Siblings with microvillous inclusion disease

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Abstract

Two male siblings from a consanguinous Pakistani family had fatal diarrhoea with an onset at 24 and 48 hours after birth. A diagnosis of microvillous inclusion disease (MVID) was established by showing characteristic light and electron microscopic features in the small intestinal biopsy specimen on day 6 of life in case 1. The typical abnormalities of MVID were also demonstrated retrospectively in case 2 by examining archival appendicular tissue from 10 years previously. These cases are consistent with an autosomal recessive inheritance for MVID. Retrospective diagnosis of MVID is possible by examining appropriate archival material, which may aid genetic counselling and future research.

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Severe protracted diarrhoea with onset in the neonatal period or early infancy (sometimes referred to as intractable diarrhoea) is rare. Causes include congenital chloridorrhoea, primary malabsorption of bile acid, congenitally short bowel, defective brush border Na^+/H^+ exchange, and congenital or acquired infection.[1–3] Accurate diagnosis is important as some cases of non-specific intractable diarrhoea, particularly when familial, can carry a grim prognosis.[3]

Microvillous inclusion disease (MVID), also known as congenital microvillous atrophy, is a well recognised disorder causing severe protracted diarrhoea during infancy.[4 5] The inheritance of MVID appears to be autosomal recessive.[4] The disease is characterised by an enteropathy and severe atrophy of the enterocyte brush border with periodic acid-Schiff (PAS) positive material in the apical cytoplasm. Ultrastructural abnormalities include severe disruption of enterocyte microvilli, characteristic intracytoplasmic inclusion bodies lined by microvilli, and membrane bound amorphous material (vesicular bodies/secretory granules) in small and large bowel enterocytes.[4]

We report an index case of MVID, born to consanguinous Pakistani parents who had three other normal children, and a previously affected sibling in whom a diagnosis of MVID was established by retrospective examination of archival paraffin embedded appendicular tissue obtained at laparotomy 10 years earlier.

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Case histories

CASE 1 (INDEX CASE)

This male infant was born at 38 weeks' gestation (birth weight 3325 g) to consanguinous Pakistani parents after a normal pregnancy (no polyhydramnios). There were four other siblings, all of whom were boys (three alive). Case 2 was the first sibling. Despite the presence of meconium in the liquor, case 1 had Apgar scores of 9 at one and five minutes. Grunting at 2 hours of age and an oxygen requirement of up to 30% initiated an infection screen and intravenous antibiotics. The oxygen requirement rapidly decreased over the next few hours and the infant was breathing air by 24 hours of age, when two hourly feeds were started. Yellow watery stools (without any blood) were passed around 18 hours of age. This continued unabated with large stool outputs of 122–209 ml/kg/24 hours despite stopping enteral feeds. The stools contained up to 2% reducing substances but these were absent after enteral feeding was stopped. The stools were negative for bacterial and viral pathogens. Stool biochemistry included sodium 58, potassium 15, and chloride 36 mmol/l; osmolality was 309 mmol/kg. Serum sodium, potassium, chloride, calcium, albumin, creatinine, and osmolality were within normal limits. A duodenal biopsy specimen on day 6 of life showed the typical light and electron microscopic features of MVID. A decision not to start parenteral nutrition was made after discussion with the parents. Profuse diarrhoea continued until death on day 9 of life.

CASE 2

This male infant was the first born to the parents of case 1. He was born 10 years earlier (at another hospital), at 35 weeks' gestation, after an apparently normal pregnancy, weighing 2880 g. Severe watery diarrhoea began on the second day of life and was associated with a 20% weight loss by day 10. No pathogens or reducing substances were identified in the stools. Plasma electrolytes including chloride were within normal limits. Sweat electrolytes were normal. Intravenous feeding was started on day 15. Recurrent billious vomiting and abdominal distension led to barium studies, suggesting malrotation of the small bowel. This was confirmed at laparotomy and corrected at 6 weeks of age. Although a 2–3 cm segment of small bowel was resected, no histology was available. Despite uneventful postoperative recovery, large stool outputs of up to 200 ml/kg/24 hours continued until death from candida septicaemia at 4 months of age. At necropsy the right atrium and ventricle were occupied by a large mycetoma. There was no other abnormality. PAS staining and ultrastructural examination of the small and large bowel mucosa were not carried out at the time.

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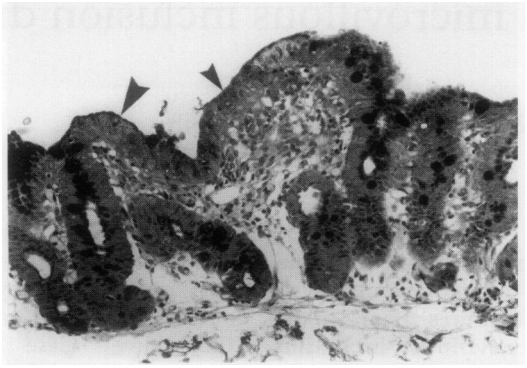

Figure 1 Duodenal biopsy sample of case 1 showing abnormal PAS staining on light microscopy. There is loss of the normal linear brush border pattern (small arrow) and apical cytoplasmic PAS positive material (large arrow). (Magnification ×150.)

Histological findings

CASE 1

Light microscopic examination of the duodenal biopsy specimen on day 6 of life showed crypt-hypoplastic partial villous atrophy with no significant inflammatory infiltrate. Surface enterocytes retained their columnar shape and showed cytoplasmic vacuolation. On PAS staining, the glycocalyx of the brush border had lost its normal linear pattern and this was replaced by aggregates of PAS positive material in the apical cytoplasm (fig 1). Staining for brush border alkaline phosphatase showed a similar pattern of abnormality.

Transmission electron microscopy showed marked shortening and focal absence of surface microvilli. The apical cytoplasm of surface enterocytes contained microvillous inclusions, lined by well formed inwardly facing microvilli, typical of MVID (fig 2). There was an increase of primary and secondary lysosomes and a scattering of vesicular bodies containing fragments of microvilli.

CASE 2

Light microscopy of the bowel mucosa at necropsy was not possible due to severe autolysis. Archival appendicular tissue appeared normal on light microscopic examination. Transmission electron microscopy was performed on material retrieved from a paraffin block which had been routinely processed 10 years earlier. Despite severe processing artefacts due to paraffin embedding, it showed changes similar to those seen in the small bowel biopsy specimen of case 1. Surface epithelial cell microvilli were severely shortened or absent. There were well formed microvillous inclusions and numerous vesicular bodies (fig 3). These abnormalities were not demonstrable in 'control' paraffin embedded archival appendicular tissue.

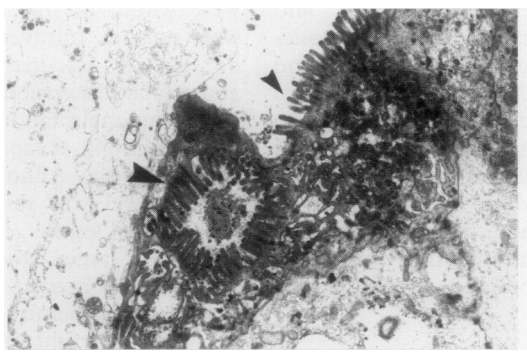

Figure 2 Transmission electron micrograph of duodenal surface epithelium (case 1) in which there is shortening and distortion of surface microvilli (small arrow). Apical cytoplasm contains a microvillous inclusion lined by microvilli (large arrow). (Magnification ×13 500.)

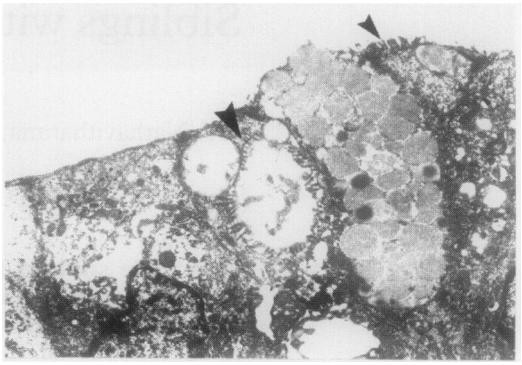

Figure 3 Transmission electron micrograph of appendical surface epithelium (case 2). There is shortening of surface microvilli (small arrow) and apical intracytoplasmic microvillous inclusions are identified (large arrow). There are artefactual processing changes as the specimen was retrieved from a paraffin block used for routine histology 10 years before this examination. (Magnification ×13 500.)

Discussion

We have described two siblings with MVID from a consanguinous Pakistani family in which there were three other unaffected siblings. This is consistent with autosomal recessive inheritance. The presence of PAS staining granules in the apical cytoplasm of the enterocyte is a useful light microscopic finding in MVID. Phillips and Schmitz reported 23 cases of MVID, which they term familial microvillous atrophy.[5] In two of their cases the diagnosis was retrospectively established by PAS staining of intestinal biopsy samples. They suggest that the distinct abnormality of PAS staining in MVID enables retrospective study in formalin fixed biopsy specimens when suitably fixed material for electron microscopy is not available.[5] Our observations, however, illustrate that a diagnosis of MVID can be established by the retrospective examination of paraffin embedded archival appendicular tissue in which the characteristic ultrastructural abnormality was demonstrable. This observation has important implications for those undertaking retrospective study of MVID for genetic counselling and for research purposes.

Cutz *et al* identified six cases of MVID among eight infants with protracted diarrhoea of early onset (within 72 hours of birth).[4] They proposed the term MVID rather than the previous term, congenital microvillous atrophy, as it identifies the characteristic ultrastructural abnormality of the disorder and avoids confusion in terminology.

Polyhydramnios is not a feature of MVID, as it is not associated with diarrhoea in utero,

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unlike some other causes of severe watery diarrhoea in early infancy.[2] The severe enteropathy in MVID leads to diarrhoea when infants are fed enterally. They often show evidence of carbohydrate malabsorption similar to our index case. Therefore, disorders such as primary lactase deficiency and glucose-galactose malabsorption should be considered in the differential diagnosis. Another well recognised feature of MVID is secretory diarrhoea with high stool electrolytes, as in case 1. The cause of secretory diarrhoea in MVID is unknown, but does not appear to be related to increased circulating intestinal polypeptide hormones.[5]

The underlying defect in MVID is unknown. The disorder appears to result from a derangement in the assembly of apical microvilli of mature small and large intestinal enterocytes.[4 5] A brush border membrane preparation from one child with MVID showed a diminution of a 200 kilodalton molecular weight band, probably representing a cellular cytoskeletal protein such as myosin.[6] The significance of this finding is unclear as it awaits confirmation by other groups. Lesions similar to MVID have been produced in cultured human fetal intestinal cells using cytochalasin. Colchicine has also been shown to produce intestinal microvillous abnormalities in the small intestine of rats.[7]

The fundamental lack of understanding has led to our current inability to institute rational and effective treatment for MVID. It is therefore not surprising that a wide array of treatments, including loperamide, cholestyramine, corticosteroids, chromoglycate, pentagastrin, somatostatin analogues, and epidermal growth factor, have been ineffective in this disorder.[5] Long term parenteral nutrition remains the only method of prolonging life in children affected by this disorder, which is often fatal. Therefore early and accurate diagnosis of MVID will enable doctors and parents to decide whether to start parenteral nutrition. Bowel transplantation offers hope to some such infants in the future.

We emphasise the importance of obtaining early small intestinal biopsy samples in the diagnostic workup of neonates with severe diarrhoea starting shortly after birth, in whom causes such as bowel infections and specific transport defects can be excluded by non-invasive investigations. This report illustrates the importance of examining archival material for establishing a diagnosis of MVID retrospectively.

We thank Dr G M Durbin, neonatal unit, Birmingham Maternity Hospital for kindly allowing us to report case 1, who was under his care.

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