Systemic lactose intolerance: a new perspective on an old problem
S B Matthews, J P Waud, A G Roberts, A K Campbell

Intolerance to certain foods can cause a range of gut and systemic symptoms. The possibility that these can be caused by lactose has been missed because of “hidden” lactose added to many foods and drinks inadequately labelled, confusing diagnosis based on dietary removal of dairy foods. Two polymorphisms, C/T13910 and G/A22018, linked to hypolactasia, correlate with breath hydrogen and symptoms after lactose. This, with a 48 hour record of gut and systemic symptoms and a six hour breath hydrogen test, provides a new approach to the clinical management of lactose intolerance. The key is the prolonged effect of dietary removal of lactose. Patients diagnosed as lactose intolerant must be advised of “risk” foods, inadequately labelled, including processed meats, bread, cake mixes, soft drinks, and lagers. This review highlights the wide range of systemic symptoms caused by lactose intolerance. This has important implications for the management of irritable bowel syndrome, and for doctors of many specialties.

A 53 year old woman with severe irritable bowel syndrome (IBS), eczema, asthma, and osteoarthritis was investigated for lactose intolerance (see below). This diagnosis has transformed her life. She has been essentially symptom free and off all medication for over two years. Similar dramatic stories have been repeated among 300 patients we have diagnosed with systemic lactose intolerance.

AN UNUSUAL CASE?
This 53 year old woman had a 10 year history of asthma, eczema and sinus problems, muscle and joint pain, and lack of concentration. This was so severe that she was worried that she was developing Alzheimer’s disease. From childhood she complained of an itchy rash and eczema, frequent diarrhoea, nausea, and sickness. She had been diagnosed as having eczema, asthma, and osteoarthritis, and was awaiting a knee replacement operation. She was taking a range of medications, including skin creams, antihistamines, asthma inhalers, antibiotics, antidiarrhoeals, and strong pain relief. We carried out a lactose intolerance test (50 g oral lactose followed by an analysis of breath hydrogen for three hours) (fig 1). By three hours her breath hydrogen had not risen to >20 ppm over the nadir, the recognised level for diagnosing lactose intolerance. However, she recorded a range of gut and systemic symptoms after ingestion of lactose. These included abdominal pain, diarrhoea, nausea and vomiting, headache, light headedness, feeling drunk, heart palpitations, joint and muscle pain. These symptoms after lactose lasted severely for three days. She was advised to remove all lactose from her diet for one month. This entailed not only avoidance of food and drinks containing “dairy” products, but she was advised also to avoid foods and drinks where lactose can be added in large quantities without being on the label. Within one month she described her skin as “wonderful”. Her asthma and sinusitis had improved, her knees were much improved, her diarrhoea and abdominal pain gone. She no longer needed any medication and was taken off the list for a knee replacement.

A DNA test now provides a vital aid to diagnosis. Intolerance to certain foods can cause a range of gut and systemic symptoms. The possibility that these are caused by lactose has been missed because of “hidden” lactose added to many foods and drinks without being on the label. This is now generally realised, confusing diagnosis based on dietary removal of dairy foods. An important change in the clinical management of lactose intolerance and IBS is now required.

LACTOSE AND LACTASE
Lactose, β galactose 1,4 glucose, is the unique sugar in the milk of all mammals, except Pinnepedia (sea lions and walruses). It is hydrolysed in the small intestine by the enzyme lactase. All mammals, except white northern Europeans and some other ethnic groups (for example, the Bedouins and African dairying tribes), are hypolactasic—that is, they have a low lactase. This is because they lose 75%–90% of the enzyme within a few years of weaning. The molecular mechanism causing this is unknown. It is not attributable to polymorphisms within the lactase gene itself or within its promoter (55 kb within 70 kb, long arm of chromosome 2 (2p21q) 17 exons). However, there is a close correlation between lactase persistence and two polymorphisms, C/T13910 and G/A22018 upstream from the lactase gene, CC/GG being associated with lactase non-persistence and lactose intolerance. The eventual level and time course of loss of lactase vary considerably with ethnic group. Chinese and Japanese lose 80%–90% within three to four years after weaning, whereas Asians and Jews can retain some 20%–30%, taking several years to reach the lowest level. The
LACTOSE INTOLERANCE

It is important to distinguish between hypolactasia, a low level of lactase, and clinical lactose intolerance. Lactose intolerance was first described by Hippocrates. But only in the past 50 years has this condition been recognised and diagnosed medically. Lactose intolerance is defined as the persistence of lactase in the small intestine in those with lactase persistence. It is caused by hypolactasia. But lactose intolerance also causes nausea and vomiting, with many patients presenting with constipation because of reduced intestinal motility rather than diarrhoea. Lactase also causes a range of systemic symptoms (table 1B), including headaches and light headedness, loss of concentration, difficulty with short term memory, severe tiredness, muscle and joint pain, various allergies, heart arrhythmia, mouth ulcers, sore throat, and increased frequency of micturition. These have been missed because of the spasmatic nature of the symptoms, the prevalence of any one symptom varying from 20% to 100% (table 1B). Yet removal of lactose from the diet can transform the life of someone with lactose intolerance, often after years of discomfort and misdiagnosis, including accusations of psychosomatic illness. Lactose intolerance causes great distress in many patients, often after years of discomfort and misdiagnosis, including accusations of psychosomatic illness. Lactose intolerance is often ruled out inappropriately. The standard test lacks sensitivity (table 2), exacerbated by the fact that there is no recommendation that symptoms should be routinely recorded during the test. The long term conditions can be insufficient to generate hydrogen. The test can cause severe symptoms, sometimes lasting for several days. Intolerance to some foods can cause IBS, with a wide range of unexplained systemic symptoms in addition to gut symptoms. The possibility that these are caused by lactose intolerance has been missed. It is not widely known that lactose is added to a large range of unexplained systemic symptoms in addition to gut symptoms. The possibility that these are caused by lactose intolerance has been missed. It is not widely known that lactose is added to a large number of foods and drinks in addition to those directly from milk and its products without stating this on the label. The occurrence of this “hidden” lactose is not widely known to clinicians or dietitians, and may explain undiagnosed cases of food intolerance. When the dairy exclusion diet apparently fails lactose intolerance is often ruled out inappropriately. The current diagnosis of lactose intolerance entails taking 50 g of lactose orally, equivalent to one litre of cows' milk, followed by measurement of breath hydrogen every 30 minutes for three hours. A breath hydrogen of 20 ppm above the nadir indicates lactose intolerance. The large intake of lactose overloads the lactase left in those who lose it after weaning, resulting in failure to diagnose lactose intolerance when symptoms recur even after removing dairy products from the diet. There is no genetic test for lactose intolerance.

We have correlated two polymorphisms, C/T13910 and G/A22018 (fig 2), closely associated with lactase persistence, with breath hydrogen, gut and systemic symptoms (table 1), induced after lactose ingestion in over 300 adults and children. DNA analysis is an important addition to the investigation of lactose intolerance, a redefinition of lactose intolerance being required. Eighty per cent of patients,
Lactose intolerance is a condition in which the body is unable to fully digest lactose, a sugar found in dairy products and milk. It is caused by a deficiency in lactase, the enzyme that breaks down lactose into glucose and galactose. There are several factors that can lead to lactose intolerance, including:

- **Inherited loss**: After weaning, lactase production decreases following anabolism of lactase-encoding genes. This is most common in adults and children.
- **Congenital complete loss**: This is very rare and may be due to a genetic mutation.
- **Secondary intestinal damage**: For example, infections such as rotavirus or Giardia, or hormonal imbalance.

Only the last of these is potentially reversible, and thus important to identify clinically. The genetics of lactose intolerance are confusing, mainly because of biochemical individuality between and within different ethnic populations. Our analysis of the two polymorphisms suggests that heterozygotes can still have severe lactose intolerance. It has been reported that homozygous CC/GG have low lactase, those who are homozygous TT/AA are lactase persistent, and those who are heterozygous CT/GA are intermediate.

We have found several TT/AA families with lactose intolerance, suggesting that this polymorphism is not the complete explanation of hypolactasia/lactase persistence. A further mechanism of loss of lactase is via endoplasmic reticulum stress, and explains why loss of lactase persists after gut infections such as rotavirus.

When lactose reaches bacteria in the hypoxic large intestine, hydrogen and other metabolites are generated.

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**THE MECHANISMS CAUSING HYPOLACTASIA AND LACTOSE INTOLERANCE**

Lactase is a unique enzyme in its formation, location and enzymatic activity. It is formed as a 1927 amino acid dimer of 320 kDa. Lactase (lactase phlorizin-hydrolase—LPH, EC 3.2.1.62/108; note amino acids as a dimer of 320 kDa. Lactate (lactase phlorizin-hydrolase) is EC 3.2.1.62/108, mistakenly used for lactase in some publications) is highly unusual, having two active sites within one polypeptide chain, one hydrolysing lactose, the other aryl and aliphatic glycosides such as phlorizin into glucose and phloretin, the latter being a potent diabetic agent. Two important natural substrates for this latter site are cerebrospine and glycosyl-pyridoxal, a vital source of vitamin B6. Lactase has no sequence similarity to its bacterial counterpart β galactosidase. There are three causes of loss of lactase (hypolactasia):

- **Congenital complete loss of lactase (very rare).**
- **Inherited loss**, after weaning (common).
- **Secondary intestinal damage**, for example, infections such rotavirus and Giardia, or hormonal imbalance.

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**Table 2** Sensitivity and specificity of the breath hydrogen test for lactose intolerance

<table>
<thead>
<tr>
<th>Sensitivity (%)</th>
<th>0-3 hours</th>
<th>3-6 hours</th>
<th>6-9 hours</th>
<th>9-12 hours</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>33.7</td>
<td>56.1</td>
<td>60.2</td>
<td>63.3</td>
</tr>
<tr>
<td>CC/GG</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CT/GA</td>
<td>42</td>
<td>60</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>TT/AA</td>
<td>14</td>
<td>31</td>
<td>34</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>CC/GG</td>
</tr>
<tr>
<td>CT/GA</td>
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<tr>
<td>TT/AA</td>
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</table>

Definitive diagnosis of lactose intolerance was based on a substantial improvement in the number and severity of symptoms after 12 weeks of complete exclusion of lactose from the diet, including hidden lactose. A breath test was positive if the breath hydrogen rose 20 ppm over the nadir during the time interval defined after ingesting 50 g lactose (1 g/kg for children). Sensitivity [%] = (TP/100)/(TP+FN) where TP+FN = total number of patients diagnosed clinically with lactose intolerance. Specificity [%] = (TN/100)/(TN+FP), where TN+FP = total number of patients diagnosed clinically as not having lactose intolerance. True positive (TP) = positive breath test in a patient diagnosed with lactose intolerance. True negative (TN) = negative breath test in a patient without lactose intolerance. False positive (FP) = positive breath test in a patient without lactose intolerance. False negative (FN) = negative breath test in a patient diagnosed with lactose intolerance. It is also possible to then calculate the positive (PV+) and negative (PV−) predictive values. PV+ [%] = (TP/100)/(TP+FP). PV− [%] = (TN/100)/(TN+FN).

The optimum time was six hours with a PV+ for all patients of 95%, and a PV− of 34%.

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**Figure 2** Lactase genotyping of polymorphisms C/T 13910 and G/A 22018: a DNA test distinguishes between homozygous and heterozygous polymorphisms. Lactase genotyping for both lactase polymorphisms was carried out in our laboratory by PCR, HotStart polymerase chain reaction. Lane 1 shows the CC 13910 (386 bp) and GA 22018 (371 bp) homoyogous lactase persistent genotypes respectively. Lanes 2 and 7 shows the CC 13910 (386 bp) and GG 22018 (238 and 133 bp) heterozygous lactase persistent genotypes respectively. Lanes 3 and 8 shows the CT 13910 (386, 238 and 148 bp) and AA 22018 (371 bp) homozygous lactase persistent genotypes respectively. Lanes 4 and 6 shows the TT 13910 (238 and 148 bp) and AA 22018 (371 bp) homozygous lactase persistent genotypes respectively. Lanes 5 and 9 shows the CT 13910 (386, 238 and 148 bp) and GA 22018 (371, 238 and 133 bp) heterozygous lactase persistent genotypes respectively. Lanes 4 and 6 are 50 bp molecular weight markers. Lanes 2 and 7 shows the CC 13910 (386 bp) and GA 22018 (238 and 133 bp) homoyogous lactase non-persistent genotypes respectively. Lanes 3 and 8 the TT 13910 (238 and 148 bp) and AA 22018 (371 bp) homozygous lactase non-persistent genotypes respectively.

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These include potential toxic agents—acetaldehyde, acetoin, butan-2,3-diol, dimethyl glyoxal (diacetyl), ethanol, formate, methane, propan-1,3-diol, indoles, skatoles and short chain fatty acids—as well as peptide and protein toxins. Lactose itself, and galactose, could be toxic if absorbed into the blood stream. These toxins act on ionic signalling pathways in the nervous system, heart and other muscles, and the immune system. Conventionally lactose intolerance causes diarrhoea via an osmotic mechanism. But we found in many patients diarrhoea persists for days, long after the lactose has gone. Thus it is probable that lactose induced diarrhoea is caused by a signalling mechanism analogous to cholera or enterotoxin. Bacterial putrefaction in the colon as a pathogen was first proposed 100 years ago by Metchnikoff.30

A problem for those sensitive to lactose, exacerbated over the past 5–10 years, is the presence of “hidden” lactose added to foods and drinks without being on the label. Lactose has gone. Thus it is probable that lactose induced diarrhoea is caused by a signalling mechanism analogous to cholera or enterotoxin. Bacterial putrefaction in the colon as a pathogen was first proposed 100 years ago by Metchnikoff.30

The ethnic origins were mainly white northern European (89%). Patients were given 50 g oral lactose and the number of symptoms recorded (table 1) before, during and 12 weeks after the oral lactose load. Breath hydrogen was measured using a hand held monitor (Bedfont, UK) every 30 minutes for 12 hours. Patients were diagnosed as lactose intolerant as described in the text. LI = lactose intolerance. A paired two tailed t test (95% CI) showed that there was no significant difference between the symptoms recorded before and during the test; p = 0.051 in patients diagnosed as lactose intolerant (with LI) and p = 0.60 in patients diagnosed without lactose intolerance (without LI). In contrast the effect of removing lactose from the diet of those diagnosed with lactose intolerance was highly significant; p = 0.001, but had no significant effect on symptoms in those diagnosed without lactose intolerance; p = 0.60. Results represent the mean (SD).

THE PROBLEM OF LACTOSE IN FOOD

Several studies have shown that patients considering themselves lactose intolerant could take one to two cups of milk (240 ml = 11 g lactose) during the day. Yogurt, ice cream, and cream can contain similar amounts to milk. The lactose content in many hard cheeses is quite low (<1 g per teaspoon). You would have to eat 1 kg of parmesan to take as much lactose as there is in a glass of milk. Thus a spoonful of parmesan on a pasta is unlikely to result in symptoms. Butter contains only traces of lactose. The threshold for lactose varies between people. Some can tolerate a glass of milk (240 ml = 11 g lactose), whereas others get symptoms with just 2–3 g lactose from a chocolate bar. We recommend that patients should experiment carefully with various foods to discover their lactose threshold. Some hypolactasics can, over months, adapt and increase their tolerance to milk. This occurs through the gut flora because mammalian lactase cannot be induced by lactose, unlike its bacterial counterpart. Lactose can be reduced in dairy products by using β-galactosidase available in health food shops. Low lactose milk is available in supermarkets made by this method, but is quite sweet as it contains the galactose and glucose from the degraded lactose.

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of coconut milk. An important question is whether such changes to a westernised diet have any relevance to the unexplained epidemic in type 2 diabetes in the Asian population, or the high incidence of coronary artery disease in some parts of the world. Also questions need to be asked about the recommendation of milk to non-white Europeans. The lack of information regarding the lactose content of foods has important implications for the millions of people who are hypolactasic, and for ethnic groups (for example, orthodox Jews) who are forbidden to eat milk products with meat. Although most (89%) of the patients in our study were white northern Europeans, a significant minority (11%) were Asian or black African. As expected there was a higher percentage of CC/CT in the latter group. Thirty eight per cent of the CC group were Asian or black African (2 from 21 were south European), compared with only 1 of 41 patients in the CT group, with no non-white northern Europeans in the TT group. There was no obvious difference in symptoms of those who were lactose intolerant within these groups. However, in view of some reports that the conclusions from clinical trials may be affected by ethnic group, a full genetic profile of non-white European is now required. Our data argue clearly that any epidemiological dietary study must take into account ethnic groups and lactose intolerance if the data are to be interpreted correctly. Coming off lactose does not prevent a patient enjoying eating and drinking to the full. A typical cordon bleu meal is shown in box 1, with a disaster meal in box 2. A recent study of the effects of different foods on the gut microbiota has shown that some foods, such as bread, can increase the number of bacteria that produce short chain fatty acids, while others, such as fruit, can decrease the number of these bacteria. This is important because short chain fatty acids can be used by the body as an energy source, while the bacteria that produce them can help to maintain a healthy gut microbiota. Therefore, it is important to consider the effects of different foods on the gut microbiota when planning a diet for lactose intolerance.

There has been much debate about the recommended daily amount of calcium. One 250 ml glass of milk contains about 300 mg of calcium, one fifth of the daily requirement (1–2 g). Some people who are lactose intolerant can obtain this by ingesting small amounts of milk throughout the day without exhibiting gut symptoms. Cheese is a good source of calcium, and a good portion of greens can supply 150 mg calcium. A serving of salmon or sardines contains up to 300 mg. Thus it is easily possible to take the necessary daily one to two grams calcium without milk. (See also http://www.lactose.co.nz; http://www.lactose.co.uk; http://www.parktonks.co.uk/milk_products; dailspace.dial.pipex.com/town/park/gfm11/).

Soya products with added calcium are readily available in supermarkets. In addition to the well known allergy to certain milk proteins, allergy to at least 16 proteins in soya milk has been found. This is rare. However, patients should be warned to look out for anything from a mild rash to a severe immune reaction to soya milk. If this occurs then they should be properly investigated and take care not to ingest any soya. Alternatives to soya are lactose reduced milk products, coconut milk, oat milk, or rice milk. There is no evidence of calcium deficiency in people eating a Chinese or Japanese diet with no lactose. Surprisingly calcium supplements can be cheaper than taking calcium via milk. Interestingly dairying is only 6000–8000 years old.

**CONCLUSIONS**

It is now clear that lactose can cause a range of debilitating systemic symptoms, in addition to the well known gut

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**Box 3 Recommended new clinical management of patients investigated for lactose intolerance**

1. Patient referred for lactose tolerance test.
2. Buccal sample for polymorphism analysis. A patient presenting with unexplained gut and/or systemic symptoms should first be tested for the two polymorphisms C/T13910 and G/A –22018.
3. New recommended lactose tolerance test:
   - If CC/GG or CC/CA immediate removal of all lactose from diet. If symptoms improve after one month diagnosis of lactose intolerance confirmed.
   - If CT/GA or TT/AA carry out lactose tolerance test.
5. Follow up in one year.
6. Calcium and vitamin D status should be monitored, and advise on the use of probiotics.

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Figure 4 Effect of 50 g lactose on breath hydrogen in the three principal genetic groups. Breath hydrogen was measured every 30 minutes after ingesting 50 g oral lactose. The results represent an example of three adults all diagnosed clinically as lactose intolerant. Boxes represents CC/GG lactase non-persistent genotype, breath hydrogen >20 ppm above the nadir at 30 minutes and continues throughout the testing period. Triangles represent CT/GA heterozygous lactase persistent genotype showing a rise in breath hydrogen >20 ppm above the nadir after sampling above 300 minutes. Diamonds represent TT/AA homozygous lactase persistent genotyped patient in which the breath hydrogen does not rise above 20 ppm throughout the testing period of 360 minutes.
symptoms (table 1). Several patients complained of constipation since childhood rather than diarrhoea. The DNA test, coupled with a revised breath hydrogen test, argues for an important change in clinical practice (box 3). We recommend measuring breath hydrogen for six hours as this increases sensitivity from 40% to 60% (table 2). Symptoms should be assessed for up to 48 hours after 50 g lactose, using a self reported questionnaire. The lack of necessity for a lactose test in those who are CC/AG avoids severe reactions in these people. Only CT/GA or TT/AA patients should undergo the hydrogen breath test. The mean values (fig 4) hide the individuality of the time course from each patient. It has been reported that the polymorphism analysis is not useful in managing IBD.42 But we show that it is required if the 80% of IBS with lactose intolerance are to be correctly identified. This had been missed previously because the patients had not been genetically or breath tested. Most patients had undergone endoscopic or barium studies, or both, with no abnormalities detected. Although the amount of lactose used by physicians around the world can vary from 1–2 g/kg or 20–100 g, 25 g being sometimes used in the USA, the current recommended amount is 50 g, or 1 g/kg for children. Our results support the argument for a new trial, coupling the genetic test with breath hydrogen, to evaluate whether a lower dose than 50 g lactose is more accurate at diagnosing lactose intolerance. Our data show that the key effect. The only time symptoms returned was when the patient unknowingly ingested food containing “hidden” lactose. In contrast excluding lactose from the diet had no significant effect (p = 0.6) on the symptoms of patients not diagnosed as having lactose intolerance.

The data reported here have important implications for the management of IBS, chronic fatigue, arthritis, and for reducing GP visits and drug costs. They also highlight the key problem of defining when and why a patient crosses the rubicon that determines illness compared with health.51 The puzzle of what determines the loss of lactase on weaning remains. The possibility that homeobox genes associated with the development of deciduous teeth are involved in loss of lactase after weaning should now be investigated.52 Our findings also explain the mystery illness that afflicted Charles Darwin for 40 years.53

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