GHAPP E-Newsletter Series

Recognizing and Managing Congenital Sucrase-Isomaltase Deficiency

Project ID: 5838

Target Audience

Nurse practitioners and physician assistants involved in the management of patients with gastrointestinal disorders.

Educational Objectives:

Upon completion of this activity, participants will be able to:

- Describe the prevalence and clinical presentation of CSID
- Discuss diagnosis and treatment recommendations for patients with CSID
- Analyze the role of the APP in CSID diagnosis and management

ANCC Accreditation

Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hours may be earned for successful completion of this activity.

Physician Assistant Statement

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. This activity is designated for 1 AAPA Category 1 CME credits. Approval is valid from 10/12/2021 to 10/12/2022. PAs should only claim credit commensurate with the extent of their participation. AAPA reference number: CME-202397.

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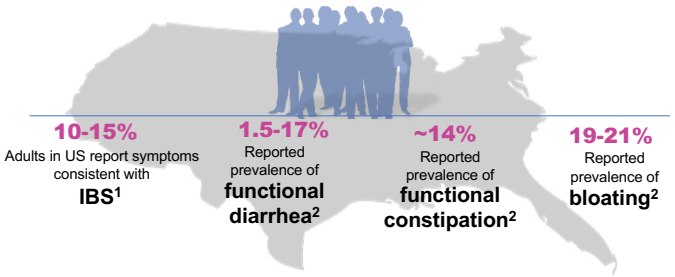
Irritable bowel syndrome (IBS) presumably affects (7-21%)[1] of the general population. Diarrhea-predominant irritable bowel syndrome (IBS-D) is associated with abdominal pain or discomfort, bloating, and loose stools[1] and these symptoms account for 10-15% of all patient primary care visits. Symptoms such as these are debilitating and embarrassing for patients to discuss with their health care provider.[2] Due to their prominent position in day-to-day patient care, advanced practice providers (APPs) can play a key role in the prompt diagnosis and provision of effective care for patients with IBS and are well placed to develop open and trusting relationships.[2]

These functional gastrointestinal (GI) symptoms (ie, symptoms that cannot be explained by the presence of structural or tissue abnormality) do not always indicate IBS. Congenital sucrase-isomaltase deficiency (CSID), the focus of this newsletter, is a prime example of a disorder that is rare and can often be incorrectly diagnosed as IBS-D.

Function GI Symptoms Are Common and May Not Always Indicate IBS



1. Chey WD et al. *JAMA*. 2015;313(9):949-958. 2. Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

CSID is an inherited primary defect of sucrase-isomaltase (SI) caused by variants in the SI gene, which ultimately leads to absence or diminished activity of SI at the brush border of the small intestine. As a result, carbohydrates are maldigested and, clinically, patients suffer from abdominal distension, cramping, pain, excessive flatulence and osmotic diarrhea,[3] symptoms that mirror those of IBS-D.[1] CSID is considered to be rare, and, based on symptoms, occurs in 5% of the native populations of Greenland, Alaska, and Canada, but in only 0.02% in North Americans of European descent. Analysis of mucosal biopsies suggests that the incidence of CSID is actually higher; one study identified a 9.3% incidence of CSID.[4]

As with IBS, APPs play a key role in the identification and management of CSID. The GHAPP 2021 IBS Virtual Roundtable Series was a series of meetings presented virtually to APPs. Faculty members with expertise in managing patients with IBS were selected and led the content development for the initiative, which delivered focused educational updates highlighting clinically-relevant advances in the management of patients with IBS and IBS-like symptoms. Following the education, the faculty provided feedback on both the need for the education with the APP community and their perceptions on the results. Participating faculty believed the initiative was successful and anticipated that the learnings gained from the program will influence the participants' clinical practice.5 As such, education on CSID, the objective of this newsletter, would surely benefit APPs in a similar manner.

The Role of Sucrase-Isomaltase in the Digestion of Carbohydrates

The brush border of the small intestinal tract is the site of terminal carbohydrate digestion that results in the production of monosaccharides. The microvilli that constitute the brush border have enzymes for this final part of digestion anchored into their apical plasma membrane as integral membrane proteins. These enzymes include SI, lactase, maltase-glucoamylase and trehalase and most dietary carbohydrates are digested by these enzymes. The sucrase site splits sucrose into glucose and fructose. These two monosaccharides can then be absorbed by brush border transporters. The isomaltase active site cleaves maltose at its α(1,4) bond and it cleaves limit dextrins at their α(1,6) bond.[6]

When SI is absent or deficient, as is the case in CSID, nonabsorbed carbohydrates enter the distal small intestine and colon where they are fermented, leading to the excessive production of short-chain fatty acids and gases such as hydrogen, methane and hydrogen sulfide. As a result, patients suffer from abdominal distension, cramping, pain, excessive flatulence and osmotic diarrhea.[7, 8] Other clinical consequences include rapid small bowel transit and malabsorption of other nutrients; excessive bacterial fermentation of malabsorbed carbohydrate with colonic gas production and acidification of the stools; and at times, chronic malnutrition and failure to thrive.[7, 9]

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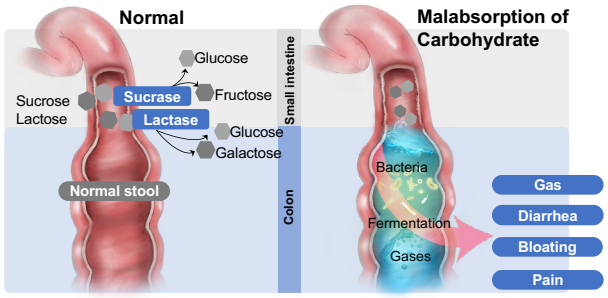
In addition to the degree of enzyme deficiency, the amount of sugar and starch in a CSID patient's diet influences the clinical appearance of the disorder. Approximately 46 - 60% of the total calories consumed in the average American diet originate from carbohydrates[7, 10-12], with 30% of carbohydrate calories deriving from sucrose.[12] In fact, the average adult consumes about 150 pounds of sugar per year and 65 pounds of sucrose.[7]

Clinical Consequences of Carbohydrate Maldigestion



1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13; 2. Canani RB et al. *Nutrients*. 2016;8:157.

Misdiagnosed/Delayed Diagnoses in CSID Patients

Data indicates that CSID symptoms begin early in life. Of 65 patients with CSID who responded to a questionnaire after being identified by a record of prescriptions for enzyme replacement therapy, 53 of 65 reported the onset of symptoms before 1 year of age, 7 between 1 and 10 years old, and 5 after 10 years of age; however, the age at which a diagnosis was made was shifted to the right, with only 17 of 65 diagnosed in the first year, 30 between 1 and 5 years, 10 between 5 and 10 years, and 8 after 10 years of age.[7, 9] As summarized in the table, misdiagnoses lead to interventions that can mask CSID symptoms, thus further delaying the correct diagnosis.[6] One study analyzed 31 patients with a presumed diagnosis of IBS-D/M found that, after esophagogastroduodenoscopy with duodenal biopsies and testing for disaccharidase deficiency, 35% of these patients actually had CSID.[13]

Misdiagnosis	Why CSID Symptoms Resolved
Protein intolerance in infancy	Infant formula is changed to eliminate glucose oligomers (maltodextrin), which are partially hydrolyzed by sucrase
Food allergies	Juices and baby foods, which may have a high sucrose load, are eliminated from the diet
Chronic nonspecific diarrhea	Treated with a lower carbohydrate, high fat diet
IBS-D	Avoidance of foods which trigger symptoms

Since misdiagnoses are common, it is important to obtain an accurate diagnosis when a patient presents with symptoms indicative of CSID. If symptoms indicate CSID (frequent, lifelong, and postprandial diarrhea, loose stools, gas, bloating), it is important to consider testing for CSID. Furthermore, CSID should be included in the differential diagnosis of patients with presumed IBS, particularly in those that are not responding to dietary modifications

As described in the figure, tests that aid in the diagnosis of CSID include disaccharidase assay via a small bowel biopsy, genetic testing, breath tests and the sucrose challenge.

Tests that Aid in Diagnosing CSID

Small bowel biopsy[1,2]	Genetic test[2]	Breath tests[2]	Sucrose challenge[3]
• Considered gold standard • Specimens sent to specialty lab	• Buccal swab, saliva, or blood • Detects 37 polymorphisms in *SI* gene	• Hydrogen-methane • ^{13}C-sucrose	• Simple test, but not validated

SI, sucrase isomaltase
1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13;
2. Cohen S. *Molecular Cellular Pediatr*. 2016;3:5;
3. Puntis JW and Zamvar V. *Arch Dis Child*. 2015;100(9):869-871.

Assessing SI function via the disaccharidase assay is the gold standard for CSID diagnosis because it is the only test able to differentiate primary from secondary CSID and can provide the enzyme activity for all disaccharidases. This test, however, is invasive because it involves collecting, freezing and shipping 2-to-3 biopsies from the distal duodenum/proximal jejunum to a specialty lab. Furthermore, false positives are common because specimens can be mishandled or the sample can be mistakenly taken from the proximal duodenum, where the disaccharidase levels are decreased by 33%.[7, 14]

There are two breath tests that can also be performed to diagnose CSID. Although disaccharide assay is the gold standard, the North American Consensus has determined that breath testing is a useful, inexpensive, simple and safe diagnostic test in the evaluation of gastrointestinal problems, including CSID.[15] The ^{13}C sucrose breath test requires the administration of a small dose of uniformly labeled ^{13}C-sucrose mixture followed by a collection of $^{13}CO_2$-enriched breath samples every 15 minutes for 2 hours. The separate administration of ^{13}C-glucose mixed in maltodextrin and

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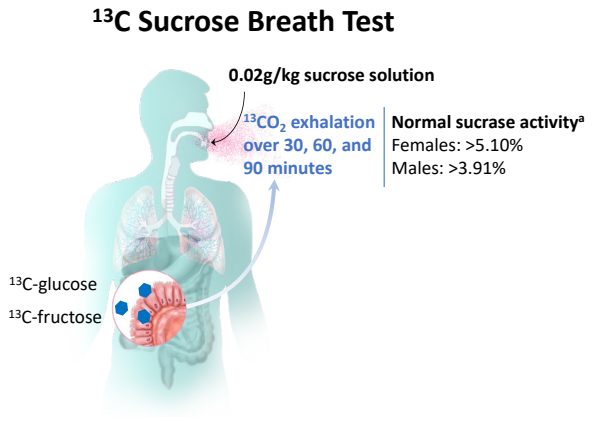
collection of $^{13}CO_2$ allows ^{13}C-sucrose hydrolysis and digestion to be expressed as a coefficient of glucose oxidation. This test is noninvasive, has excellent sensitivity and specificity, and, unlike the sucrose hydrogen methane breath test, it does not require a heavy sucrose load, which can lead to gastrointestinal symptoms.[7]



[a]90-minute sucrose digestion.
1. Robayo-Torres CC, et al. *J Ped Gastroenterol Nutr*. 2009;48(4):412-8;
2. Rezaie A et al. *Am J Gastroenterol*. 2017;112(5):775-84;
3. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13.

Other tests include the sucrose challenge, which involves stirring ingesting 4 tablespoons of ordinary table sugar (dissolved in water) and monitoring for signs and symptoms of CSID 4-to-8 hours after ingestion. This test can result in severe gastrointestinal symptoms and is currently not validated.[16] Patients with suspected CSID can also be considered for genetic testing, which tests 37 common pathogenic variants of the SI gene.[17]

Management of CSID with Dietary Modifications and Enzyme Replacement Therapy

Since patients with CSID may experience malnutrition and failure to thrive, nutrition status should be determined once CSID is diagnosed. The parents and child (if old enough to understand) can then be educated on a diet for CSID. Diet education is crucial for achieving optimum nutrition status and minimization of symptoms of CSID. Historically, the primary treatment option for CSID has been implementing a lifelong sucrose, and possibly starch-restricted, diet adapted to the requirement of the patient. Given that all patients with CSID are sucrose intolerant, a sucrose-free diet should be implemented before starch intake is modified. If patients do not respond to the low sucrose diet, the patient may have absent or reduced levels of isomaltase or maltase (which is common in CSID), making it difficult for them to digest starch and a low starch diet should be initiated.[18] Examples of foods that are high in sucrose or starch are demonstrated in the figure.

Carbohydrate-Rich Foods High in Sucrose or Starch

Eliminate sugar first
- Table sugar
- Beet sugar
- Brown sugar
- Cane sugar
- Caramel sugar
- Coconut sugar
- Confectioner's sugar
- Date sugar
- Raw sugar

Reduce starch if still symptomatic
- Potatoes
- Rice
- Bread
- Pasta
- Limit dextrins
- Maltodextrin
- Modified tapioca starch
- Glucose polymers
- Maltose (brown rice syrup, corn syrup solids, malt)

McMeans AR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S37-S38.

Although dietary restriction alone should be theoretically effective, only a minority of patients remain consistently asymptomatic. Follow-up studies of children with CSID treated with sucrose- and starch- restricted diets have demonstrated that only 10% of patients remain consistently asymptomatic, and 60% to 75% still experience diarrhea, gas, and/or abdominal pain. Furthermore, it is nearly impossible to maintain a low sugar diet; studies demonstrate that only ~50% of these children are compliant with the prescribed diet.[9] Therefore, enzymatic replacement therapy is important in managing CSID.

Sacrosidase is derived from baker's yeast (Saccharomyces cerevisiae) and has been used for many years by the food industry to convert sugarcane (sucrose) to molasses and keep the centers of cream-filled candies liquid.[7] Sacrosidase Oral Solution is currently the only FDA approved enzyme replacement therapy for the treatment of genetically determined sucrase deficiency (part of CSID).[19]

A two-phase (dose response preceded by a breath hydrogen phase) double-blind, multi-site, crossover trial was conducted in 28 patients (aged 4 months to 11.5 years) with confirmed CSID. During the dose response phase, the patients were challenged with an ordinary sucrose-containing diet while receiving each of four doses of sacrosidase: full strength (9000 I.U./mL) and three dilutions (1:10 [900 I.U./mL], 1:100 [90 I.U./mL], and 1:1000 [9 I.U./mL]) in random order for a period of 10 days. Analysis of the overall symptomatic response as a function of age indicated that in CSID patients up to 3 years of age, 86% became asymptomatic. In patients over 3 years

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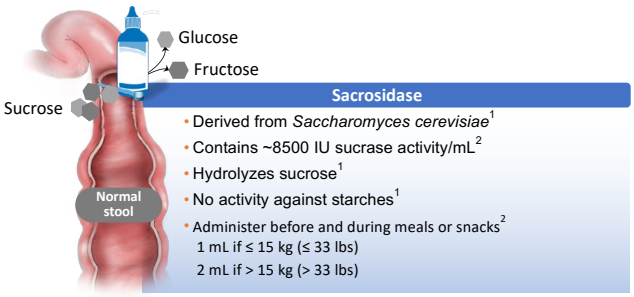
of age, 77% became asymptomatic. Thus, the therapeutic response did not differ significantly according to age. Furthermore, patients showed a marked decrease in breath hydrogen output when they received sacrosidase in comparison to placebo.[19]

The usual dosage of sacrosidase is 1-to-2 mL with each meal or snack. The solution should be kept refrigerated and should not be mixed in hot or acidic beverages (e.g., juice). The most commonly reported adverse events are constipation, insomnia and headaches. Sacrosidase is contraindicated in patients known to be hypersensitive to yeast, yeast products, glycerin (glycerol), or papain as it may cause an allergic reaction. Diabetics administered sacrosidase should be closely monitored since administration can raise blood glucose levels.[19] It is also important to remember that sacrosidase hydrolyzes sucrose, not isomaltase or maltase. Therefore, if a low sucrose diet or sacrosidase is ineffective, then the patient should be considered for a low starch diet.

Clinical Consequences of Carbohydrate Maldigestion



1. Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999;28(2):137-42; 2. Sucraid® (sacrosidase) [prescribing information]. QoL Medical, LLC; Vero Beach, FL; 2019.

Conclusions: The Role of the APP in CSID Diagnosis and Management

Getting the correct diagnosis for CSID can take years in some cases. APPs play a key role in developing open and trusting relationships with patients, which can promote earlier detection of this condition.[2] These relationships allow APPs to better assess patients' clinical symptoms and order the appropriate testing. Due to a similar presentation as IBS, CSID can be incorrectly diagnosed as IBS-D. However, through APP education and awareness, CSID can be diagnosed and treated earlier in patients to provide improvement of this condition.

Key Takeaways on CSID

Most dietary carbohydrates are digested by sucrase-isomaltase

Although classified as a rare disorder, CSID is likely more common than previously believed

The optimal diagnostic strategy for CSID remains unclear; while disaccharidase assay is the current gold standard, the ^{13}C sucrose breath test offers a noninvasive, practical strategy to help establish the diagnosis

CSID should be included in the differential diagnosis of patients with presumed IBS, particularly in those that are not responding to dietary modifications

Treatment of CSID should be individualized based on patient preferences, using an iterative approach that incorporates dietary management and/or enzyme replacement therapy

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