PostScript

LETTERS

Intractable diarrhoea of infancy caused by neutrophil specific granule deficiency and cured by stem cell transplantation

Intractable diarrhoea of infancy (IDI) can often become life threatening and still poses a major diagnostic challenge. It embraces a diverse group of disorders¹ and in a significant number of infants the underlying cause cannot be identified. We describe a child who presented with IDI where routine investigations were unhelpful, but more detailed tests

of neutrophil function revealed a congenital defect of neutrophil specific granule formation.

A three week old baby girl of Pakistani origin of non-consanguineous parents living in the UK was referred because of pyrexia of unknown origin, as well as vomiting and severe watery diarrhoea associated with failure to thrive. *Rhodococcus equi* isolated after repeated blood culture responded to treatment with teicoplanin and Co-trimoxazole. The umbilical cord finally separated at five weeks of age. No pathogens were isolated from repeated stool cultures. Oesophagogastroduodenoscopy and colonoscopy were unremarkable. Small bowel and colonic mucosal biopsies showed villous atrophy, a moderate non-specific inflammatory infiltrate, but no

granulomas (fig 1A, B). Microvillous inclusion disease was ruled out by electron microscopy. Antienterocyte and goblet cell antibodies were negative. Standard cellular and humoral immune tests were normal.

The child's diarrhoea persisted and she was unable to gain weight without parenteral nutrition. Over the following months she developed a number of pyogenic subcutaneous abscesses as well as septicaemia. Because of the constellation of clinical features, further investigations were performed. A blood film was re-examined and showed markedly reduced granules (fig 1C). Electron microscopy showed that although neutrophils had normal numbers of primary granules there were reduced numbers of specific granules (fig 1E). A neutrophil oxidative burst test was abnormal with a reduced stimulation index of 4-14 (normal >50). Neutrophil granule proteins were assayed by ELISA, as previously described,²⁻⁶ and proteins classically found in specific granules were found to be absent (table 1). No mutations were found in the myeloid specific transcription factor CCAAT/enhancer binding protein-epsilon gene, known to be associated with some cases of neutrophil specific granule deficiency.^{7,8}

Because of the severity of the child's illness, she underwent unrelated donor stem cell transplantation at 13 months of age using busulfan, cyclophosphamide, and Alemtuzumab as conditioning. Granulocyte transfusions were given during the two week period of neutropenia prior to engraftment. The post-transplant course was complicated by a *Candida glabrata* chest infection, skin graft versus host disease, and mild veno-occlusive disease. The child is now well at 2½ years old, with full donor cell engraftment post-transplantation, on full oral feeds, and off all immunosuppressive medication. Gastrointestinal symptoms and recurrent infections have settled completely.

Neutrophil specific granule deficiency is a rare primary immunodeficiency disease associated with frequent and severe bacterial infections. Specific granules contain lactoferrin, lysozyme, and defensins and are important in the extracellular mobilisation of inflammatory mediators.⁹ Mutations in the CEBPE gene cause some cases of specific granule deficiency but no mutations were detected in this case. The clinical clues to the diagnosis of a primary neutrophil disorder in this case were the delayed separation of the umbilical cord after birth and the episode of neonatal *Rhodococcus* septicaemia, which has previously been described predominantly in patients with immunodeficiency, particularly AIDS. The enteropathy in this child is likely to have been caused by suboptimal containment of bacterial commensals within the gut lumen leading to a chronic inflammatory mucosal reaction. Intermittent release of gut bacteria into the bloodstream may have led to episodes of septicaemia and recurrent abscesses. This is not only the first report linking IDI to this primary immunodeficiency disease but also the first published case of bone marrow transplantation as a definitive curative treatment for this condition.

Figure 1 Gut histology and neutrophil morphology in our patient with neutrophil specific granule deficiency. (A) 100× and (B) 200× haematoxylin-eosin section of duodenum showing villous atrophy, a non-specific lymphocytic infiltrate, and no granuloma. (C) Haematoxylin-eosin staining of the patient's neutrophils in peripheral blood showing reduced granule staining compared with a control (D). Electron microscopy of the patient's neutrophils (E) compared with a control (F) showing primary but not secondary granules. Scale bar = 1 µm.

Table 1 Neutrophil granule protein concentrations

	Patient	Control
Myeloperoxidase (ng/ml)	9744	21312
Defensins (ng/ml)	0	3808
Human cationic antimicrobial protein (hCAP18) (ng/ml)	87	51200
Lactoferrin (ng/ml)	0	3920
Neutrophil gelatinase associated lipocalin (NGAL) (ng/ml)	7	2575
Gelatinase (ng/ml)	537	7478

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Bilateral thoracoscopic splanchnicectomy in chronic intestinal pseudo-obstruction: report of two paediatric cases

Chronic intestinal pseudo-obstruction (CIPO) is a rare, highly morbid disorder characterised by signs and symptoms of intestinal obstruction in the absence of mechanical obstruction.¹ With no specific aetiology to tackle, management of CIPO focuses on symptom control and maintenance of an adequate nutritional status. Intractable chronic abdominal pain is a frequent and distressing feature in CIPO.

Here we report on the effect of bilateral thoracoscopic splanchnicectomy (TS) in two boys, one mentally retarded, with severe CIPO refractory to conventional therapy. Their debilitating chronic abdominal pain and markedly impaired quality of life (QoL) was iteratively alleviated by transient bilateral coeliac blocks (CB). After 26 and 9 successful CB, respectively, TS was performed. The greater and lesser splanchnic nerves were coagulated and divided bilaterally in both patients (fig 1).

The postoperative course was uneventful. Mild diarrhoea occurred on the first day after CB and was followed by a lasting improvement in bowel habits. Resolution of complaints and clinical signs, including a dramatic improvement in psychomotor and social behaviour of the mentally retarded boy, persisted over a follow up period of 30 and 25 months, respectively.

Management of CIPO remains challenging. Various therapeutic options have been proposed: dietary measures, total parenteral nutrition, prokinetic drugs, surgical procedures (for example, feeding gastrostomy or jejunostomy), gastrointestinal decompression procedures, gastric or intestinal pacing, bowel resections, and small bowel transplantation.^{2,3} Nevertheless, QoL often remains disappointingly poor. Chronic abdominal pain is a distressing feature in CIPO. Pain is especially difficult to assess in toddlers and in mentally retarded children. In teenagers, chronic pain is related to low self care and decreased participation in school and social activities.⁴

CB and TS both proved efficient for pain relief in cancer of the pancreas and in chronic pancreatitis.^{5–7} CB with local anaesthetic agents appears quite safe but offers only transient relief. Conversely, CB performed with destructive agents offers longer lasting relief but carries a risk of serious side effects, including paraplegia and circulatory arrest.^{8,9} We made the safe choice of anaesthetic CB for its reversibility as an unconventional therapeutic test. Transient diarrhoea, followed by improvement in bowel habits, was observed after CB and TS in both patients. This likely reflects relief of the gut from inhibitory sympathetic efferent signals, leading to an increase in motility and decrease in water absorption by excitatory cholinergic innervation.¹⁰ The role of the intrinsic enteric nervous system in the generation of excessive sympathetic reflex remains unclear. Improvement in gut motility after CB or TS suggests that, despite marked abnormalities (hyperganglionosis), the enteric nervous system was still able to organise adequate peristalsis after interruption of hyperactive sympathetic inhibitory reflexes. Furthermore, in both patients, immediate pain relief was observed after CB and TS, emphasising the prominent role of sympathetic afferent pathways in their painful symptoms. Altogether, these observations suggest that sympathetic reflexes played a central role in the physiopathology of painful CIPO in these two young patients.

The large number of procedures before TS (our patients underwent 26 and 9 CB, respectively) illustrates both the striking improvement provided by CB that strengthened treatment compliance and the reluctance of physicians to perform an irreversible procedure for an unconventional indication.

Based on our experience, we propose considering TS for children with refractory painful CIPO and poor QoL after a successful therapeutic trial with iterative CB. TS offers great

Figure 1 Thoracoscopic localisation and section of splanchnic nerves. Right pleural cavity, patient head on the right hand side. The greater (GS) and lesser (LS) splanchnic nerves were identified (A) and sectioned under visual control (B). D, diaphragm; V, intercostal vessels; L, lung.