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Congenital sucrase–isomaltase deficiency: diagnostic challenges and response to enzyme replacement therapy

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ABSTRACT

Congenital sucrase–isomaltase (SI) deficiency is a rare genetic condition characterised by a deficiency in the brush-border SI enzyme, resulting in an inability to metabolise sucrose and starches. Six cases of congenital SI deficiency treated with Sucraid (sacrosidase, a yeast-derived enzyme that facilitates sucrose digestion) are described. Typical presenting symptoms were watery diarrhoea, abdominal pain and bloating, sometimes noticeably worse after ingestion of fruit. Diagnosis is challenging since conventional hydrogen breath testing after an oral sucrose load is impractical in young children, and many laboratories no longer look for maldigested sucrose using faecal sugar chromatography. Confirmation is by disaccharidase assay of duodenal or jejunal mucosa obtained endoscopically. All six patients showed little improvement following advice regarding dietary management, but experienced a marked reduction in symptoms with sacrosidase administration; no adverse events were reported. Sacrosidase is an effective and well-tolerated treatment for patients with congenital SI deficiency. Gene testing and clinical trial of sacrosidase may become an alternative to endoscopic biopsies for diagnosis.

What is already known on this topic

- Congenital sucrase–isomaltase deficiency is a rare genetic condition where maldigestion of sucrose and starch causes diarrhoea, abdominal pain and bloating.
- Finding sucrose on faecal sugar chromatography can be a useful diagnostic clue prior to confirmation with duodenal/jejunal biopsy and mucosal disaccharidase assay.
- Commonly, symptoms are not well controlled by dietary restriction alone, but considerably helped by oral Sucraid (sacrosidase, a yeast-derived sucrase) with meals.

What this paper adds

- Diagnosis is now more difficult because many laboratories are no longer offering faecal sugar analysis, and hydrogen breath testing suggested as an alternative is problematic in children too young to cooperate (<4 years).
- Sacrosidase is effective and safe during long-term use.
- A combination of a novel gene test and clinical trial of sacrosidase may make mucosal enzyme assay unnecessary in most patients in the near future.

INTRODUCTION

Congenital sucrase–isomaltase deficiency (CSID) is an autosomal-recessive disease caused by mutations in the sucrase–isomaltase (SI) gene.[1] Patients with this rare disorder have an inability to metabolise specific carbohydrates, including sucrose, maltose and starch,[2] and ingestion of these substrates causes a variety of symptoms including diarrhoea, abdominal pain and bloating.[2] Severity of symptoms is influenced by residual enzymatic activity, levels of carbohydrate intake, gut motility and colonic fermentation.

CSID is usually diagnosed in infancy, although some individuals with milder symptoms are not diagnosed until adulthood,[2] and many patients are probably misdiagnosed as having a functional disorder. Duodenal or jejunal mucosal biopsy and assay of disaccharidases is the gold standard technique for diagnosis.[2] Sucrase activity ranges from reduced to absent, and isomaltase or maltase activity is similarly variable. There is a clinical need to identify a simple method for diagnosis. Non-invasive techniques include hydrogen or isotope-labelled breath tests, and faecal sugar chromatography.[1 3] In the past, stool sugar chromatography was often an initial investigation for watery diarrhoea and would show heavy excretion of sucrose in children with CSID. Many biochemistry laboratories in the UK have now abandoned this investigation.[3]

Historically, treatment of CSID has relied on dietary reduction of sucrose and starch;[4] however, only 50% of children were compliant with the diet and 60–75% still experienced diarrhoea and/or abdominal pain. Several studies have demonstrated the efficacy of the yeast-derived enzyme sacrosidase for relieving symptoms.[1 2] We describe clinical presentation, diagnosis and response to treatment with Sucraid (sacrosidase) in six children with CSID. All families were given standard dietary advice[4] by a paediatric hospital dietitian, but with little effect on symptoms. Initially both sucrose and starch are eliminated from the diet. This very restricted intake is followed by a gradual reintroduction of starch to determine a level of tolerance. Low sucrose, low starch foods include meat, egg, poultry, fats and vegetables. Formula milks containing sucrose or starch should not be given in infants, and sip feeds in older children should be avoided as these contain sucrose as sweetener.

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Table 1 Patient characteristics and response to Sucraid

Patient; age at referral (years)	Symptoms	Faecal sugar chromatography	Physical findings	Response to enzyme replacement therapy	Follow-up
2	Diarrhoeal stools 2/day; excessive flatulence and abdominal distension	Not tested	Growth normal	Formed stools; reduction in abdominal distension and flatulence; improved sleep through the night; willing to consume a wider range of foods	Age 5 years; bowels open 1/day; occasional mild diarrhoea and abdominal pain; severe diarrhoea if enzyme replacement omitted
1.25	Diarrhoeal stool 3/day and severe colic; diarrhoea worsened when put on hydrolysed protein formula containing starch	Sucrose present	Growth normal	Formed stools	Age 16 years; normal stools; avoids sucrose in diet; diarrhoea if enzyme replacement omitted
2.5	Diarrhoeal stool 4–5/day; abdominal bloating	Sucrose present	Growth normal; perianal excoriation	Formed stools 1–2/day; observed by parents to be much happier child	Age 7; diarrhoea if enzyme replacement omitted
2	Watery diarrhoeal stool, 5–6/day, worse after drinking fruit juice	Sucrose present	Growth normal	Formed stools, 3/day	Age 10 years; diarrhoea if enzyme replacement discontinued
0.5	Watery diarrhoeal stool 6–8/day, worse after drinking fruit juice or eating fruit; brother with CSID	Sucrose present	Growth normal	Formed stools 3–4/day	Age 8 years; diarrhoea if enzyme replacement omitted
2.5	Watery diarrhoeal stool 5–6/day, much worse after fruit; bloating and abdominal pain	Not tested	Growth normal	Stools more formed, 5/day	Age 3 years; symptomatic if enzyme replacement omitted

CSID, congenital sucrase–isomaltase deficiency.

Fruits contain differing amounts of sucrose, and low-sucrose fruit may be tolerated (eg, blackberries, grapes, pears).[4]

PATIENTS AND FINDINGS

There were four female and two male infants diagnosed with CSID over a 16-year period; characteristics are shown in table 1. All except patient 5 (whose brother had already been diagnosed with this condition) had oesophagogastroduodenoscopy and small bowel mucosal biopsies. Tissue samples were histologically normal, with low-sucrase activity (table 2). All families reported a poor response to dietary modification, and good clinical response to enzyme replacement therapy with 8500 U Sucraid at mealtimes. During follow-up, symptoms were reported to recur if enzyme was omitted.

DISCUSSION

Common clinical themes in these patients include persistent watery diarrhoea with normal growth, and in some cases a clear history of diarrhoea worsening following ingestion of sucrose (fruit, fruit juice) or formula containing glucose polymer. As CSID is a rare disorder, diagnosis is often delayed while more common causes of diarrhoea are investigated or because of initial misdiagnosis as a functional disorder.[1 2]

Table 2 Disaccharidase activity in small bowel mucosa

Patient	Maltase activity*	Sucrase activity†	Lactase activity‡
1	12.2 IU/g	**2.3 IU/g**	2.9 IU/g
2	**11.3 U/g**	**1.1 U/g**	9.6 U/g
3	**1.7 IU/g**	**0.1 IU/g**	9.6 IU/g
4	**1.9 IU/g**	**0.2 IU/g**	**1.3 IU/g**
6	**3.6 IU/g**	**0.2 IU/g**	3.6 IU/g

Measurements outside the normal range are shown in bold. Patient 5 (table 1) was not biopsied due to family history and sucrose in stool.
*Reference range: 12.0–45.0 IU/g.
†Reference range: 4.0–15.0 IU/g.
‡Reference range: 2.0–12.0 IU/g.

The standard method for confirming diagnosis (duodenal or jejunal mucosal biopsy and assay of disaccharidases) is invasive and associated with several drawbacks, including false-negative results and a complex freeze/thaw process that can adversely affect findings. Detailed advice to families regarding dietary management is available through the patient support group website: CSIDinfo.com. A trial of strict dietary management under expert dietetic supervision is important, not least because enzyme replacement therapy is expensive (currently around £600/month). It is clear that many patients remain symptomatic after dietary guidance and find sacrosidase of considerable benefit.

In four of the cases presented here, stool chromatography was very helpful in pointing towards the diagnosis; however, most analytical laboratories within the UK have stopped offering this test in the face of many unnecessary and pointless requests that have led to the mistaken belief it is of little value.[3] The suggestion that breath hydrogen testing makes sugar chromatography redundant[3] is misconceived and misses the point that accurate breath sampling in young children who cannot cooperate is extremely difficult.

Four mutations in the SI gene are responsible for the majority of clinical symptoms of CSID,[5] and a diagnostic genetic test including a panel of 11 mutations associated with CSID is now available (http://www.centogene.com). This panel is expected to identify around 83% of patients of European ethnicity with symptomatic disease. A positive gene test result combined with a successful trial of sacrosidase has the potential to allow diagnosis of CSID without endoscopy. The cost of endoscopy and enzyme assay is approximately £1500 compared with £180 for the gene test and £300 for a 2-week trial of treatment.

In conclusion, CSID may be underdiagnosed and clinicians should be alert to the possibility of this condition in children with persistent diarrhoea. New and simpler approaches to investigation are required. The symptoms of all six patients reported in this study could not be controlled by dietary management alone, and all improved following the initiation of Sucraid (sacrosidase) treatment, with recurrence if this was discontinued.

Symptoms can be severe and interfere significantly with normal activities such that long-term treatment is appropriate.

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Notes