Acta Pædiatr 85: 1076–9. 1996

Abnormal intestinal permeability in children with autism

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D'Eufemia P, Celli M, Finocchiaro R, Pacifico L, Viozzi L, Zaccagnini M, Cardi E, Giardini O. Abnormal intestinal permeability in children with autism. Acta Pædiatr 1996;85:1076–9. Stockholm. ISSN 0803–5253

We determined the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children who had no clinical and laboratory findings consistent with known intestinal disorders. An altered intestinal permeability was found in 9 of the 21 (43%) autistic patients, but in none of the 40 controls. Compared to the controls, these nine patients showed a similar mean mannitol recovery, but a significantly higher mean lactulose recovery (1.64% ± 1.43 vs 0.38% ± 0.14; $P < 0.001$). We speculate that an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioural abnormalities. □ *Autism, intestinal permeability*

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The sugar intestinal permeability test (IPT) is regarded as a valuable and non-invasive test for monitoring small intestinal mucosal damage in children, with a sensitivity previously demonstrated to be higher than that of intestinal biopsies (1–4). The procedure is based on the simultaneous oral administration of two sugars with different molecular size and absorption routes, and the estimation of urinary recovery of each molecule.

Autism is a pervasive developmental disorder with onset in infancy or childhood, affecting social, communicative and imaginative development (5). Its etiology and pathogenesis and still poorly understood. Gastrointestinal disorders have been reported in children with autism and adults with other psychiatric diseases. In such patients an association between malabsorption and behaviour abnormalities has been suggested (6, 7). Reichelt et al. have recently found a close relationship between dietary change and the onset of symptoms in autistic patients, suggesting an increased absorption of peptides from the gut. No evidence of mucosal damage has been demonstrated in such patients (8, 9).

To investigate the presence of gut mucosal damage in children with autism, we performed the IPT in a group of autistic subjects who had no clinical and laboratory findings of known intestinal disorders.

Forty autistic children were referred to our clinic for metabolic and gastrointestinal investigations by the Italian Association of Parents of Autistic Children. The diagnosis of autism had been established according to the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (5) by a Psychiatric Academic Working Group cooperating with this Association. All patients had a diagnosis of infantile autism as they were reported as presenting signs of the disorder before 30 months of age. Of the 40 patients 21 were selected for entry into the study. The main excluding criteria were: (i) clinical evidence of any gastrointestinal disease; (ii) individual or family history of allergy; (iii) positive PRICK tests and/or serum specific IgE for the most commonly encountered allergens such as cow's milk, whole egg, codfish, rice, soy, corn, wheat flour, chicken, tomato, beef, apple, orange, chocolate and olive-oil; (iv) positive serum antigliadin and antiendomysial antibodies; (v) positive detection of Giardia cysts in stools as well as of (vi) serum antibodies to *Helicobacter pylori*. Patients were also excluded if they had been taking drugs such as anticonvulsants because of their potential interference with the intestinal permeability test.

The study patients' ages ranged from 4 to 16 years (15M, 6F) and all were between the 25th and 75th percentile for height and weight. Intellectual quotients (IQ), as determined by the Standford and Binet scale, ranged from 66 to 80 (mean IQ 70.2). Thus, our sample of patients was represented most by high-functioning autistic children. In all 21 patients, neurologic examination, EEG, brain-imaging, investigations for inborn errors of metabolism and for the "fragile X chromosome" syndrome, were normal. None of these patients could be partitioned into a clinical condition due to a specific aetiology.

Control subjects were 40 healthy age-matched children who had no clinical or laboratory findings of food allergy or of other known intestinal diseases. There were 18 male subjects and 22 female subjects all between the 50th and 75th percentile for height and weight.

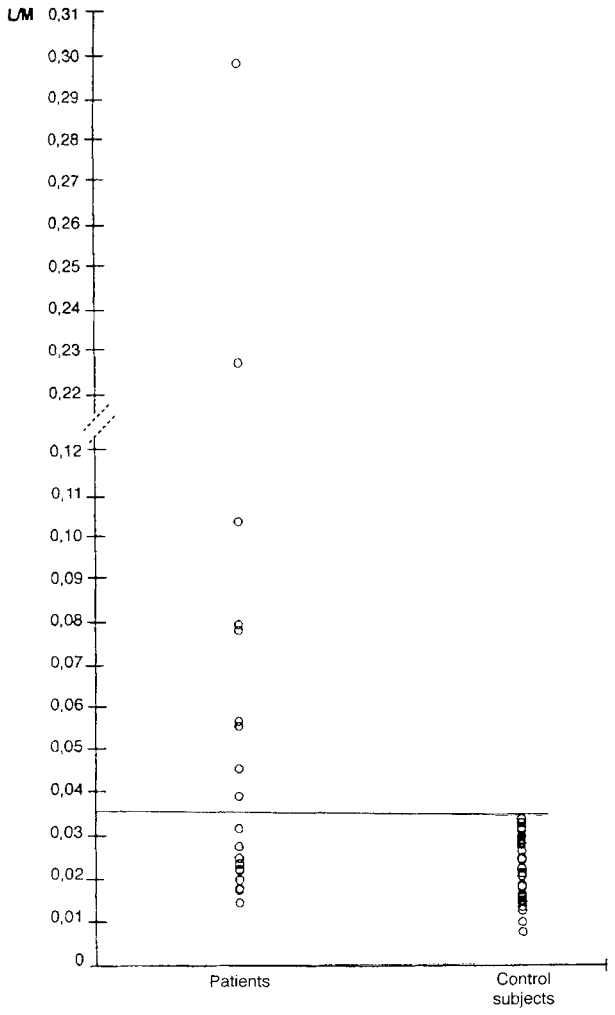

Fig. 1. L/M recovery ratio in 21 autistic patients and 40 healthy controls. The horizontal bar indicates the cut-off limit.

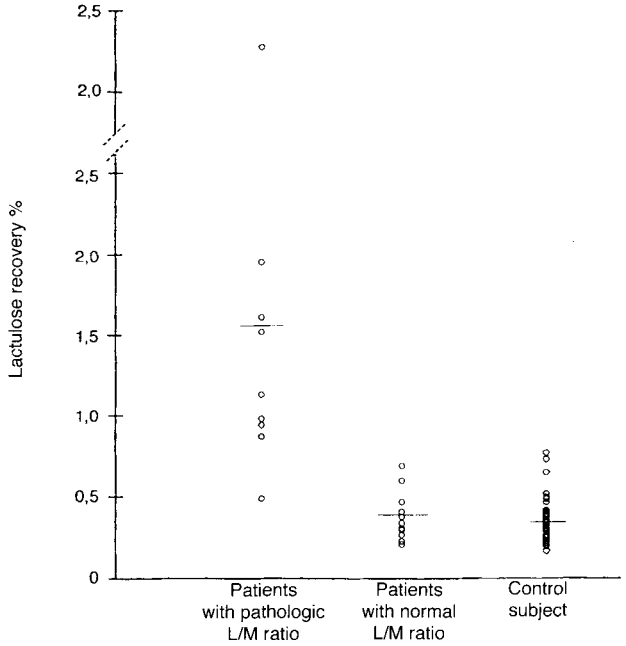

Fig. 2. Lactulose recovery in 9 autistic patients with pathologic L/M recovery ratio, 12 autistic patients with normal L/M recovery ratio and 40 healthy controls. The horizontal bars indicate the mean value.

At entry to the study, no patients or controls had taken any drug within the previous week. Informed consent was obtained from the parent of each patient and control before the initiation of any procedures. Patients' parents did not give the consent for duodenal biopsy. The details of the IPT procedure have been presented elsewhere (10). Data are presented as the mean ± SD. The Mann-Whitney test for unpaired data was used to evaluate differences in IPT results between the two study groups.

Results are expressed as the percentage of mannitol and lactulose recovered in the urine samples, and L/M recovery ratio. The cut-off value was set at 0.035, as previously described (10).

In the 40 controls the L/M recovery ratio ranged from 0.010 to 0.034 and no significant differences in the mean of mannitol, lactulose and L/M recovery ratio were found with respect to the sex characteristic. Among the 21 autistic patients, there were 12 (57%) children in whom the L/M recovery ratio was normal (range 0.017–0.032), and 9 (43%) with an abnormally high L/M recovery ratio (range 0.036–0.298) (Fig. 1). Compared to the controls, these nine patients showed a similar mean mannitol recovery (15.96% ± 4 vs 16.66% ± 5.54; $p = ns$), but a significantly higher mean lactulose recovery (1.64% ± 1.43 vs 0.38% ± 0.14; $p < 0.001$) (Figs 2 and 3). Thus the abnormal ratio observed in the nine autistic patients was mainly due to the increased lactulose recovery. When comparing the 12 autistic patients with normal IPT to the controls, no statistically significant differences in mannitol and lactulose urinary recovery or in L/M recovery ratio were found (Figs 1, 2 and 3). No significant differences were observed between the two subgroups of autistic children with respect to weight, height, sex, age and IQ .

Our study demonstrates a high frequency of altered intestinal permeability in autistic children. An abnormal intestinal permeability has been found in patients with intestinal disorders, trauma and systemic diseases (1, 2, 11, 12). Additionally, Wood et al. (13) performed IPT in adults affected by schizophrenia and other chronic psychiatric disorders, and showed that 35% of these patients had an abnormal intestinal permeability which could not be attributed to established bowel diseases. In such patients, however, endoscopy and distal duodenal biopsy showed a normal small intestinal mucosal morphology.

In our study, alteration of the ratio found in the nine autistic patients was mainly due to an increased urinary

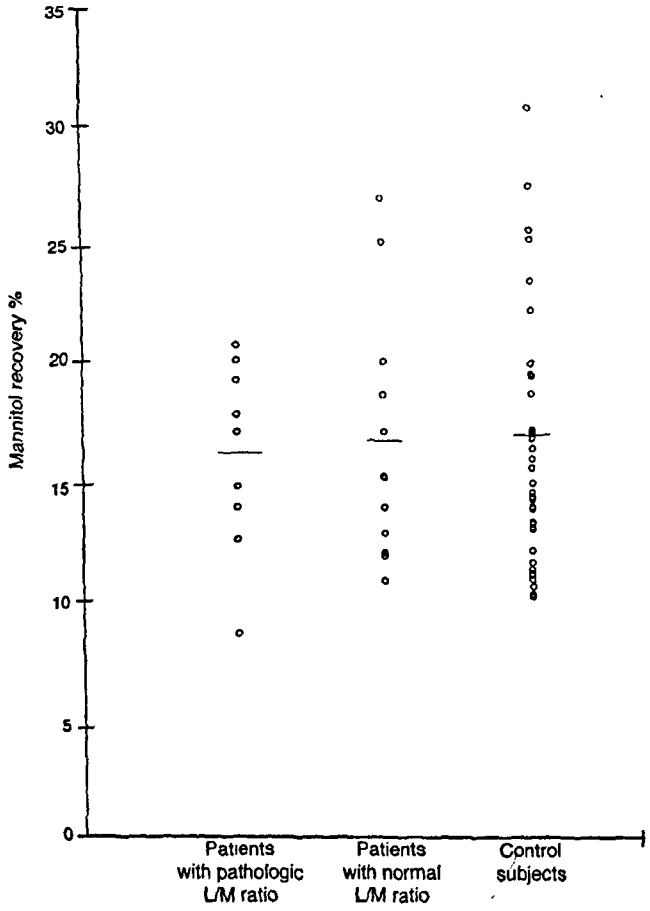

Fig. 3. Mannitol recovery in 9 autistic patients with pathologic L/M recovery ratio, 12 autistic patients with normal L/M recovery ratio and 40 healthy controls. The horizontal bars indicate the mean value. Three groups were not significant.

lactulose recovery. This pattern of urinary excretion may be explained by differences in molecular size between mannitol and lactulose and their routes of absorption. Mannitol passes through more abundant transcellular routes of aqueous pores in the cell membrane (transcellular pathway), whereas lactulose passes through fewer intercellular junctional complexes and extrusion zones at the villous tips (paracellular pathway). The latter pathway is considered the route of permeation for molecules with molecular mass > 180 Dalton, such as peptides (14). Thus the alteration of intestinal permeability as found in our series of autistic patients highlights some damage to tight junctions of the gut mucosa.

In the past, attention has been drawn to similarities between autism and the effects of some peptides like opioid drugs, in both humans and animals. The "opioid excess" theory of autism postulated that excessive levels of opioids in the central nervous system might affect and modify the classical neurotransmission system (15, 16). Accordingly, some authors have recently found increased peptide levels in the urine of autistic children (17–19). It was therefore suggested that in these patients the passage through the gut mucosa of peptides derived from foods might induce behavioural abnormalities by stimulation of opioid-like receptors (19).

Our results show that in some patients with infantile autism damage to tight junctions of the gut mucosa as evidenced by IPT occurs in the absence of established gastrointestinal disorders. Such alteration could represent a "possible" mechanism for the increased passage through the gut mucosa of peptides derived from foods. The next will be to assess whether there is a relationship between behavioural abnormalities and alteration of small intestinal function. The occurrence of altered intestinal permeability in a fraction of autistic patients may reflect the multifactorial pathogenesis of the disease.

Acknowledgments.—We thank Olga Mannarino for technical assistance.

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Received Sept. 18, 1995. Accepted in revised form March 22, 1996