Traveller's diarrhoea with a vengeance in children of UK immigrants visiting their parental homeland

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SUMMARY Six healthy children, born in the UK, travelled to their parental homeland and developed a severe form of traveller's diarrhoea. This was characterised by rapid loss of weight and chronic diarrhoea. On return to this country, investigation in 5 of them showed an abnormal, small intestinal mucosa. There was a high incidence of pathogens and potential pathogens found in stools and duodenal juice. Immunodeficiency was found in 2 of them. Small intestinal mucosal damage related to gut infection in previously well children appears to be of cardinal importance in the interaction between chronic diarrhoea and malnutrition. This observation may point the way to future research into the primary role of gut infection in the initiation of the cycle of malnutrition and chronic diarrhoea in developing communities.

In many countries, chronic diarrhoea and malnutrition interact to provide a major cause of death and severe illness in childhood. In Britain such interaction is rarely seen; yet recently at this hospital we have encountered a number of healthy young children, born in Britain, who became severely ill when they first visited their parental homeland. Acute diarrhoea became persistent and was accompanied by rapid weight loss.

In view of the children's previous good health and nutrition this experience is relevant to the interaction between nutrition and gastrointestinal infection in childhood.¹

Case histories

Between September 1978 and July 1979, six boys aged between 6 and 35 months, born in England but taken for a first visit to their parents' country of birth, were admitted to this hospital with severe chronic diarrhoea. They had visited the Indian subcontinent or Morocco. Before departure all had a history of good health, adequate nutrition, and normal growth. This was corroborated, if possible, by child health centre records or inferred from recent family photographs. Details of individual children are shown in Table 1.

Table 1 *Clinical features and treatment*

Case	Age at admission (months)	Country	Duration of visit (weeks)	How soon after arrival did symptoms start (weeks)	Time between return to UK and admission	Condition on admission	Treatment
1	6	Pakistan	12	2	4 days	8-10% dehydrated, 10 stools daily	Parenteral alimentation for 6 weeks. Cows' milk protein-free diet for one year
2	8	Pakistan	8	3	2 days	10 stools daily	Intravenous fluids for 2 days then graded slowly to normal diet
3	12	Morocco	5	2	12 hours	7% dehydrated, pyrexia, abdominal pain, 9 stools daily	Parenteral alimentation for 10 days then graded slowly to normal diet
4	18	Pakistan	20	1	3 days	Pyrexia, 6 stools daily	Metronidazole 500 mg daily × 6
5	23	India	10	3	2 weeks	Pyrexia, fever, 10 stools daily	Parenteral alimentation for 6 weeks. Multiple antibiotics then graded slowly to normal diet after 3 months
6	35	India	10	6	5 days	Abdominal distension, 5 stools daily	Intravenous fluids 3 days. Metronidazole 800 mg daily × 3 then graded slowly to normal diet

Most of the children were symptomatic within 3 weeks of arrival abroad. All had diarrhoea of acute onset, sometimes accompanied by fever and vomiting. The initial illness did not appear remarkable for the countries they visited, but the symptoms became persistent and the children lost weight. On admission 5 of them were below the 3rd centile for weight. Each was admitted to this hospital within hours or days of his return to England, except for Cases 1 and 5 who were referred from other hospitals. In all, the presenting symptom was chronic diarrhoea which had persisted from the initial illness. No specific details of treatment abroad were given, other than vague histories of 'infection', 'clear fluids' in three (Cases 2, 4, and 5). No child had brought medical records from abroad.

Each child was investigated and treated as intensively as his clinical condition warranted. The principles of management were to proceed from a glucose electrolyte mixture, regrading to a normal diet, or to use intravenous fluid if dehydration and severity of diarrhoea so indicated (Table 1). Three children were so malnourished and diarrhoea so intractable that parenteral alimentation was used.

Laboratory investigations relating to small

intestinal histology, stool microbiology, immunological function, and relevant haematology and biochemistry are listed in Table 2. In all but one child, small intestinal mucosa was obtained by peroral paediatric double port Crosby capsule.

In all children stools were cultured for bacterial pathogens and viruses, examined for the presence of parasites, and studied with the electron microscope for viral particles. At the time of small intestinal mucosal biopsy, duodenal juice was examined microscopically for the presence of parasites such as *Giardia lamblia* (Table 2).

Small intestinal biopsy demonstrated an enteropathy in all cases biopsied (Figs 1 and 2). The mucosal damage was particularly severe in children (Cases 1 and 5) in whom the weight loss was profound and who also had a very low serum albumin level. It was especially severe in Case 5 who showed *Escherichia coli* adherent to damaged enterocytes on electron microscopy. Two children showed a temporary impairment of T-cell lymphocyte transformation with phytohaemagglutinin. One of these had persistent IgG and IgA hypogammaglobulinaemia, with a temporary neutropenia and impaired opsonisation. All children

Table 2 Laboratory investigations

Case	Histology of small intestinal mucosa	Microbiology of stool and duodenal juice (as indicated)	Immunological studies serum immunoglobulins (IU/ml)	Haematology and biochemistry on admission
1	Patchy severe enteropathy, IEL 27. Disaccharidases all low Normal mucosa 3 weeks later	<i>E. coli</i> O114. <i>Adenovirus</i> sp.	IgG 74 normal. IgA 24 normal. IgM 147 high normal. Opsonisation normal. T-cell transformation impaired for 3 weeks	Hb 11.3 g/dl. Indices normal. Serum protein 45 g/l, albumin 26 g/l, serum iron normal
2	Mild enteropathy, IEL 50. Disaccharidases all low	<i>E. coli</i> O86 <i>E. coli</i> O128 <i>Candida</i> sp.		Hb 10 g/dl, serum protein 70 g/dl, albumin 36 g/l, serum iron low, TIBC high, saturation low
3	No biopsy performed	<i>Shigella flexneri</i> 4B <i>E. coli</i> O111 <i>E. coli</i> O142 <i>Campylobacter</i> sp. <i>Candida</i> sp.	IgG 123 high normal. IgA 93 high. IgM 120 normal.	Hb 12 g/dl, serum protein 48 g/l, albumin 21 g/l, serum iron low
4	Mild enteropathy, IEL 50	<i>Pentatrichomonas hominis</i> trophozoites	IgG 188 high. IgA 54 normal. IgM 141 normal.	Hb 11.6 g/dl, serum protein 41 g/l, albumin 33 g/l, serum iron low
5	(1) Severe enteropathy, IEL 12. Disaccharidases all low. (2) 5 weeks later, normal mucosa. (3) 1 year later, normal mucosa	<i>Pseudomonas aeruginosa</i> for 8 weeks. <i>E. coli</i> O128 for 6 weeks. <i>Klebsiella</i> sp. (1) Duodenal juice <i>Pseudomonas aeruginosa</i> 2×10^5 org/ml, <i>E. coli</i> : O128 1×10^5 org/ml. (2) Duodenal juice sterile	IgG 10 very low. IgA 8 very low. IgM 340 very low. Neutropenia } for 3 weeks Low opsonisation } T-cell transformation impaired for 5 weeks. For at least 2 years persistent unrecordable levels of IgG and IgA	After one blood transfusion: Hb 9 g/dl, serum protein 35 g/l, albumin 20 g/l, serum iron low
6	Mild enteropathy, IEL 48. Low lactase activity. Other disaccharidases normal	No stool pathogens. Duodenal juice (after treatment) yeasts only	Serum IgG 168 high normal. IgA 72 normal. IgM 192 high normal. <i>G. lamblia</i> fluorescent antibody titres positive 1/60	Hb 12 g/dl, protein 61 g/l, albumin 37 g/l

IEL = intraepithelial lymphocytes per 100 epithelial cells.

gained weight after treatment. The 4 children whose weight centiles were known before departure from the UK recovered to at least this centile after treatment, most of them within a few weeks. Times of follow-up varied, but where possible growth was monitored over months and growth rates have been maintained (Table 3).

Fig. 1 (Case 5.) Small intestinal biopsy showing severe villous atrophy with crypt hypertrophy. $\times 80$.

Fig. 2 (Case 6.) Small intestinal biopsy. Villous atrophy with crypt hypertrophy. $\times 80$.

Discussion

The children described here presented a clinical picture of chronic diarrhoea and malnutrition all too familiar in much of the world, but rare in the UK. They suffered persistent diarrhoea and a strikingly rapid loss of weight. Unlike many children in countries where diarrhoeal disease contributes so much to death and morbidity, these children had enjoyed good health since birth in England until their acute illness while abroad. Yet once diarrhoea became persistent, the children markedly lost weight and the severity of the illness on presentation in London was surprising in view of their previous wellbeing. Why then did they become so ill?

Acute diarrhoea within a short time of arrival abroad is referred to as traveller's diarrhoea and it classically involves affliction with previously unencountered pathogens.² Both food and water may contain many pathogens³ and in these children's parental homelands both could offer a source of large numbers of previously unencountered organisms compared with food and water consumed in England.

In view of the good health of the children before their journey abroad we must assume that infection played a key role in determining the clinical severity of the illness and that the diagnosis was a particularly severe form of traveller's diarrhoea. However, subsequent anorexia with resulting poor food intake and also limited medical treatment may have played a role, albeit secondary. Traveller's diarrhoea is typically a self-limiting illness, yet the mean duration of symptoms before admission was 9.2 weeks.

This persistence may be explained in turn by persistent infection, persistent small intestinal mucosal damage (that is enteropathy), and by immunodeficiency which could be age related, as 5 of the children were under age 2 years.

The severity of the illness in Case 6 with presumed giardiasis and a mild enteropathy may relate to infestation with this parasite as prolonged symptoms

Table 3 Details of height and weight centiles

Case	Height centile		Weight centile		
	At admission	At birth	Before leaving UK*	At admission	At follow-up
1	3rd	3rd	?	2 kg below 3rd	3rd within 6 months
2	50th	50th	25th at 2 months	3rd	25th within 8 weeks
3	10th	3rd	10th at 1 year	500 g below 3rd	10th within 3 weeks
4	10th	3rd	10th	500 g below 3rd	10th within 3 weeks
5	50th	3rd	50th	500 g below 3rd	50th at discharge 75th within 1 year
6	60th	80th	?	500 g below 3rd	10th within 2 weeks

*Last known weight.

in traveller's diarrhoea due to *G. lamblia* are well known, sometimes with rapid weight loss.^{4,5} A similar explanation may exist for Case 4, a child infected with the protozoan flagellate, *Pentatrichomonas hominis*. However, it is largely a colonic parasite and the presence of a small intestinal enteropathy may be of more importance in explaining the child's illness. The remaining 4 children, who had a mean duration of symptoms of 7 weeks, required intravenous fluids on admission, 3 in turn requiring subsequent parenteral alimentation. All had mixed infections with known strains of enteropathogenic *E. coli* in their stools plus recognised or possible pathogenic organisms.

For all children, daily stool samples were cultured. In Cases 2, 3, 4, and 5 the disappearance of the possible pathogens quoted in Table 2 and the stopping of diarrhoea were separated by no longer than 3 days. In Case 6, treatment with met. onidazole was started without examining duodenal juice for presence of *G. lamblia*. The diarrhoea stopped within 2 days and there was serological evidence consistent with giardiasis. In Case 1 an enteropathogenic strain of *E. coli* had been consistently demonstrated in the referring hospital and his clinical course reflected the existence of an enteropathy. When treatment was given (Table 1) the condition of all children soon improved (Table 3). The concordance between clinical recovery and the disappearance of organisms from stool cultures supports a pathogenic role for at least some of the potential pathogens found in the stools.

In the individual affected child, it is difficult to ascribe symptoms to one particular organism among possible pathogens, and the multiplicity of organisms may be important in the severity of these children's illnesses. Mixed infections are rare in our experience but if they do occur may be associated with more severe clinical disease.⁶

The presence of small intestinal mucosal damage in all children biopsied, perhaps as a direct result of infection, may be of more importance. The most severe lesions were in those with the most pronounced weight losses and the lowest serum albumin levels. Was this enteropathy then a post-enteritis enteropathy and its persistence of critical importance in the severity of the children's illness? The relationship of this enteropathy to the abnormal bacterial flora is not certain, although in Case 5 the adhesion of *E. coli* O128 to damaged enterocytes would appear to be important aetiologically. High dosage and continuing exposure to bacterial pathogens may also be important. There was complete healing of the small intestinal mucosa in the 2 patients who had the most severe enteropathy at the time that they had clinically recovered, were

taking a normal diet, and the infections had cleared from stool cultures.

Immunodeficiency was found in 2 children (Cases 1 and 5). Serum immunoglobulins were normal or raised in all except Case 5, who had low IgA and IgG levels. These have persisted for 2 years. If this hypogammaglobulinaemia were congenital, it is surprising that he remained so healthy as an infant. He and Case 1 had temporary evidence of T-cell dysfunction, as has been described in 5 of 27 severely malnourished children.⁷ The significance of these findings in these 2 children in relation to the whole illness is unclear, but it is possible that the enteropathy in some way has affected local immune function in the gut and even systemically, and thus played a part in the persistence of bacterial pathogens and in the enteropathy itself.

The microbiological findings and the small intestinal enteropathies found in these children, plus their previous good health and nutrition, suggest that persistent small intestinal mucosal damage related to gut infection may be of primary importance in the interaction between chronic diarrhoea and malnutrition in these children. Such infection may also have initiated the cycle of chronic diarrhoea, malnutrition, and small intestinal damage in countless more children living in developing communities. This observation stresses the need for research into the possible primary role of gut infection in such circumstances.

On a practical note, immigrant parents of UK-born infants should give some thought to the potential health hazards in taking children, especially those under 2 years, to their ancestral homeland.

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