Congenital lactase deficiency
A clinical study on 16 patients

E SAVILAHTI, K LAUNIALA, AND P KUITUNEN
Department of Paediatrics, University of Helsinki, and University of Kuopio, Finland

SUMMARY There are at least 20 rare autosomal recessive disorders that are excessively common in Finland of which congenital lactase deficiency is one. During the last 17 years we have found 16 cases. In each case the mother noted watery diarrhoea, generally after the first feed of breast milk, and at the latest, by age 10 days. The lactose malabsorption was verified at a mean age of 36 (range 3–90) days, by which time the infants were dehydrated and 15 of them weighed less than at birth (mean weight for age was —2.8 SDs). On a lactose-free elimination diet (a group of 6 on Nutramigen and a group of 10 on soy-based formula) the children caught up in growth. One infant in each group showed allergic symptoms. While the infants were being breast fed their faeces contained 20 to 80 g/l lactose. In 24 peroral lactose tolerance tests, the greatest rise in blood glucose concentration was 0.8 mmol/l. Only 2 patients showed abnormal absorption when tested within a week of lactose elimination, and in each absorption tests became normal during the elimination period. Slight to partial villous atrophy of the jejunum was present in 4 early specimens, but in later ones the mean villous height was normal. The mean height of the epithelial cells was reduced and there were fewer intraepithelial lymphocytes in patients. The lactase activities in jejunal biopsy specimens were lower than in most patients with acquired lactase deficiency, with some overlap. The maltase and sucrase activities were normal.

Since the early reports of Holzel et al.,1 Lifschitz,2 Launiala et al.,3 and Levin et al.4 on congenital lactase deficiency, so little has been written on the subject that the mere existence of the disease has been doubted.5 It is indeed an insignificant handicap if recognised early, but can jeopardise the life and well being of an infant if fully dependent on lactose-containing food. Many aspects of the deficiency are unknown.

We report our experiences with 16 children exhibiting congenital lactase deficiency (CLD) whom we have treated during the last 17 years. We give evidence for the autosomal recessive mode of inheritance of CLD and document the good growth and psychomotor development of the affected children. Studies on absorptive function, jejunal morphology, and current nutritional state are described as well.

Patients

Patients were referred to the university hospitals of Helsinki (13 cases) and Kuopio (3 cases) which together serve a population of 2.5 million. Three of the early patients came from outside the hospital area. Patients have been followed up at outpatient clinics of the hospitals, most of them annually. Case 11 was lost to follow up after age 1 year. Two further children probably had CLD—one, a small preterm infant, soon failed to attend the outpatients clinic, and the parents of the other refused control biopsy. A specimen from the latter infant was taken from the duodenum and showed low sucrase and maltase activities. These 2 children are excluded from this report.

Methods

The growth of the children was plotted against standard curves for Finnish children.7

Faecal analysis for reducing substances was carried out using the Clinitest method of Kerry and Anderson.8 Thin layer chromatography for the identification of faecal sugars was done on a perchloric acid eluate. Estimation of the quantity of sugars was done with reference spots of known amounts run in parallel with the unknown.9

In peroral lactose tolerance tests a dose of 2 g per kg of lactose was administered and blood lactose
measured at 0, 20, 40, and 60 minutes. In peroral glucose-galactose tests 1 g of each sugar per kg was given.

Fat content of 3-day faecal collection was measured according to van de Kamer et al. D-xylose absorption was studied either from 5-hours’ urinary collection (more than 15% of test dose was considered normal), or by measuring blood D-xylose 1 hour after the administration of xylose (normal rise more than 1.4 mmol). Jejunal biopsy specimens were taken, with a Crosby-Kugler biopsy device, at ligamentum Treitz or up to 20 cm distal from it. Specimens were studied under a dissecting microscope and divided for formalin fixation for routine histology and disaccharidase assay. Villous height, crypt length, epithelial cell height, and the numbers of intraepithelial lymphocytes in the specimens were measured as described. Disaccharidase activities of the specimens were measured according to a modification of the methods of Dahlqvist.

**Controls.** For each patient an age-matched control was chosen from among controls in two studies. If several specimens were studied from the same patient the age at which the last specimen was taken for morphometry was used for selecting the control. Normal values for sucrase, maltase, and lactase were based on unpublished results of population studies on lactase deficiency. The reference values for sucrase and maltase were based on 347 specimens displaying normal morphology. In the calculation

---

**Fig. 1** Distribution of lactase activities in patients with congenital lactase deficiency (dotted bars). When several measurements were done on specimens of one patient, the mean value was used for classification.

**Table 1** Clinical data of patients

<table>
<thead>
<tr>
<th>Case</th>
<th>M/F</th>
<th>Siblings</th>
<th>Birth weight for gestational age*</th>
<th>Age (S.D.)</th>
<th>Height (cm S.D.)</th>
<th>When first put on lactose-free diet</th>
<th>Reducing substance in faeces studied during breast milk feeding</th>
<th>Chromatography (g/l)</th>
<th>Clinist (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>2 healthy</td>
<td>3000/1-2</td>
<td>320/1-2</td>
<td>3200/1-2</td>
<td>Not studied</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
</tr>
<tr>
<td>M</td>
<td>2 healthy</td>
<td>3000/1-2</td>
<td>320/1-2</td>
<td>3200/1-2</td>
<td>Not studied</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
<td>2400/1-2</td>
</tr>
</tbody>
</table>

*Infants were born after 36 to 41 weeks of gestation. Cases broken together are siblings.
of the lactase reference value, 103 cases with a lactase activity below 20 U/g protein were excluded. The distribution of lactase activities in these 103 specimens was compared with the values in the present study (Fig. 1).

Results

Hereditv. Our 16 patients with CLD came from 12 families (Table 1). The total number of children in the families was 29 and no neonatal death had been reported. There were two brothers (Cases 8 and 9) and two sisters (Cases 4 and 5), and two lots of brothers and sisters. There were 9 boys. None of the parents displayed symptoms after eating lactose.

The expected number of affected individuals in families with at least 2 children is according to a priori method 12·2, standard error 1·7. The observed number was 14 (Table 1).

Symptoms. Symptoms were noted by mothers early, in half of the patients at the first feed. Watery diarrhoea was noted at age 10 days at the latest. In every infant symptoms appeared during breast feeding and 10 of the infants had received nothing but breast milk before admission to hospital. Babies were vigorous, they fed well, and were constantly hungry. The overall good condition of the babies is borne out by the fact that the early symptoms led to a thorough examination in only one (Case 15), if the child was the first in the family to be affected. Most infants were studied only when it was realised that despite adequate feeding the weight was declining. Vomiting was present in only 4 cases. With the exception of Case 16, the weight of the others was below birthweight when put on a lactose-free diet (Table 1). Case 16 displayed the highest activity of lactase in his biopsy specimen (Table 2).

At admission many patients were moderately dehydrated, but none was in vascular collapse. After intravenous correction of dehydration, all were put on breast milk in the hospitals. The effect of subsequent lactase removal on faeces

Table 2 Morphology and disaccharidase activities of jejunal biopsy specimens

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Villous height/crypt length ratio</th>
<th>Epithelial cell height (μm)</th>
<th>Intraepithelial lymphocytes/100 epithelial cells</th>
<th>Disaccharidase activities, units/g protein</th>
<th>Lactase activity</th>
<th>Lactase/sucrase ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malate</td>
<td>Sucrase</td>
<td>Lactase</td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
<td>1.3</td>
<td>28.8</td>
<td>15</td>
<td>251</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>296</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>494</td>
<td>146</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>2.5</td>
<td>32</td>
<td>34</td>
<td>404</td>
<td>122</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>2.8</td>
<td>31.1</td>
<td>12</td>
<td>368</td>
<td>111</td>
<td>0.8&lt;0.3&lt;0.3</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>1.4</td>
<td>31.6</td>
<td>25</td>
<td>287</td>
<td>86</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0.3</td>
<td>2.1</td>
<td>28</td>
<td>8</td>
<td>353</td>
<td>178</td>
<td>3.2</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>2.5</td>
<td>32.9</td>
<td>15</td>
<td>478</td>
<td>NS</td>
<td>3&lt;0.3&lt;0.3</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>1.4</td>
<td>31.6</td>
<td>25</td>
<td>287</td>
<td>103</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>0.3</td>
<td>1.9</td>
<td>27</td>
<td>13</td>
<td>851</td>
<td>178</td>
<td>2&lt;0.3&lt;0.3</td>
</tr>
<tr>
<td>11</td>
<td>0.5</td>
<td>2.5</td>
<td>31.8</td>
<td>13</td>
<td>353</td>
<td>178</td>
<td>2&lt;0.3&lt;0.3</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>2.1</td>
<td>28</td>
<td>11</td>
<td>478</td>
<td>NS</td>
<td>3&lt;0.3&lt;0.3</td>
</tr>
<tr>
<td>13</td>
<td>1.1</td>
<td>2.4</td>
<td>27</td>
<td>18</td>
<td>485</td>
<td>161</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>0.1</td>
<td>2.1</td>
<td>25.3</td>
<td>14</td>
<td>NS</td>
<td>NS</td>
<td>4.4</td>
</tr>
<tr>
<td>15</td>
<td>0.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>355</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0.3</td>
<td>2.5</td>
<td>30</td>
<td>14</td>
<td>254</td>
<td>56</td>
<td>10</td>
</tr>
<tr>
<td>Whole group mean, 2.6</td>
<td>2.9</td>
<td>29.6</td>
<td>14</td>
<td>14</td>
<td>340</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Controls' mean, 3.3</td>
<td>3.2</td>
<td>32.0</td>
<td>26.7</td>
<td>86</td>
<td>175-748</td>
<td>47-213</td>
<td>20-136</td>
</tr>
</tbody>
</table>

*Value for brush border lactase reported in study 23. †Value for brush border lactase reported in study 24. Where several specimens were studied the most recent value was used for calculations. §95% confidence limit.
was striking in all but one patient: the watery diarrhoea stopped within hours and lactose-free feeding could be started, and resulted in good gain in weight. Case 6 required a month of intravenous nutrition before tolerating oral feeding. Three attempts at feeding with Nutramigen led to vomiting and diarrhoea. A chicken-based formula was tolerated at age 5 months and gave a good gain in weight. Hirschsprung’s disease was suspected in two patients (Cases 4 and 7) and in Case 4 a jejunostomy was performed needlessly. Before 1974 (6 cases) Nutramigen was used as basic formula and was tolerated by all except Case 6. Soy-based formula was used in the later 10 cases. In Case 15 it probably caused a haemorrhagic enterocolitis: 5 days after the start of soy formula the baby displayed symptoms of vomiting and bloody diarrhoea, and the weight declined. A rectal biopsy specimen showed inflammation. Low values of C3 and C4 in sera later became normal. The course on Nutramigen was uneventful.

The children were free of symptoms while on a lactose-free diet. Some older ones have experienced diarrhoea and abdominal cramp after experimenting with ice-cream, and they prefer to eliminate lactose.

**Growth.** Birthweight and height of the patients were slightly below normal (Table 1). When put on lactose-free diet, their mean weight (for age) was -2.8 SDs; the height was less retarded (-1.2). By age 1 year they had caught up to -1.0 and -0.8 SDs for weight and height. At age 2 years (13 cases) their mean weight was -0.5 SDs and height -0.5; in 5 cases aged over 10 years the catch-up growth has been complete (mean weight 0.0, height -0.1). No other anomalies were connected with CLD. Psychomotor development has been normal.

**Laboratory data.** Haemoglobin concentration at admission was increased in 6 cases. All those studied (13 cases) had metabolic acidosis with some respiratory compensation.

In 11 cases reducing substances were found in faeces by the Clinitest method (Table 1). Thin layer chromatography showed a concentration of 20-90 g/l of lactose in faeces when babies were on breast milk. Contents of glucose and galactose varied widely (traces to 25 g/l). The pH of faeces was between 4.5 and 5.5 in 4 patients studied. In 2 patients faeces were not studied and lactose malabsorption was found by the lactose tolerance test. Altogether 24 lactose tolerance tests were done on 13 infants (Fig. 2). In 15 tests no increase in levels of blood glucose was seen. The greatest rise was 0.8 mmol/l at 40 minutes.

In Cases 4, 5, 9, 10, and 11, lactose tolerance tests performed between ages 1-8 and 13-5 years resulted in abdominal symptoms and loose stools, which were passed within 2 hours of the lactose dose. The stools did not contain lactose. In Cases 1-4 an oral glucose-galactose tolerance test caused a rise in blood glucose concentration to between 2.0 and 3.3 mmol/l.

During lactose feeding or within one week of its elimination, 2 patients had abnormal results in absorptive tests (Table 3). A later test gave a normal result in each.

Studies on blood folate levels, B12, serum iron, total iron binding capacity, serum ferritin, calcium, phosphate, alkaline phosphatase, manganese, and zinc were done at the most recent follow-up in Cases 4, 5, 6, 8, 9, 10, and 15 at ages 1.9 to 13.5 years. A D-xylose absorption test, with measurement of blood xylose level 1 hour after ingestion was done (Table 3). All these measurements were normal. Serum cholesterol level was reduced: (P<0.05) the mean value was 4.4 mmol/l (SD 1.2). (The mean for healthy Finnish children is 4.9 mmol/l.20) Triglycerides were normal (mean 1.1 mmol).

**Fig. 2 Maximal rise in blood glucose in 24 lactose tolerance tests of patients.**

<table>
<thead>
<tr>
<th>Table 3 Tests for absorptive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal fat excretion (g/day)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>&lt;4</td>
</tr>
<tr>
<td>&gt;4</td>
</tr>
</tbody>
</table>

- **During lactose ingestion or within a week of its elimination:**
  - Faecal fat excretion: 3 >4
  - D-xylose excretion: 3 >15%
  - Blood xylose test: 1 >1.4

- **Lactose eliminated >1 week:**
  - Faecal fat excretion: 4 >0
  - D-xylose excretion: 3 >0
  - Blood xylose test: 7 >0
Jejunal morphology. In 2 specimens (Cases 1 and 15) partial villous atrophy (villus height 150–250 μm) was seen, and in 2 others slight changes in the villous structure (VH 250–300 μm) (Cases 6 and 10). In Case 1 a later specimen at age 2-2 years showed an increase in maltase and sucrase activities, but still a low lactase activity (Table 2). Case 15 had suffered from intestinal soy allergy; his lactose intolerance was most recently tested at age 1-8 years: the test showed no rise in the level of blood glucose. Case 6 showed normal morphology in a later specimen. In Case 10 lactose intolerance was tested at age 3-1 years, and no rise in the blood glucose concentration was seen.

The mean length of crypts in patients was increased compared with controls (150 versus 127 μm) resulting in significantly reduced (P<0.05) VH/CL ratio (Table 3). The mean villous height in the most recent specimens (379, SD 99 μm) was the same as in 16 specimens of age-matched controls (mean 387, SD 86 μm). The epithelial cell height was reduced in comparison with that of age-matched controls (P<0.05). The numbers of intraepithelial lymphocytes were significantly fewer (P<0.001) than in controls, who were on unrestricted normal diet. In every case the diagnosis of CLD was based on the finding of low (highest value at 10 U/g protein) lactase activity (Table 2). Values for maltase and sucrase were normal in all except Case 9 (Table 2). The ratio of lactase to sucrase was 0-18 or less. The distribution of lactase activities is different from that found in adult cases with acquired lactase deficiency (Fig. 1). The deficiency is more severe in congenital than in acquired lactase deficiency, but some groups overlapped.

Discussion

In earlier investigations three pairs of siblings (including one of the pairs in this study) and 15 boys were found among a total of 18 children affected with CLD. In the present study we found 4 pairs of siblings among 16 children and an almost equal distribution of boys and girls. The parents of patients were asymptomatic. With the virtual disappearance of diarrhoea as a cause of death in the first year of life in Finland in the 1960s, we believe that every case of CLD in our population has been discovered. We therefore analysed the possibility of autosomal recessive inheritance by methods of complete ascertainment. The number of cases observed was close to the number expected for such inheritance. Our finding of 16 patients from hospitals serving a population of 2.5 million is extraordinarily high, considering that only 18 cases of CLD have been reported altogether. Long-term follow-up and definitive diagnosis based on the analysis of jejunal disaccharidase have been made for only 5. However, the structure of the Finnish population has favoured the preservation of autosomal recessive diseases and 20 such diseases have been recognised as excessively common in Finland. Our observation of large numbers of CLD adds one more to the list. The diagnosis of CLD is easy when it is suspected. Typical symptoms are watery diarrhoea starting soon after beginning breast (or cows’ milk) feeding, good appetite, liveliness, and absence of vomiting. The osmotic diarrhoea and loss of nutrients is of such magnitude that growth is not possible. Dehydration and acidosis develop, but babies can sometimes survive for months in this state. No neonatal deaths had occurred in families of the study. Reducing substances could be shown by simple Clinitest method and faeces were very acidic, too. At age 1-7 years or later, lactose was no longer excreted in faeces, but probably fermented by the colonic bacteria, resulting in flatulence and abdominal pains. In the recent cases we instituted lactose-free diet after analysing sugars in faeces by thin layer chromatography and finding a large amount of lactose. The response to lactose elimination was prompt when done within the first month of life. The diagnosis was made on the basis of a jejunal biopsy specimen taken several months later when children were thriving. In these specimens there was selective deficiency of lactase and the morphology was normal or close to normal. The permanence of the deficiency could be followed by a lactose tolerance test; in these tests we always found a rise in blood glucose clearly less than 1 mmol/l. In many of our early cases the diagnosis was confirmed by several jejunal specimens studied in different laboratories.

The outcome and psychomotor development of the affected children has been good. Some difficulties were encountered in the early cases where ignorance of the disease caused delay in diagnosis. A jejunostomy operation was performed needlessly in one case and prolonged intravenous nutrition was required in another. The latter child was probably intolerant of Nutramigen which occasioned some of the difficulties. We later saw an acute enterocolitis, probably due to soy allergy. A food allergy should always be suspected if children with CLD do not thrive on a lactose-free diet.

The diet of the affected children is profoundly different from that of healthy ones, especially in the first year of life when milk is the most important nutrient. No nutritional deficiencies could be found. But they had somewhat lower cholesterol levels than healthy Finnish children, probably because they consume smaller amounts of saturated butter.
fats and replace them with polyunsaturated vegetable oils.

The intestinal function was normal in the children. Two abnormal measurements were seen shortly after the beginning of lactose-free diet, but all later studies gave a normal result for absorption of fat and D-xylose.

Slight to partial villous atrophy was present in 4 specimens; one of these was taken during lactose feeding and two within a week of its termination. One subsequent control specimen showed normal villous structure. In 3 others the permanence of lactose malabsorption was tested later by lactose tolerance tests or renewed disaccharidase assay. Apparently a prolonged feeding of lactose in the absence of the splitting enzyme causes these reversible jejunal changes, which are accompanied by a defect in absorptive function in some. In 2 children, damage to the villous structure of the jejunum might have been caused by secondary food intolerance: in each lactose intolerance was recognised before the development of food intolerance, during breast milk feeding, and the persistence of lactose intolerance was demonstrated. A comparison of the most recent specimens of patients with those of age-matched controls showed no difference in mean villous height, although crypts were elongated. The mean height of the epithelial cells was reduced in specimens of patients as has been observed in secondary disaccharidase deficiencies,26 probably due in part to the loss of brush border material.24

The smaller amount of intraepithelial lymphocytes in specimens from patients compared with controls may be due to the different diet of the groups and their different antigenic stimulus. We did not find any reduction in the numbers of immunoglobulin-containing cells in specimens of these patients (E Savilahti, M Perkkö, 1982 unpublished data).

There has been much confusion about the role of lactose and proteins in cows' milk as a cause of infant diarrhoea. Secondary lactose malabsorption also plays a part in intestinal cows' milk allergy.36 However, symptoms begin later in this disease, only after consumption of cows' milk, and the damage of the jejunal mucosa is moderate to severe.37 There is inflammation of the jejunal mucosa and numbers of intraepithelial lymphocytes are increased,11 12 27 whereas in specimens of our patients with CLD there was no inflammation and the number of intraepithelial lymphocytes was low. We therefore are convinced that all our cases represent primary, permanent deficiencies of lactase.

In most of our patients the lactase activity was very low and below that in acquired lactase deficiency. At the same time patients had normal activities of maltase and sucrase, and the ratio between lactase and sucrase activities was usually very low. However, there is overlap with acquired deficiency, and chromatographic studies on our patients24 favour the idea that the pathogenesis of congenital and acquired lactase deficiency is alike: switching off of the enzyme production. Only the time of onset is different, and in most cases the severity of the defect.

We describe clinical features of congenital lactase deficiency and stress the importance of its early detection. Our report adds one more congenital disease with a probable autosomal recessive mode of inheritance to the Finnish disease inheritance.

We thank Ritva Metsola and Marjut Appelqvist for skilful technical assistance.

The study was supported by a grant from the Sigrid Jusélius Foundation.

References
Savilahti, Launiala, and Kuitunen


Correspondence to Dr Erkki Savilahti, Children’s Hospital, University of Helsinki, SF-00290 Helsinki 29, Finland.

Received 27 September 1982