BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

Infant death due to CMV enterocolitis

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Summary

An infant was admitted with symptoms of diarrhoea and vomiting. After initial improvement she unexpectedly died. Postmortem confirmed a diagnosis of cytomegalovirus (CMV) enterocolitis. The authors report this case and review other published cases of immunocompetent infants who presented with this infection. Clinicians should consider stool CMV PCR test or referral for endoscopy and biopsy in young babies who present with profuse and prolonged episodes of diarrhoea. The value of ganciclovir in immunocompetent infants who suffer with CMV gastrointestinal involvement is still not clear.

BACKGROUND

Cytomegalovirus (CMV) is a common agent recognised as a prominent pathogen in humans. It is a significant cause of morbidity and mortality in the immunocompromised.[1] CMV is one of the most common congenital infections with a prevalence of 0.5–13.9 cases in every 10 000 birth.[2]

Perinatal CMV infection is often acquired through the genital tract during delivery or via breast milk and is usually asymptomatic. Similarly, most immunocompetent babies with congenital CMV infection are asymptomatic with physical signs in approximately 10% only.[3]

CMV gastrointestinal (GI) infection is generally infrequent in perinatal CMV.[4] GI tract involvement has been well described in immunocompromised patients and may be a cause of serious illness.[3]

GI CMV complications usually manifest with perforation, diarrhoea, bleeding, ulceration or obstruction. GI CMV infections have been reported in immunocompetent older children with underlying GI diseases such as inflammatory bowel disease and cow milk protein allergy.[5 6]

In previous reports, CMV-enterocolitis was associated with profuse diarrhoea which was not always bloody, presumably related to different immunopathogenic mechanisms. The most severe GI manifestations were reported in immunosuppressed or congenitally infected infants although some preterm babies with acquired CMV infection presented with a clinical picture that mimicked necrotising enterocolitis.[7]

CASE PRESENTATION

A 6-week-old female infant who was a normally developing and growing baby (weight 3.7 kg, 25th centile for age) presented to our local emergency department in August 2010 with a history of non-bloody diarrhoea and vomiting for 4 days. This was associated with fever. She looked dehydrated and shocked and she had a weight loss of around 16% of the previous recorded weight. There was no organomegaly or lymphadenopathy. Initial fluid resuscitation (20 ml/kg of normal saline) and intravenous cefotaxime (50 mg/kg/dose) was administrated on admission.

The background history revealed non-consanguineous parents with mother of Southeast Asian origin. During pregnancy, the mother was under midwifery- led care and there were no relevant antenatal events or maternal recent infections. The baby was delivered by emergency section following a prolonged rupture of membranes but was born in a good condition and established on breast feeding. Baby was discharged home few days after birth. She had no recorded episodes of illness till the present admission.

Management over the next 48 h consisted of intravenous fluids replacement (maintenance plus estimated losses replaced over 48 h). Broad-spectrum antibiotics were continued awaiting culture results. The initial investigations revealed metabolic acidosis (pH 7.26), hypernatraemia (Na^+: 151 mmol/l), thrombocytosis (platelets: 1052×10^9/l), leucocytosis (white cell count: 51×10^9/l) and increased C reactive protein (59 mg/l). Liver enzymes were within normal range.

Her clinical condition improved over the next 3 days although her GI losses continued. Her vital signs normalised gradually. Serial blood investigations revealed stable sodium levels and decreasing urea and infection markers. Her condition was discussed on a regular basis with the regional paediatric intensive care unit and renal paediatric team which offered guidance on fluid management and advised no indication for intensive care. On day 3 of admission oral and enteral fluids were partially established. The baby was on gradually increasing enteral fluids via NG tube and she was also taking limited amount of fluids orally with corresponding titration of intravenous fluids. Replacing stool losses continued using oral replacement solution and an input/output chart was closely monitored. On the last medical assessment she was breastfeeding on demand and she was described as unsettled but otherwise looked well although she had relative tachycardia which was related to the crying. Eighty four hours after admission, she was found unresponsive with no signs of life. She did not respond to the resuscitation efforts.

The postmortem identified the cause of the death as severe CMV associated enterocolitis on the background of disseminated CMV infection with dehydration.

Table 1 Overview of retrieved case reports

Year reported	Age	Country of presentation	Presentation	Treatment	Outcome
1996[4]	6 weeks	Taiwan	Fever/diarrhoea/perforated ileum	Surgical intervention	Resolved
1997[6]	5 weeks	Netherlands	D&V*/PR bleeding/CMPI† comorbidity	Supportive treated CMPI	Resolved
1999[3]	2 months	USA	Fever/Prolonged‡ non-bloody diarrhoea	Intravenous ganciclovir	Resolved
1999[5]	5 weeks	USA	Prolonged non-bloody diarrhoea	Intravenous ganciclovir	Resolved
2004[9]	2 months	UK	Bloody diarrhoea/shock/CMPI comorbidity	Elemental feeds	Resolved
2004[10]	8 weeks	USA	Prolonged non-bloody diarrhoea/fever	Intravenous ganciclovir	Resolved
2010[7]	3 months	Italy	Bloody diarrhoea	Intravenous/oral ganciclovir	Resolved
2010[7]	1 month	Italy	Non-bloody diarrhoea	Intravenous/oral ganciclovir	Resolved
2010[7]	3 months	Italy	Non-bloody diarrhoea/vomiting/GOR§	Intravenous/oral ganciclovir	Resolved

*D&V, diarrhoea and vomiting.
†CMPI, cow milk protein intolerance.
‡Prolonged diarrhoea: more than 5 days.
§GOR, Gastro-oesophageal reflux.

Histological evidence of acute enterocolitis and hepatitis was identified with CMV DNA present in blood, lungs, kidneys, heart, pancreas and bone marrow. Postmortem histology images were not available for this report.

The full blood count and blood film results were not suggestive of immunodeficiency in the baby. In view of the wide range on CMV incubation and in order to decide whether this was a congenital or acquired infection, Guthrie card sample was rechecked for CMV DNA and it was negative. The sensitivity of this test could be as high as 96%.[8] Parents' permission was obtained before this case report being published.

DISCUSSION

Literature search

We conducted a literature search on CMV infections with lower GI presentation in immunocompetent infants. We used Journals@Ovid Full Text on 9 February 2011 using key words (bab* or infant or perinatal or child* or pediatric or paediatric) and (CMV or cytomegalovirus) and (diarrhea or diarrhoea or enter*) searching in titles, keywords and abstracts. We excluded papers related to children over 1 year old, preterm or immunocompromised patients including HIV and transplantation cases. We reviewed the references of the publications selected to confirm we did not miss any relevant cases. Seven papers were obtained in total including case reports of nine infants in addition to the infant reported in this paper. Table 1 summarises the cases.

In our review, CMV enterocolitis mainly presented with prolonged, profuse and sometimes bloody diarrhoea in addition to other non-specific general symptoms such as fever and lethargy.

The babies were previously well and some of them were breast fed. There was no relevant maternal perinatal history in any of the cases. On the initial assessment of these infants, the majority of them had no organomegaly or unusual rashes. Laboratory tests showed variable results. Most of the babies had leukocytosis and thrombocytosis.[5 7 9 10] Subsequent serum samples in some of the cases confirmed high titres of CMV IgG/IgM antibodies.[7 10] None of the cases had detectable pathogens in routine stool cultures (which do not usually include CMV PCR). Later urine samples yielded CMV in some of the cases and one study monitored serial urine samples.[5 7 9]

The reported cases were initially managed with supportive care. The clinical course varied between infants. In some cases, babies were very unwell and the dehydration and electrolytes imbalance led to PICU admission.[9] Other cases were less severe although all babies needed parenteral or nasogastric nutrition. It was interesting to note that two of the cases had cow milk protein intolerance[6 9]

We tried to look at the clinical threshold that prompted clinicians to request CMV specific investigation in addition to GI endoscopy. Apart from the case of the ileac perforation it appeared from the reports that the prolonged course of enteral losses, weight loss, the need of parenteral nutrition and bloody diarrhoea, were all factors which prompted clinicians to request non-routine stool and serum investigations (including CMV specific tests). The variability in severity has probably affected the clinical choice and the timing of the investigations in these cases.

In three cases[7] clinicians detected CMV DNA in the stool and suggested the diagnosis before endoscopy. Stool CMV PCR is a validated test which has shown good sensitivity in immunosuppressed patients.[11] In the other six cases, infants underwent upper and lower GI endoscopy (or bowel resection in one case)[4] after persistence of diarrhoea between 5 days and 2 weeks. The histological findings in these six cases were suggestive of CMV enterocolitis including neutrophilic inflammation, inclusion bodies and epithelial changes with nuclear enlargement.

The management varied as well. Six of nine cases reported in our literature search were treated with ganciclovir, one with surgery and the rest with supportive treatment only.

Ganciclovir is a guanosine analogue that selectively inhibits CMV DNA polymerase. We could find no published studies of the use of ganciclovir in CMV enterocolitis in infancy but that may simply reflect the rarity of the condition. In adults however, there is evidence that ganciclovir has proven efficacious in treating and preventing CMV infection in patients who have undergone transplants and in those with HIV.[12]

In one study,[7] three babies were followed up until their urine, serum and stool samples yielded no viruses and CMV IgM became undetectable within 6–13 months after commencing ganciclovir. In the remaining cases babies were followed up and no concerns about their growth and general health were noted.

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Learning points

- CMV enterocolitis in immunocompetent infants is a very rare pathology that might be underreported due to diagnostic difficulties.
- It usually presents with prolonged bloody or non-bloody diarrhoea and other general symptoms and it can occasionally lead to hypovolaemic shock and subsequently death.
- There is no evidence to recommend routine use of antiviral agents in treating immunocompetent infant with CMV enterocolitis.
- We would recommend considering stool CMV PCR with or without referral for endoscopy and biopsy in young babies who present with profuse and prolonged diarrhoea that persists beyond a few days.

Competing interests None.

Patient consent Obtained.

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