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CLINICAL CASE

Congenital sucrase–isomaltase deficiency: A case report

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KEYWORDS
Congenital sucrase–isomaltase deficiency;
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Abstract
Background: Congenital sucrase–isomaltase deficiency (CSID) is an autosomal recessive disease characterized by absent sucrase activity with variable decrease in isomaltase activity. The prevalence of CSID in Portuguese population is unknown and there are few reported cases.
Case report: We report the case of a six-month-old male infant admitted for chronic profuse diarrhea and failure to thrive that began after food diversification. The investigation showed that he had CSID. The therapeutic option was the addition of baker's yeast to the diet which was followed by complete resolution of symptoms and excellent weight recovery.
Discussion: This case highlights the relevance of clinical observation and awareness in a condition where diagnosis is essentially clinical. The available therapeutic options are addressed with pragmatic use of baker's yeast.

PALAVRAS-CHAVE
Deficiência congénita de sacarase-isomaltase;
Sacrosidase;
Fermento;
Saccharomyces cerevisiae

Défice congénito de sacarase-isomaltase: relato de um caso

Resumo
Introdução: O défice congénito de sacarase-isomaltase é uma doença autossómica recessiva caraterizada pela ausência da atividade da sacarase e diminuição variável da atividade da isomaltase. A prevalência desta patologia na população portuguesa é desconhecida e há poucos casos divulgados.

Abbreviations: CSID, congenital sucrase–isomaltase deficiency; DNA, deoxyribonucleic acid; IgE, immunoglobulin; EPCR, polymerase chain reaction; SI, sucrase–isomaltase.

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Relato de caso: Lactente masculino de 6 meses, internado para estudo de diarreia crónica profusa coincidente com o início da diversificação alimentar e associada a má evolução ponderal. A investigação mostrou tratar-se de uma deficiência congénita de sacarase-isomaltase. A medida terapêutica escolhida foi a adição de fermento de padeiro na dieta, com resolução da sintomatologia e excelente recuperação ponderal.
Discussão: Discute-se a importância de uma elevada suspeição clínica numa patologia cujo diagnóstico é essencialmente clínico e também as opções terapêuticas disponíveis, com ênfase no uso do fermento de padeiro.

1. Introduction

Congenital sucrase–isomaltase deficiency (OMIM #222900) is caused by homozygous or compound heterozygous mutation in the *SI* gene, which encodes sucrase–isomaltase on chromosome 3q26.

Sucrase–isomaltase is an enterocyte-specific small intestine brush-border membrane disaccharidase. It is required for hydrolysis of sucrose and some starches. Upon ingestion of disaccharides and oligosaccharides, the failure to breakdown sucrose into fructose and glucose results in osmotic-fermentative diarrhea.

CSID is the most common congenital disorder of carbohydrate metabolism. Its estimated prevalence in North America and Europe ranges from 0.05% to 0.2%,[1] although this diagnosis is believed to be frequently missed.

Onset usually occurs during infancy after weaning from breast milk or lactose-only formula onto foods containing sucrose or starch. Clinical manifestations include osmotic-fermentative diarrhea, abdominal distension and discomfort, flatulence, vomiting and diaper rash.[2] Severe symptoms may lead to failure to thrive, dehydration and malnutrition. Adolescents and adults may present with signs of 'irritable bowel syndrome'. Carbohydrates result in a dose-dependent acceleration of colonic transit[3] and therefore symptoms may only occur with the ingestion of large amounts of sucrose.[2]

CSID is a heterogeneous disorder. Identified mutations lead to a range of posttranslational defects resulting in an absence of sucrase activity and varying degrees of isomaltase deficiency. Heterozygotes have intermediate enzyme values and are usually asymptomatic in adulthood, but may have mild symptoms in infancy.

Several tests can be used to diagnose CSID, with measurement of intestinal disaccharides' activities being the gold standard.[2] It will show complete or almost complete lack of sucrase/isomaltase activity with normal lactase activity and normal villous architecture.

The hydrogen breath test is a non-invasive method for detecting carbohydrate malabsorption. This test is based on the fact that unabsorbed sugar is converted to hydrogen gas by colonic bacteria, which is eliminated *via* expired air.[3] However, it is not specific for the diagnosis of CSID and false-negative results may be obtained because of many factors affecting the hydrogen production.[3] An evolution of the hydrogen breath test is the measurement of isotope-labeled CO_2 in breath using ^{13}C or ^{14}C by mass spectrometers. A sucrose breath test for screening and confirmation of CSID using a novel non-invasive ^{13}C-sucrose labeled substrate has been developed and validated, and is an accurate and specific noninvasive confirmatory test for CSID.[4] However, obtaining breath samples may be difficult in small children. Evidence of unabsorbed sugars (Clinitest®) also provides indirect evidence of poor carbohydrate digestion. However, Clinitest® looks for reducing sugars in the stool and sucrose, as stated later, is not in its natural form a reducing sugar. Therefore, negativity of Clinitest is not actually a false negative test; it is a true negative test in the context of Sucrase Isomaltase deficiency when looking for sucrose.

Fecal carbohydrates can also be measured by high-performance liquid chromatography, but this test has some false negatives due to transport times required, that allow consumption of sugars by fecal flora. Other diagnostic methods available include the glycemic curve and stool tests (fecal pH lower than 5.5 with or without reducing sugars without steatorrhea).[3,5] Molecular genetic test for mutation in *SI* gene is also available.

The mainstay of treatment is a lifelong adherence to a sucrose- and starch-restricted diet.[5] Effective enzyme replacement with whole yeast cells has been reported.[6] Purified yeast enzyme, sacrosidase, is a highly effective therapy and allows a normal diet.[4]

CSID's prognosis is good. Affected patients tend to experience spontaneous improvement of their symptoms with age, because colonic bacteria become able to metabolize non absorbed carbohydrates into organic acids (lactic acid and short chain fatty acids), most of which are then absorbed.[3] Patients learn to identify their tolerance limits, but remain exposed to occasional episodes of diarrhea when they ingest amounts of carbohydrates that exceed their ability to metabolize and digest. This can explain the small number of diagnosed cases.

2. Case report

The patient is a 6-months-old Caucasian male infant admitted in our hospital for chronic diarrhea and failure to thrive. He is the only child of young, healthy and non-consanguineous parents. His father had a history of frequent episodes of diarrhea in youth, which were never the subject of any investigation.

The boy's medical history is irrelevant until the age of 4 months. He was bottle-fed with a hypoallergenic formula and was thriving until 4.5 months, at which time food diversification began with vegetables, meat and fruit. Some days after this dietary modification, he began to have 9–10 episodes per day of non-bloody watery stools and poor weight gain. No diaper rash was ever observed. Formula changes were attempted without improvement. He was admitted in another hospital at the age of 5.5 months for evaluation of severe diarrhea and malnutrition.

At that hospital, he underwent an extensive study. Stools were negative for pathogenic bacteria, virus and parasites. Fecal component analysis (neutral fat, fatty acids, muscle fibers, leukocytes) was normal, as well as all the following investigations: blood count, liver and renal profile, protein electrophoresis, C-reactive protein, blood immunoglobulins, anti-transglutaminase antibodies, allergens-specific IgE testing for baby foods, sweat test, thyroid function and abdominal ultrasound. He was treated empirically with metronidazole and ceftriaxone without improvement and was subsequently transferred to our hospital.

Physical examination in our hospital showed an alert, nondysmorphic infant with severe reduction in muscle mass and subcutaneous fat. Besides that, physical examination was non-informative. Frequent loose watery stools were noted.

Given the clinical features and previous laboratory tests, we hypothesized that we were probably facing an osmotic diarrhea due to CSID. In fact, we confirmed that there was a marked decrease in stool output during fasting and high stool osmolality (247.6 mOsm/kg). He underwent a glucose tolerance test without associated symptoms and then a sucrose tolerance test that led to watery diarrhea within hours of the study. Reducing substances were measured and were negative during both tests; no acid hydrolysis of feces was carried out in the laboratory. The clinical response was in favor of CSID.

During the hospitalization, we noticed a maculopapular rash evocative of cow's milk protein allergy. Facing two co-existing diseases, we could not use the common protein extensively hydrolyzed formulas as most are lactose-free and contain glucose polymers that require sucrase–isomaltase, which was lacking in our patient. Thus, the infant began a protein extensively hydrolyzed formula containing lactose (Althera®) and became asymptomatic ever since (no diarrhea, no rash and favorable weight gain). He was discharged exclusively fed with Althera®. The intentional re-exposure to a formula with cow's milk proteins caused a relapse of cutaneous lesions. Likewise, another sucrose tolerance test triggered the recurrence of the diarrhea.

At the age of 7 months, vegetables and fruit were reintroduced and diarrhea occurred. We were then sure that it was a case of CSID and we were facing the problem of how to manage the condition. The hypothesis consisted in the use of enzyme replacement sacrosidase, the adoption of a free sucrose diet or the addition of baker's yeast to the diet. We have chosen the baker's yeast and the infant remains completely asymptomatic, has excellent weight gain, and is on a normal diet. The baker's yeast is added to the diet and the mother uses the minimum amount required to ensure there is no diarrhea.

3. Discussion

CSID's diagnosis waivers complex evaluation exams, but requires a high index of suspicion. Infants presenting with persistent, watery diarrhea after weaning and the introduction of starch and sucrose in the diet should be evaluated for CSID. Diagnosis can be achieved with a simple strategy: first, a trial of fasting (a marked decrease in stool output during fasting suggests an osmotic diarrhea), then a glucose tolerance test in order to exclude the very rare situation of glucose–galactose intolerance, followed by the oral sucrose absorption test. In the case of CSID, the ingestion of sucrose (but not glucose) will trigger the onset of diarrhea within hours.

Reducing sugar assay is used to detect the reducing ends of carbohydrate molecules. Clinicians should note that Clinitest® yields a high degree of false-negative results, as happened in our case. Clinitest® is only positive in this situation for maltose or dextrin-maltose not digested due to isomaltase absence, but most of the times the maltase-glucoamylase enzyme can, for a moderate starch amount, replace that activity. So its result may not provide reliable information especially if negative, although positivity may be regarded as a useful sign to confirm diagnosis. Other explanations for Clinitest®'s false-negative results are the large interval between fecal collection and analysis and the transport at room temperature, both of which result in the growth of bacteria that consume the existing sugars. Moreover, this test has poor sensitivity from diaper stools because the liquid portion of the stool, which contains the water-soluble sugars, is absorbed by the diaper filling. A handy trick to circumvent this issue is to place the diaper with the plasticized waterproof surface in contact with the skin, so that the liquid component is not absorbed.

In our opinion, molecular genetic test for mutation in CSID involves significant costs and brings no additional clinical benefit compared with simpler diagnostic procedures. It must be noted that more than 25 mutations have been identified[7] which makes it very difficult in clinical practice to establish a single molecular test suitable for the diagnosis of all CSIDs.[8]

Another important discussion point concerns the therapeutic options. Enzyme replacement therapy with sacrosidase (Sucraid®) facilitates breakdown of sucrose into simpler forms for absorption. It helps to relieve the gastrointestinal symptoms with no side effects and allows patients to maintain a normal diet.[4,9,10] Nonetheless, sacrosidase is not available in every country and importing it may be quite expensive.

Baker's yeast is composed of lyophilized *Saccharomyces cerevisiae*. *In vitro*, lyophilized and fresh *S. cerevisiae* (fresh baker's yeast) has appreciable sucrase activity, low isomaltase and maltase activity and no lactase activity.[6] Yeast sucrase reduces breath hydrogen excretion in patients with CSID who are given a sucrose load and allows most patients to consume a sucrose-containing diet.[6,11] The sucrase activity is partially inhibited by undiluted gastric juice, therefore patients with CSID can ameliorate the sucrose malabsorption by ingesting a small amount of viable yeast cells on a full stomach.[6] Baker's yeast addition to the diet was the therapeutic option in our

case, with the advantage of being inexpensive and easily accessible.

The coexistence of cow's milk protein allergy implied the need to use an extensive hydrolyzed formula with lactose, but in most cases of CSID a formula based on lactose as source of carbohydrate is effective during exclusive bottle-feeding.

4. Conclusion

This typical case of CSID reinforces the important role of careful anamnesis to reach the diagnosis. The clinical suspicion, after being hypothesized, does not require exhaustive research. Our case enhances the therapeutic success of the addition of baker's yeast in the diet as an effective enzyme replacement therapy for patients with CSID.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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