Two Novel Mutations in the Lactase Gene in a Japanese Infant with Congenital Lactase Deficiency

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Intestinal lactase is required for the hydrolysis of lactose that is the most essential carbohydrate in milk and the primary diet source of newborn. Congenital lactase deficiency [CLD (MIM 223000)] is a severe gastrointestinal disorder and is characterized by watery diarrhea due to an extremely low or the lack of lactase activity in the intestinal wall from birth. CLD is a rare disease and occurs more frequently in Finland. Recent studies have shown that mutations in the coding region of the lactase (LCT) gene underlie CLD in patients from Finland and other European countries. Here, we report two novel mutations in the LCT gene in a Japanese female infant with clinical features consistent with those of CLD. She suffered from severe watery diarrhea from the age of 2 days on breast milk/lactose containing cow’s milk formula. With the lactose-free hydrolyzed cow’s milk formula, diarrhea was stopped, and she has now developed well on a lactose-free diet. She shows a lactose-intolerance pattern on the lactose challenge test. Sequence analysis revealed the two mutations in her LCT gene: c.4419C>G (p.Y1473X) in exon 10 transmitted from her mother and c.5387delA (p.D1796fs) in exon 16 transmitted from her father. Both mutations cause premature truncation of lactase polypeptide and are supposed to be responsible for CLD. To our knowledge, this is the first report on mutations in the LCT gene in Japan. We suggest that an increased awareness is required regarding CLD.

Keywords: congenital lactase deficiency; cow’s milk allergy; lactase gene; oral lactose challenge test; watery diarrhea

Received February 9, 2012; revision accepted for publication April 21, 2012. doi: 10.1620/tjem.227.69

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Intestinal lactase is required for the hydrolysis of lactose that is the most essential carbohydrate in milk and the primary diet source of newborn. Congenital lactase deficiency [CLD (MIM 223000)] is a severe gastrointestinal disorder characterized by watery diarrhea due to an extremely low or the lack of activity of lactase in the intestinal wall from birth. Affected infants are suffered from severe watery diarrhea shortly after the first feed with breast milk or lactose-containing formulas (Savilahti et al. 1983). Despite adequate feeding, they are dehydrated and have poor weight gain, because they are unable to hydrolyze lactose that accounts for 40% of energy ingested among infants. This disease is a rare autosomal disorder and occurs more frequently in Finland. Recently, mutations in the coding region of the lactase (LCT) gene were revealed to be the underlying cause of CLD and the molecular background is being identified. The LCT gene consists of 17 exons encoding 1927 amino acids comprising four homologous domains, I - IV. Domain IV harbors lactase activity. One mutation, c4170T>A (p.Y1390X) in exon 9, is enriched in Finnish population, and 84% of Finnish patients were homozygous for this mutation. Y1390X is located in domain IV, and results in a truncation of lactase (Kuokkanen et al. 2006; Behrendt et al. 2009).

Here, we report a Japanese female infant with clinical features consistent with those of CLD who has two novel mutations in the LCT gene in a heterozygous form: c.4419C>G (p.Y1473X) in exon 10 and c.5387delA (p.D1796fs) in exon 16. Both of the mutations are located in the domain IV and supposed to be causative of CLD. To our knowledge, this is the first report on mutations in the LCT gene in Japan, and our findings suggest that an increased awareness is required regarding CLD.

Clinical Report

The patient is the first child of healthy nonconsanguinous Japanese parents. She was born at term after an uneventful pregnancy with a birth weight of 3,124 g. When the patient was fed breast milk and lactose-containing formula, she developed watery diarrhea at the age of 2 days. At the age of 4 days, she was admitted to the department of pediatrics because of poor weight gain and dehydration.
On admission, her weight was 2,722 g, and the serum levels of blood urea nitrogen, creatinine, sodium, and potassium were 29.4 mg/dL, 0.4 mg/dL, 157 mEq/L, and 5.4 mEq/L, respectively. Dehydration resolved after intravenous infusion was initiated, but severe watery diarrhea continued to be observed. The result of a stool culture was negative; in addition, rapid antigen tests for rotavirus and adenovirus were negative. Watery diarrhea promptly disappeared when the oral intake was discontinued at the age of 9 days and did not recur when she was administered a diet with lactose-free hydrolyzed cow’s milk formula at the age of 10 days. She showed a remarkable improvement in weight gain, and the intravenous infusion was discontinued at the age of 12 days. She was discharged from the hospital at the age of 17 days, showed good body weight gain, and was free from gastrointestinal symptoms. She was suspected to have CLD or cow’s milk protein allergy, and was admitted to our hospital for a lactose challenge test at the age of 4 months. The oral lactose challenge test with 2 g/kg of lactose showed no increase in the blood glucose level within 120 min and was followed by watery diarrhea within a few hours (Fig. 1). The serum level of total immunoglobulin E (IgE) antibody was 3 IU/mL and that of serum-specific IgE antibody to whole cow’s milk measured using a chemiluminescent enzyme immunoassay was 0.07 lumicount; class 0 (MAST33; SRL, Tokyo, Japan). Lymphocyte stimulation tests for α-lactalbumin, β-lactoglobulin, α-casein, β-casein, and κ-casein were negative (stimulation indices were 0.7,

Fig. 1. Oral lactose challenge test at the age of 4 months. After oral administration of 2 g/kg of lactose, no increase was observed in the blood glucose within 120 min and watery diarrhea developed. In contrast, a marked increase was observed in the blood glucose level after drinking 1 g/kg of glucose and no gastrointestinal symptoms were observed.

Fig. 2. Sequence analysis of the LCT gene. a. LCT Ex10 c.4419C>G (p.Y1473X). b. LCT Ex16 c.5387delA (p.D1796fsX)
0.9, 1.1, 1.3, and 1.0, respectively). The oral lactose challenge test was repeated at the age of 5 months, and the patient continued to show a lactose-intolerance pattern (no increase in the blood glucose level).

After experiencing acute gastroenteritis, she passed blood-tinged stools for a few weeks and underwent sigmoid colonoscopy with biopsy. The colonoscopy showed lymphoid nodular hyperplasia with patchy erythema, and histological examination indicated a relatively high number of eosinophils (about 10 per high power field) and a small number of neutrophils in the lamina propria. Although these findings were consistent with those of mild proctocolitis, they were not sufficiently strong to confirm the presence of a food allergy.

To confirm whether lactose intolerance was primary or secondary, we performed sequence analysis of 17 exons of the LCT gene after the patient’s parents provided written informed consent. The Ethics Committee of the Tohoku University School of Medicine approved the present study. The result showed two novel mutations: c.4419C>G (p.Y1473X) in exon 10 and c.5387delA (p.D1796fs) in exon 16 (Fig. 2). The p.Y1473X mutation was transmitted from her mother, and the other mutation (p.D1796fs) was transmitted from her father.

The patient is now administered a lactose-free diet, and her psychomotor development was appropriate for her age at the latest examination at the age of 11 months.

Discussion

CLD is one of the rare autosomal disorders commonly occurring in the Finnish population because of a founder effect and genetic drift. A few cases of CLD in patients with different ethnic origins have also been reported. The incidence of CLD was estimated to be 1:60 000 newborns in Finland on the basis of the number of patients who had been diagnosed until 1998 (Järvelä et al. 1998). After the molecular background of CLD was confirmed, the number of patients newly diagnosed with CLD in Finland increased, and the novel LCT mutations were reported in the CLD patients with different ethnic origins (Torniainen et al. 2009). In Japan, only few cases of CLD have been reported since Akabane and Arakawa published the first case in 1965 (Akabane 1965; Yabuuchi et al. 1966; Nose et al. 1979). Infants who develop severe watery diarrhea after consuming breast milk/lactose-containing formula are unlikely to be suspected of having CLD because this disease is thought to be very rare.

The nascent lactase polypeptide comprises four homologous domains, I-IV. After posttranslational processing, the mature lactase contains only domains III and IV. Domain IV comprises lactase activity, and domains I-III act as intramolecular chaperone which is critical for the maturation during lactase-folding process (Kuokkanen et al. 2006; Behrendt et al. 2009). To date, nine mutations are known to underlie CLD and there are quite evenly distributed covering both the pro-region and the mature lactase (Kuokkanen et al. 2006; Torniainen et al. 2009). Five of them result in a premature stop codon. One of the missense mutations, G1363S, located in the domain III, leads to defective lactase activity and impaired trafficking of mutant lactase polypeptide to the cell surface at physiological temperature (Behrendt et al. 2009).

In the case of our patient, she was suspected of having CLD or cow’s milk protein allergy in the early neonatal period, because her symptoms improved with a change in her diet from breast milk/lactose-containing formula to hydrolyzed cow’s milk formula, which is lactose-free. Small bowel biopsy would be useful to distinguish CLD from cow’s milk protein allergy (Heyman 2006), but it is an invasive procedure and requires excellent technical skills. Accordingly, since it would need to have been performed in a 4-month old baby, we performed sequence analysis as the diagnostic examination. Sequence analysis revealed that she has one nonsense mutation and one frame-shift mutation in domain IV. These mutations lead to premature truncation of lactase protein being causative of CLD. Sequence analysis would be useful for the diagnosis if a CLD patient also has cow’s milk protein allergy.

Our findings suggest that CLD is possibly more common in Japan than it was thought to be. CLD patients may be treated as patients with cow’s milk protein allergy, using lactose-free hydrolyzed cow’s milk formula. Sequence analysis is useful for diagnosing CLD, which is sometimes difficult to distinguish from cow’s milk protein allergy. Pediatricians should have an increased awareness regarding CLD.

Conflict of Interest

The authors have no conflict of interest associated with this article.

References


