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Protracted Diarrhoea, Immunodeficiency and Viruses

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Abstract. Protracted diarrhoea (PD) in infancy is a common presenting symptom of severe combined immunodeficiency (SCID), but the pathophysiological mechanisms are usually unexplained. An infant is presented with fatal SCID in whom PD was associated with multiple viral excretion from the intestinal tract and the presence of large PAS-positive macrophages at the villous tips of the jejunum. The possibility of immunodeficiency should be considered in all infants with PD and viruses may play an important role in the pathogenesis of some cases of PD occurring in infants with immunodeficiency.

Key words: Diarrhoea – Immunologic deficiency syndromes – Viruses – Rotavirus – Adenoviruses – Caliciviruses – Astroviruses – Macrophages

Protracted diarrhoea (PD) in infancy often poses difficult problems, not only of management, but also of diagnosis [1] and is a common presenting symptom of patients with severe combined immunodeficiency (SCID). The aetiology of PD seen in immunodeficiency (ID) is in many cases unclear. However, a major role of the gut associated lymphoid system is to assist in the protection against the wide range of entric antigens encountered daily, and a breach in these defences in ID, leads to diverse clinical syndromes of infection, allergy or autoimmunity. Apart from bacteria, viruses are also firmly established as a cause of acute diarrhoea in childhood [2] and recently have been implicated as one cause of the PD seen in children with ID [3]. We report an infant with SCID, who had intractable diarrhoea and concurrent chronic intestinal infection with five viruses.

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Case Report

H. U., an Asian boy of first cousin parents, was born at fullterm by normal delivery weighing 3.3 kg. He was bottle fed from birth. At two weeks of age he developed profuse watery diarrhoea associated with the presence of numerous rotaviruses in the stool demonstrated by electron microscopy. The diarrhoea settled only when a chicken based diet was commenced at six weeks of age [1] and he began to gain weight. He continued to excrete not only rotavirus in the stool, but also calicivirus from five weeks of age and on other occasions small round viruses (Fig. 1). At four months of age his diarrhoea returned, became intractable and was associated with increasingly severe failure to thrive. Subsequently, he excreted not only the three previously noted viruses but also large numbers of adenovirus and astrovirus.

At five months of age he was investigated and found to have severe combined immunodeficiency. Levels of IgG and IgA were low (IgG 19 iu/l; IgA < 2 iu/l) and levels of IgM low from nine months(13 iu/l); salivary IgA was undetectable. Total lymphocyte count in venous blood was normal (5.8×10^9/l), the thymus was absent radiologically and tonsils and lymph nodes were not present. T cells, measured by E rosette formation, comprised only 8% of peripheral blood lymphocytes, whereas B cells amounted to 68%. In vitro lymphocyte response to PHA was absent and there was no response to candida antigen either intradermally or by in vitro stimulation. Red cell adenosine deaminase and inosine nucleoside phosphorylase were normal.

A small intestinal biopsy, taken at the duodeno-jejunal flexure at six months of age, showed partial villous atrophy. There was a striking reduction of plasma cells within the lamina propria and, large, granular, PAS-positive macrophages were present at the villous tips; these were variable in shape and size. No evidence was found of small intestinal bacterial overgrowth, giardiasis or of viruses in the jejunal juice.

Prophylactic treatment against pneumocystis carinii with co-trimoxazole was commenced at four months of age and intramuscular immunoglobulin injections at five months. In addition, at seven months of age, he received a ten day course of pooled, irradiated, expressed breast milk (200 ml/day), known to have antibodies to rotavirus, but this was not associated with any clinical improvement, nor any diminution in faecal excretion of viruses. Similarly, no improvement was demonstrable, clinically or immunologically, following a three month course of the synthetic thymic hormone analogue, TP5 (Ortho Pharm. Co.). At nine months of age excretion of adenovirus, in addition to rotavirus and calicivirus, was observed. Subsequently, astrovirus and unidentified small round viruses were detected and at eleven months of age, concurrent excretion of at least five different viruses was seen.

At 12 months of age because of continuing failure to thrive and protracted diarrhoea, a bone marrow transplant was performed with his father as donor. This was unsuccessful and he died of disseminated adenovirus infection.

Discussion

The mechanisms underlying protracted diarrhoea in children with ID are unclear; it is however more prevalent when impaired cell mediated immunity is present [4]. In patients with T cell deficiency states, varying degrees of villous atrophy are common [5], but giardiasis and/or bacterial overgrowth of the small bowel are rarely seen [4], in contrast to patients with pure B cell deficiency [6]. On the basis of the case described here, and a further two immunodeficient children with chronic rotavirus infection [3], it is now clear that chronic faecal excretion of gastroenteritis-associated viruses may be associated with protracted diarrhoea. Furthermore, Middleton (personal communication 1981) has noted prolonged faecal excretion of viruses in patients with severe combined immunodeficiency, involving rotavirus; „minireovirus"; one with picorna/parvovirus; and astrovirus, often in multiple infections. The extent of the association between

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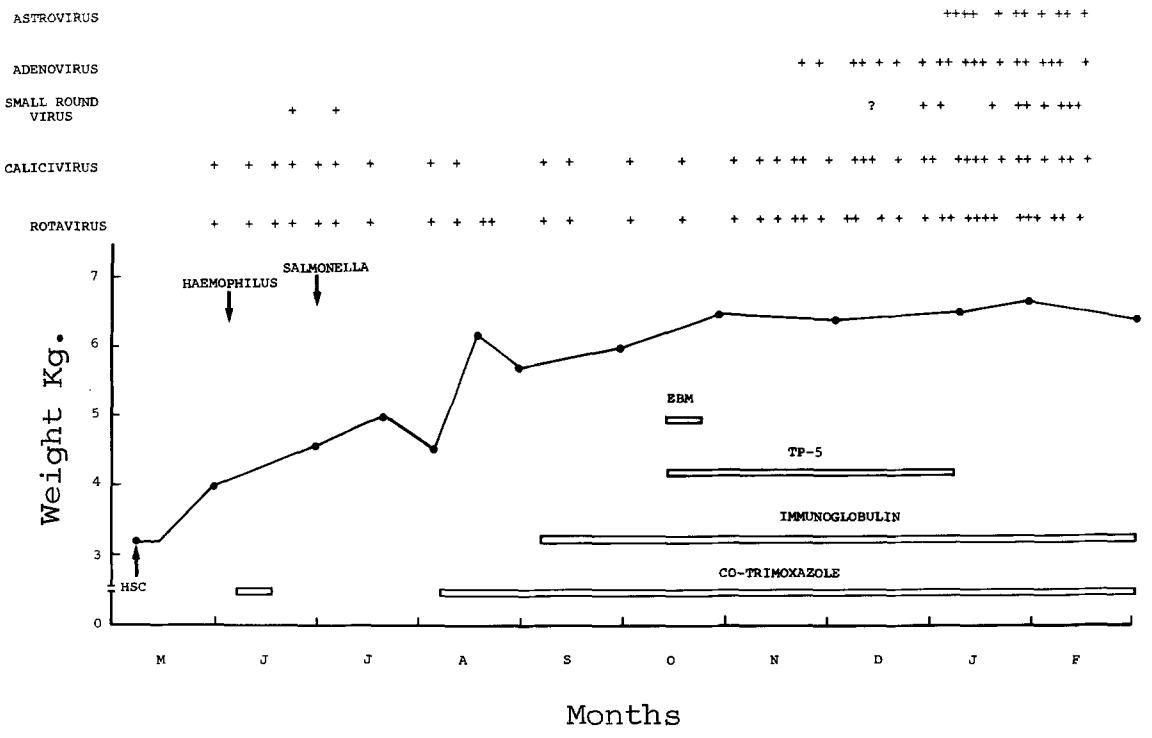

Fig. 1. Weight, intercurrent infections, treatment and viruses identified in stools by electron microscopy, between two and twelve month of age

protracted diarrhoea and chronic viral infection in patients with SCID remains, however, to be defined. These observations do however invite the speculation that viruses, acting singly or in concert, may be playing an important role in the pathogenesis of some cases of hitherto unexplained intractable diarrhoea seen in patients with ID.

The presence of large, PAS-positive macrophages at the villous tips of jejunal biopsies has been previously noted in T-cell deficiency states [5]. Ament [7] has also reported similar cells widely distributed in the lamina propria of jejunal biopsies obtained from patients with chronic granulomatous disease. We have previously seen identical cells in biopsies from children with both of these conditions (unpublished observations), and the similarity between these cells and those seen in Wipple's disease, where rod shaped inclusion bodies are also found, suggests that in ID they represent an abnormal response to a chronic mucosal infection. However, we have not been able to demonstrate infecting organisms on electon microscopic examination of the mucosa.

The administration of pooled, irradiated expressed breast milk (EBM) to our patient was not associated with clinical improvement nor with decreased viral excretion. That this was so may have been related to the low anti-rotavirus antibody titre (1:40) of the milk available and treatment with EBM may have been more successful had titres in breast milk been higher, as they may be during the winter months.

Our patient emphasises the importance of considering the diagnosis of ID in any infant with PD, particularly when associated with chronic, possibly multiple, viral excretion. Similarly, the identification of PAS-positive macrophages at villous tips in infants with PD should also alert one to this diagnosis. Whilst the pathophysiological mechanisms linking chronic viral excretion and PD remain conjectural, it is now clear that in ID such a relationship exists. Electron microscopic examination of stools for virus particles should therefore be performed in all infants with PD.

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