

Intestinal permeability in children: variation with age and reliability in the diagnosis of cow's milk allergy

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Objective: To analyse to what extent age may alter intestinal permeability (IP) in children and to assess its reliability according to clinical manifestations in cow's milk allergy (CMA). **Design:** A routine prospective study was performed in 200 children (12.5 ± 23 mo, 0.5–168 mo) presenting with clinical manifestations suggesting CMA. Controls ($n = 105$) were those with a negative cow's milk challenge, whereas CMA children ($n = 95$) fulfilled ESPGHAN criteria. Permeability was measured as a percentage of urinary excretion of lactitol (L, %) and mannitol (M, %) (0.1 g/kg for each, oral absorption after a 6 h fast, 5 h urine collection, analysis by gas chromatography) and determination of the L/M ratio (L/M, %). **Results:** In control children, L/M correlated negatively with age ($r = -0.33$, $p = 0.0006$), whereas in those with CMA no correlation was found. Median L/M was significantly higher in CMA children ($n = 95$) than in controls ($n = 105$), $4.35 \pm 7.57\%$ (95% CI 5.30–8.39%) vs $1.97 \pm 0.87\%$ (95% CI 1.76–2.09%), ($p = 0.0001$). With a L/M cut-off value defined as mean + 2 SD of controls, in CMA IP exhibited a 68% sensitivity and a 77% negative predictive value. The highest sensitivity (70%) was seen at ages 6–12 mo and the lowest (58%) at age more than 3 y. An abnormal IP was seen in 80% of CMA children with digestive manifestations, in 43% with extra-digestive, 68% with mixed and 40% with anaphylactic manifestations.

Conclusion: IP correlates negatively with age in control children and is altered in children with CMA. The test is at its most accurate in the diagnosis of CMA when done at ages 6–12 mo, when there are digestive manifestations.

Key words: Age, children, cow's milk allergy, intestinal permeability

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Comparative measurement of the urinary excretion of orally absorbed non-metabolizable sugars, lactulose or lactitol (L), a marker of larger molecule absorption and mannitol (M), a marker of small molecule absorption, allows the detection of alteration of intestinal permeability (IP) in intestinal conditions such as cystic fibrosis, inflammatory bowel disease, coeliac disease, digestive surgery, small-bowel bacterial overgrowth, parasitic or infectious gastroenteritis and diabetes mellitus type I (1–9).

In adults as well as in children (10, 11), IP has been shown to be a good tool in the diagnosis of food allergy. In hypersensitive subjects, ingestion of the offending food decreased M urinary excretion and increased both L urinary excretion and L/M urinary ratio (10, 11). Cow's milk allergy (CMA) modified IP during both digestive and cutaneous manifestations (11, 12).

The purpose of the study was to analyse to what

extent age may alter IP in children and to assess its reliability according to clinical manifestations in CMA.

Patients and methods

Patients

A routine prospective study was performed in 200 children (12.5 ± 23 mo, 0.5–168 mo) with clinical manifestations, digestive, extra-digestive, mixed and anaphylactic, suggesting CMA. All the children were subjected to a blinded cow's milk challenge. Control children were analysed as those with a negative cow's milk challenge, whereas CMA children were those with clinical evidence according to ESPGHAN criteria (13).

The clinical manifestations of both controls and CMA children are summarized in Table 1 and the final diagnoses in control children are reported in Table 2.

Table 1. Clinical manifestations in CMA children and controls.

	CMA children n = 95	Controls n = 105
GER	20 (21%)	33 (31.5%)
Vomiting	7 (7.3%)	3 (2.8%)
Acute diarrhoea	8 (8.5%)	1 (0.9%)
Abdominal pain	6 (6.3%)	4 (3.8%)
Constipation	2 (2.1%)	3 (2.8%)
Failure to thrive	10 (10.5%)	33 (31.5%)
Chronic diarrhoea	2 (2.1%)	6 (5.7%)
Digestive hemorrhage	2 (2.1%)	1 (0.9%)
Eczema	26 (27.3%)	13 (12.5%)
Urticaria	3 (3.1%)	1 (0.9%)
Anaphylactic choc	4 (4.3%)	1 (0.9%)
Recurrent bronchitis and asthma	3 (3.2%)	4 (3.8%)
Recurrent ENT infections	1 (1.1%)	1 (0.9%)
Malaise	1 (1.1%)	1 (0.9%)

Children with anaemia (haemoglobin <10 g/dl), cystic fibrosis (pathological sweat chloride test >60 mEq/L), inflammatory bowel disease (pathologic endoscopic lesions with characteristic histology), coeliac disease (positive serological titres of antigliadin IgG and IgA antibodies and anti-endomysium IgA antibodies), digestive surgery, small-bowel bacterial overgrowth (positive hydrogen breath test), parasitic or infectious gastroenteritis (positive stool culture) and diabetes mellitus (hyperglycaemia and abnormal glycosylated haemoglobin). All the children with incomplete urine collection or fecal contamination were also excluded from analysis.

Methods

IP was carried out in all children before cow's milk challenge, i.e. with a normal diet containing cow's milk elements. IP was studied on the morning following an overnight fast and after voiding and discarding overnight urine. Children were given a mixture of 10% M and 10% L in aqueous solution, 900 mOsm/L (Pharmacie Centrale des Hôpitaux, Paris, France), at a dosage of 0.1 g/kg of body weight for each sugar. The solution was given alone, and children were allowed water only during the 3rd, 4th and 5th hours of urine collection. During the following 5 h, all urine, including that passed at the end of the 5 h, was collected with gentamicine as a preservative. In younger children, urine collection was carried out with a specific adhesive urine bag (Urinocol) that was set without previous voiding at the beginning of the test. It was verified that endogenous production of M and L was negligible. The urine volume was measured, and aliquots were stored frozen. Samples were later analysed for M and L content by gas chromatography. Children with incomplete urine collection or fecal contamination were already excluded from study. Gas chromatography was performed with a Hewlett-Packard 5890 Serie II gas chromatograph equipped with an autosampler and a

Table 2. Final diagnosis retained in 105 control children.

GER without oesophagitis	40 (38%)
Failure to thrive	24 (23%)
Eczema	14 (14%)
Irritable bowel syndrome	13 (12%)
Allergic asthma	2 (2%)
Others	12 (11%)
<i>Helicobacter pylori</i> gastric infection	12
Lactose intolerance	1
Diet errors	1
Allergic urticaria	1
Laryngomalacia	1
Pyloric stenosis	1
Systemic infection	1
Polymalformative syndrome	1
Reflux oesophagitis	2
Allergic angioedema	1

flame ionization detector. A fused silica capillary column (50 m × 0.25 mm) coated with BPX-5 (SGE, Villeneuve-Saint-Georges, France) was used with helium as the carrier gas at a 1.5 bar head pressure. A urine sample (100 ml), supplemented with internal standard (100 ml of an ethyl acetate solution of 10 mM/l of docosane for the assay of M and 1 mM/l of triacontane for the assay of L) was evaporated to dryness under nitrogen at 60°C and then submitted to derivatization by the addition of 100 ml of a mixture of N,O-bis(trimethylsilyl)-trifluoroacetamide with 1% trimethylchlorosilane and pyridine (1:1; v/v) and allowed to react for 1 h at 60°C. One millilitre of the solution was injected via the autosampler. Temperature programming was performed from 80°C to 340°C with 6°C per minute. Peak areas were automatically integrated, M and L areas reported to docosane and triacontane areas, respectively, leading to M and L results expressed as milligram per liter.

Results were expressed as a percentage of urinary excretion of L (L, %) and M (M, %) and then determination of the urinary L/M ratio (L/M, %). Cut-off between normal and abnormal values was estimated at mean + 2 SD of values obtained in controls. All studies were done with the informed consent of parents.

Statistics

Calculation of median and 95% confidence interval (95% CI) of all quantitative parameters was done using the StatView System. Mean and SD were also defined in order to calculate IP cut-off values upon different age groups. Since all the parameters exhibited a large distribution of results (not belonging to the normal low), statistical evaluation was carried out using non-parametric tests as the Anova test for continuous variables and the chi-squared test of homogeneity for categorical variables. Correlation between different parameters was assessed using the simple regression correlation. A *p* value <0.05 was considered statistically significant (14).

Sensitivity and negative predictive values of IP were calculated in comparison with cow's milk challenge according to Griner et al. (14). The efficiency of IP was calculated as the percentage of patients correctly classified by the test result as having or not having CMA, i.e. the true positive children + the true negative children / the total number of tested children $\times 100$ (14).

Results

Variation of IP with age

In controls ($n = 105$), the correlation with age was nil for L, positive for M ($r = 0.30$, $p = 0.001$) and negative for L/M ($r = -0.33$, $p = 0.0006$). As a result, IP varied significantly with age, with median L/M calculated at 2.39% (0–6 mo), 2.00% (6–12 mo), 1.97% (1–3 y) and 1.31% (>3 y), ($p = 0.007$) for each group. In CMA children ($n = 95$), no correlation was found between age and L, M, or L/M.

Modification of IP induced by CMA

Median L/M was significantly higher in CMA children ($n = 95$) than in controls ($n = 105$), 4.35% (95% CI 5.30–8.39%) vs 1.97% (95% CI 1.76–2.09%), ($p = 0.0001$). With a L/M cut-off value defined according to age (3.95%, 0–6 mo; 3.5%, 6–12 mo, 3.38%, 1–3 y and 3.27%, >3 y), IP exhibited a 68% sensitivity and a 77% negative predictive value in CMA children. The efficiency of the test was 84.5%. The highest sensitivity (70%) occurred in 6–12-mo-old children and the lowest (58%) in >3 -y-old children (Table 3). IP was altered (i.e. above cut-off values) in 80% of children with digestive manifestations, 42% with extra-digestive, 68% with mixed and 40% with anaphylactic manifestations (Table 4). The L/M ratio was significantly higher during CMA with digestive manifestations than during other clinical presentations ($p = 0.0005$) (Table 4). Among children with digestive symptoms, IP was abnormal in 100% of cases with vomiting, chronic diarrhoea and digestive bleeding, 80% of gastroesophageal reflux (GER), 70% of failure to thrive, 63% of acute diarrhoea, 50% of constipation and abdominal pain (Table 5).

Discussion

The present study confirms that IP varies according to age and is altered in children with CMA. The best reliability of the test in the diagnosis of CMA occurs in 6–12-mo-old children with digestive manifestations.

The markers chosen for the study are M, a small molecule (MW 182) approximately the size of glucose, thought to cross the epithelium through epithelial pores, and L, a larger molecule (MW 342) thought to be able to cross the epithelium only through the paracellular junctions (3). M would thus mainly reflect the absorp-

Table 3. Accuracy of intestinal permeability in cow's milk allergy.

Age (mo)/No.	Sensitivity (%)	NPV (%)	Test efficiency (%)
0–192 mo	68	77	84.5
95 CMA patients			
105 controls			
0–6 mo	70	71	82.7
47 CMA patients			
34 controls			
6–12 mo	70	81	86.9
20 CMA patients			
26 controls			
12–36 mo	62	74	81.8
21 CMA patients			
23 controls			
>36 mo	58	88	89.6
7 CMA patients			
22 controls			

Negative Predictive Value = NPV.

tive surface area and L the disruption of paracellular spaces; the L/M ratio would be related to morphological changes in the mucosa (15), i.e., a gradual opening of the paracellular pathways and destruction of intestinal cells in relation to different pathological factors and/or varying degrees of malnutrition (1–9).

Actually, clinical interpretation of urinary recovery ratios of L (or lactulose) and M is hampered by our incomplete understanding of the mechanisms of trans-mucosal passage. Comparing urinary recovery of orally applied probes in rodents, cats and humans has shown that interspecies variations may occur following in vivo functional differences in the small intestine (16). The high urinary recovery of M in humans and cats might be the result of vascular countercurrent multiplication, increasing the solvent drag through pores that allow the passage of M but not of L (17). The L/M ratio could therefore depend on both a normal functioning of villus epithelial cells in metabolite absorption and a normal villus blood flow (17), at least partially responsible for the water transepithelial passage or solvent drag. Whatever the interpretation, IP appears to correlate well with clinical conditions, with decreased M recovery during villous atrophy (3, 4) and increased L recovery in gut inflammatory states (2).

A negative correlation between urinary L/M recovery ratio and age was found in control children. The decrease in the L/M ratio is associated with a decrease in L and an increase in M recoveries. Catassi et al. (18) also found that the L/M ratio decreased during the first week of life and at 1 mo was higher than in the age range 5 mo to 11 y, suggesting both a tightening of intercellular spaces and/or an increased solvent drag, potentially through increased blood flow at the villus tip (17). By contrast, a recent study by Goto et al. (19) in Gambia suggests that older children have a higher L/M ratio than younger ones, the lowest L/M ratio being found in exclusively breastfed infants. This positive correlation of L/M ratio with age in a developing

Table 4. Intestinal permeability during CMA according to clinical manifestations.

	M (%)	L (%)	L/M (%)	L/M > mean + 2 SD of controls, n (%)
Digestive, n = 35				28 (80 %)**
Mean ± SD	7.16 ± 5.18	0.60 ± 0.70	10.30 ± 10.95*	
Median	(6.79)	(0.43)	(4.73)*	
25%	(3.44)	(0.24)	(4.01)*	
75%	(9.08)	(0.07)	(10.80)*	
Extra-digestive, n = 14				6 (42 %)
Mean ± SD	9.27 ± 4.91	0.31 ± 0.22	3.80 ± 2.5	
Median	(9.62)	(0.27)	(3.49)	
25%	(5.68)	(0.14)	(2.49)	
75%	(12.27)	(0.44)	(4.41)	
Mixed, n = 41				28 (68 %)**
Mean ± SD	8.16 ± 5.05	0.39 ± 0.31	5.33 ± 3.58	
Median	(8.71)	(0.33)	(4.17)	
25%	(3.78)	(0.13)	(3.56)	
75%	(11.53)	(0.53)	(5.72)	
Anaphylactic choc, n = 5				2 (40 %)
Mean ± SD	8.29 ± 2.02	0.31 ± 0.20	3.46 ± 2.05	
Median	(7.69)	(0.40)	(3.83)	
25%	(6.74)	(0.10)	(1.83)	
75%	(10.58)	(0.46)	(5.36)	

* p 0.005, upon Anova multiple variance analysis; digestive group vs the other groups.** p < 0.05, upon chi-square test; digestive and mixed groups vs the other groups.

country suggests that when age is accompanied by a progressive worsening of nutritional status (protein and trace elements deficiency) and an increased incidence of infection, mucosal alteration could prevail, being only partially prevented by breast milk in these older children in need of additional nutrients (19).

We have already shown food-induced alterations of IP in children with CMA enteropathy and atopic dermatitis, the L/M ratio being significantly higher than in controls (11). The fact that CMA disrupts the

correlations observed between IP and age indicates that food-induced local inflammation may alter both mucosal structure and probably, in the absence of villous atrophy, of local regulation of blood flow through modifications of local cytokine release (20).

Interpretation of IP tests is complicated by uncertainties regarding the cut-off appropriate to distinguish between normal and abnormal values. The L/M normal values depicted in the present study, ranging from 1.76% to 2.09%, compares relatively well with previous

Table 5. Intestinal permeability during CMA according to age and clinical manifestations.

	Age (0.5–168 mo) n = 95	Age (0.5–6 mo) n = 47	Age (6–12 mo) n = 20	Age (12–36 mo) n = 21	Age (>36 mo) n = 7
Clinical manifestations	Abnormal L/M/Total (%)	Abnormal L/M/Total (%)	Abnormal L/M/Total (%)	Abnormal L/M/Total (%)	Abnormal L/M/Total (%)
Vomiting	7/7 (100)	5/5 (100)	2/2 (100)	ND	ND
Chronic diarrhoea	2/2 (100)	ND	ND	2/2 (100)	ND
Digestive hemorrhage	2/2 (100)	2/2 (100)	ND	ND	ND
Malaise	1/1 (100)	1/1 (100)	ND	ND	ND
GER	16/20 (80)	8/10 (80)	5/6 (84)	3/4 (75)	ND
Failure to thrive	7/10 (70)	3/4 (75)	2/3 (67)	2/3 (67)	ND
Urticaria	2/3 (67)	1/1 (100)	ND	1/2 (50)	ND
Acute diarrhoea	5/8 (63)	4/5 (80)	1/2 (50)	0/1 (0)	ND
Eczema	15/26 (58)	6/11 (55)	2/4 (50)	6/9 (66)	2/3 (67)
Abdominal pain	3/6 (50)	2/4 (50)	1/1 (100)	ND	0/1 (0)
Constipation	1/2 (50)	1/2 (50)	ND	ND	ND
Anaphylactic choc	2/4 (50)	1/1 (100)	1/2 (50)	ND	1/1 (100)
Recurrent bronchitis and asthma	1/3 (34)	0/1 (0)	ND	ND	1/2 (50)
Recurrent ENT infections	0/1 (0)	ND	ND	ND	ND

ND = not done.

data obtained in 10 British children aged 3–18 mo, i.e., 1.8–5.00% (21). Wider ranges were observed in 33 Scottish children aged 7 mo to 14 y, i.e., 0.50–9.00% (22). In 30 healthy Dutch children aged 0–16 y, the normal upper limit (mean + 2 SD) of the L/M ratio was 9.00% (23). In 9 healthy Finnish children aged 2–23 mo L/M ratios were always below 5.00% and in 19 others aged 7–26 mo febrile but free from intestinal symptoms, urinary L/M ratios ranged from 0.05% to 12.00% (7). In other studies using lactulose and rhamnose instead of mannitol, L/R ratio normal upper limit was 7.00% (15). Variations may depend on several factors; for example, factors relating to the population studied, whether or not there is a deficiency of iron (24), or relating to the technical conditions of the test, such as the concentration of markers or the osmolarity of the solution (25).

For Jalonen (26), IP changes were similar whether children exhibited gastrointestinal or skin manifestations, there being a significant rise in L/M ratio following cow's milk ingestion by day 3 in both situations. In the present study, a clear correlation is made between alterations of the L/M ratio and the occurrence of digestive manifestations compared to eczema, recurrent bronchitis and ENT infections. This could indicate that during intestinal manifestations the local reaction alters the intestinal epithelium barrier capacity. Not surprisingly, the more important alterations are seen in young age, where cow-milk-induced enteropathy prevails, so the best efficiency, sensitivity and NPV of IP in the diagnosis of CMA were observed in 6 to 12-mo-old children.

Conclusion

IP is altered in children with CMA and correlates negatively with age. The best accuracy of the test in the diagnosis of CMA occurs in 6–12 mo children with digestive manifestations.

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