REVIEW

Neonatal congenital microvillus atrophy

N Pecache, S Patole, R Hagan, D Hill, A Charles, J M Papadimitriou

Postgrad Med J 2004;80:80–83. doi: 10.1136/pmj.2003.007930

Congenital microvillous atrophy (CMVA) is the leading cause of neonatal secretory diarrhoea with onset either in the first 72 hours of life (early onset) or at 6–8 weeks after birth (late onset). To date over 30 cases have been reported worldwide. The prognosis for this life threatening condition continues to be poor. Therapeutic agents like somatostatin and epidermal growth factor are either ineffective or of marginal benefit. Overall five year survival after small bowel transplantation is currently ~50%. The following brief review is aimed towards helping neonatologists/perinatologists in the early diagnosis, and management of CMVA and in counselling the parents appropriately.

Congenital microvillous atrophy (CMVA) is the leading cause of secretory diarrhoea in neonates with onset often within the first few hours after birth.^{1–2} The prognosis for this life threatening condition, especially with onset in the neonatal period, continues to be poor. We recently treated a female neonate of 36 weeks' gestation with CMVA where the presentation was severe dehydration on day 5 after congenital diarrhoea. After extensive discussions with the parents regarding the inevitable grim prognosis they decided to solely enterally feed their daughter. She died on day 33. The final diagnosis was made only on day 28 after extensive investigations. Repeated queries from the parents during these four weeks regarding the diagnosis and prognosis of their daughter necessitated a literature review that helped us counsel them appropriately while organising the multidisciplinary management team. For the literature review the databases Medline, EMBASE, CINAHL, the Cochrane Library, reference lists of review articles, and abstracts published in *Pediatric Research* were reviewed. A hand search of paediatric and perinatal journals was also conducted. The following brief review is based on this literature search and is aimed towards helping neonatologists/perinatologists in the early diagnosis, and multidisciplinary management of this potentially devastating illness in the perinatal period while counselling the parents appropriately.

EPIDEMIOLOGY

CMVA is a disorder characterised by severe intractable secretory diarrhoea presenting from birth. It was first reported in 1978 by Davidson *et al* as a syndrome of severe diarrhoea with failure to thrive and villus atrophy.^{3–4} Later in 1997

Assmann *et al* described it as an autosomal recessive disorder in consanguineous parents.⁵ A female preponderance of 2:1 has been reported in CMVA, with the age of onset either in the first 72 hours of life (early onset) or at 6–8 weeks after birth (late onset).⁶ To date over 30 cases have been reported worldwide.⁷

PATHOPHYSIOLOGY

Intestinal cytoskeletal changes such as a striking reduction in the myosin bands as well as a genetic defect causing abnormality of their binding to actin cables have been reported in CMVA.^{7–10} These changes are proposed to cause a block in the exocytosis of periodic acid-Schiff (PAS) positive material (for example, polysaccharides, glycoproteins, glycolipids, and neutral mucopolysaccharides) that then accumulates in the apical cytoplasm of intestinal epithelial cells. This results in inability of the mature enterocytes to absorb ions and nutrients, leading to malabsorption syndrome. The mechanisms of the secretory diarrhoea have been proposed to be due to decreased absorption in the presence of normal secretion.^{7–10}

CLINICAL PRESENTATION

CMVA is usually characterised by polyhydramnios, growth retardation, and some degree of developmental delay later in infancy.⁷ Associated abnormalities include Meckel's diverticulum, abdominal adhesions, inguinal hernias, renal dysplasia, absent corpus callosum, and hydronephrosis.¹¹ CMVA has been reported in association with Down's syndrome and aganglionic megacolon.¹²

Abdominal distension at birth is soon followed by secretory diarrhoea (up to 100–500 ml/kg/day) with a remarkably raised level of faecal sodium without an osmotic gap.⁸ However, mucosal atrophy can cause osmotic diarrhoea that is aggravated by enteral feeding. In osmotic diarrhoea the stool microscopy is negative for white and red blood cells (exudative diarrhoea) and fat (steatorrhea). Rapid and severe dehydration is inevitable unless intravenous rehydration is undertaken. Necrotising enterocolitis has recently been reported to complicate the clinical course of CMVA.¹³ Hypophosphataemic rickets has been reported in an 11 year old boy with CMVA.¹⁴ Leaking of phosphate into the intestine plays an important part in its pathogenesis. The high incidence of sepsis was speculated to be related not only to the central venous catheter for

See end of article for authors' affiliations

Correspondence to:
Dr Sanjay Patole,
Department of Neonatal
Pediatrics, King Edward
Memorial Hospital for
Women, Bagot Road,
Subiaco, Western
Australia 6008;
skpatole@hotmail.com

Submitted 19 March 2003
Accepted 18 August 2003

parenteral nutrition but also to translocation of pathogenic bacteria across an impaired intestinal barrier as documented by systemic inflammation and massive pneumatosis intestinalis.

DIAGNOSIS

A detailed history, clinical examination, and a plethora of investigations is necessary to come to a diagnosis due to the various conditions associated with diarrhoea in the neonatal period (boxes 1 and 2). Technical difficulties are also involved in obtaining a satisfactory jejunal biopsy specimen in the first week of life. Though severe hypoplastic partial villous atrophy and an absence of the normal PAS positive brush border is very suggestive, electron microscopy (fig 1) is needed to confirm the characteristic feature of internalised microvilli and lack or paucity of microvilli on the surface enterocytes.¹⁵ In the case that we faced the intestinal microvillous changes were mild, with focal epithelial abnormalities, predominantly on the villi seen by light microscopy. The PAS stains showed focal loss of the brush border (fig 2). Cases with clinical features like CMVA, with abnormal microvillus brush border but without the characteristic inclusions have been reported as “microvillus dystrophy”.^(16, 17) Whether these two disorders are related is currently not clear.

MANAGEMENT

Currently, apart from prevention/treatment of dehydration and total parenteral nutrition support there is no effective lifesaving option for CMVA except for intestinal transplantation.^{18–21} Antisecretagogue agents like somatostatin, octreotide, loperamide, and chlorpromazine may reduce the stool output but the overall benefit is marginal.^{22–23} Epithelial growth factor and colostrum, which induce growth of the intestinal mucosa, are ineffective.²⁴

The difficulties in transplantation of the gastrointestinal tract relate to the abundance of lymphocytes, which serve as a strong stimulus for rejection and the potential for infection due to the intestinal bacterial flora.²⁵ As colonic enterocytes also express microvilli, the native colon could be a source of postoperative secretory diarrhoea after intestinal transplantation in patients with CMVA. Thus removal of the ileocaecal valve and at least a part of the native colon at the time of

Figure 1 Electron microscope photograph of an epithelial cell showing the characteristic inclusions with microvilli.

Figure 2 Light microscope photograph PAS stain. Near normal length duodenal villus, with loss of definition and irregularity of the brush border and with some PAS positive material in the cells over the tip of the villus.

transplantation is recommended.^{18–21} However successful retention of the entire native colon, along with the ileocaecal valve, and 15 cm of ileum resulting in improved fluid

Box 1: Causes/associations of neonatal diarrhoea

- Bacterial infections: salmonella, shigella, campylobacter, *Escherichia coli*, clostridia; urinary tract infection, congenital tuberculosis, *Vibrio cholerae*; *Klebsiella pneumoniae*, *Blastocystis hominis*.
- Viral infections: rotavirus, enteric adenovirus, corona virus, echo 11,18, coxsackie B12, duovirus, transfusion acquired cytomegalovirus.
- Problems with formula: too concentrated formula,²⁴ contamination of formula by *Enterobacter sakazaki*,^{25–26} formula protein intolerance enterocolitis,^{27–29} milk and soy protein intolerance.^{30–33}
- Inborn errors of metabolism.^{34–35}
- Hirschsprung's disease.³⁶
- Drug withdrawal.^{37–40}
- Permanent diabetes mellitus.⁴¹
- Neonatal lupus.^{42–43}
- Hyperthyroidism.⁴⁴
- X-linked immune dysregulation/insulin dependent diabetes mellitus/intractable diarrhoea.⁴⁵
- Diarrhoea/hyper-IgE and absence of islets of Langerhans cells.⁴⁶
- Syncytial giant cell hepatitis.⁴⁷
- Congenital chloride diarrhoea.^{48–50}
- Congenital selective malabsorption of glucose and galactose.⁵¹
- Congenital disorder of glycosylation.^{52–53}
- Congenital sucrase isomaltase deficiency.⁵⁴
- Congenital microvillous atrophy.⁶
- Congenital diarrhoea/intestinal inflammation/epithelial immaturity.⁵⁵
- Tricho-hepato-enteric syndrome.⁵⁶
- Phototherapy.^{57–58}
- Medications: erythromycin, cisapride.

Box 2: Approach to a neonate with diarrhoea

History

- Maternal history: infections, flue-like illness (box 1), hyperthyroidism,⁴⁴ drug use in pregnancy,^{37–40} systemic lupus.^{42 43}
- Family history: consanguinity,^{3 4 10} sibling involvement.⁵
- Pregnancy details: polyhydramnios,⁷ dilated fetal bowel loops,⁵⁰ frog position of the fetus.⁵⁰
- Delivery details: condition at birth and need for resuscitation.
- Neonatal course: onset of diarrhoea, nature/frequency of stool,⁶ feeding details (breast milk versus milk formula, type/preparation/concentration of formula),^{24–30} weight loss, lethargy, temperature instability, phototherapy for jaundice,^{57 58} medications.

Clinical examination

- Hydration status.
- Female gender.⁶
- Low birth weight.
- Intrauterine growth retardation.^{41 56}
- Dysmorphic features.⁵³
- Jaundice (infections).^{47 57 58}
- Hepatosplenomegaly (infections).⁵²
- Heart blocks.⁴³
- Hair abnormalities (trichomalacia).⁵⁶
- Craniosynostosis, abnormal vertebrae, absent corpus callosum, Meckel's diverticulum, mesenteric duct remnants.^{6 10}

Investigations

- Serum electrolytes and osmolality (osmotic versus secretory).⁵⁵
- Stool: reducing substances,^{51 54} cultures, electrolytes, osmolality.
- Blood count and cultures (infection).
- Blood gases (acidosis).
- Urine culture (infection).
- Abdominal radiographs.³⁶
- Thyroid function tests.⁴⁴
- Liver function tests.^{47 56}
- Plasma glucose and insulin^{41 52 53}
- Urinary drug screen.^{34 35}
- Lupus antibodies.⁴³
- Immunoglobulin assay.^{45 46}
- Intestinal biopsy and electron microscopy.^{6 36}

and electrolyte balance and catch up growth has been reported.²¹

OUTCOME

The prognosis for this life threatening condition continues to be poor. Most cases of early onset disease die between 3 and 9 months of age due to dehydration, malnutrition, and sepsis. Those with late onset of the disease often succumb in the second decade of life after complications of long term total parenteral nutrition support.²⁶ Current data suggest an overall five year survival rate of approximately 50% after small bowel transplantation specifically for CMVA.⁷ Accurate diagnosis is thus important for parental counselling.

Authors' affiliations

N Pecache, S Patole, R Hagan, D Hill, Princess Margaret and King Edward Memorial Hospitals, Neonatal Clinical Care Unit, Subiaco, Western Australia

A Charles, J M Papadimitriou, Department of Pathology, University of Western Australia, Western Australia

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