease remain to be proved by prospective follow-up studies. However, there seems to be a good case for extensive screening.

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