Unusual association of diseases/symptoms

Cluster of neurological manifestations of rotavirus infection in children

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Rotavirus infection in children in the resource-rich countries is usually benign but complications are reported rarely. Four children presented within 4 weeks with neurological symptoms and stool virology positive for rotavirus. All four made a quick recovery and were discharged home after a few days without medication. At 6 weeks all were well, with no further neurological episodes. This is the first reported cluster of this nature. Potential mechanisms for how rotavirus causes its rare neurological complications are briefly discussed, along with clinical implications for clinicians managing such patients.

BACKGROUND

Neurological manifestations of rotavirus infection are rare in children. Four children presented to our hospital within 4 weeks in late winter 2009 with neurological symptoms, all of whom had rotavirus gastroenteritis. This is the first time a cluster of this nature has been reported, and represents an important contribution to the literature. As discussed below, although rotavirus is an extremely common infection, the detection of rotavirus in the stool of a child with neurological symptoms may influence management decisions.

CASE PRESENTATION

Case presentation is summarised in table 1.

Case 1: A previously healthy 1-year-old girl presented with two episodes of unresponsiveness within the space of a few minutes. On each occasion, she appeared to stop breathing and became unresponsive, but there were no changes in colour or body tone and no limb jerking, and on both occasions she recovered after 10 s. She had vomited

twice that morning. On admission, she was febrile (37.9°C) and irritable, but neurological examination was otherwise normal. The day after admission she developed diarrhoea that persisted for several days.

Case 2: A previously well 3-year-old girl presented following a seizure. She had a 3-day history of diarrhoea, vomiting and fever. She had a generalised tonic-clonic seizure while afebrile which lasted less than 5 min, with a further short seizure on admission. Examination was normal. She had three further self-limiting seizures, and was treated with phenytoin and lorazepam following which she had a respiratory arrest. She had a sixth afebrile seizure 10 min later.

Case 3: A 2-year-old boy with a history of febrile convulsions was admitted following a generalised febrile tonic-clonic seizure lasting 20 s. He had been febrile for 1 day and had had a single episode of diarrhoea and vomiting. On admission, he was febrile (38.0°C), but neurological examination was normal with no signs of meningism. He

Table 1 Summary of cases in cluster

	Age and sex	Presenting history	Examination findings	Blood results	CSF results	Stool virology	Other investigations	Treatment received*
Case 1	1 year old girl	Two short episodes of unresponsiveness	Febrile, irritable, otherwise normal	Low bicarbonate (14 mmol/l), high lactate (2.7 mmol/l), negative cultures	Normal, negative cultures	Positive for rotavirus	Normal EEG, no other imaging	Ceftriaxone
Case 2	3 year old girl	Diarrhoea, vomiting, multiple afebrile seizures	Normal examination	Metabolic acidosis on venous gas, negative cultures	Failed LP	Positive for rotavirus	Normal cranial CT, no MRI	Ceftriaxone, azithromycin, acyclovir, phenytoin, lorazepam
Case 3	2½ year old boy	Febrile seizure, followed by four afebrile seizures	Febrile, otherwise normal	High CRP (86 mg/l), negative cultures	Normal, negative cultures	Positive for rotavirus	Normal cranial CT, no MRI	Ceftriaxone, acyclovir, phenytoin
Case 4	2 year old boy	Vomiting and drowsiness, fluctuating GCS, single seizure, diarrhoea	Reduced GCS, otherwise normal	Normal, other than positive blood culture (contaminant)	Normal, negative cultures	Positive for rotavirus	Normal cranial CT and MRI	Ceftriaxone, acyclovir

*All drug doses and frequencies were standard UK protocols as detailed in the British National Formulary.

CSF, cerebrospinal fluid; CRP, C-reactive protein; EEG, electroencephalogram; GCS, Glasgow Coma Scale; LP, lumbar puncture.

subsequently had four further generalised seizures while afebrile, each lasting a few minutes.

Case 4: A 2-year-old boy was admitted with a history of vomiting and drowsiness. The previous evening he had fallen off his bed and hit his head. There was no loss of consciousness, but he started vomiting 30 min later. He continued to vomit throughout the night, and was intermittently drowsy the following morning. On admission, examination was normal and CT brain showed no abnormalities. He spiked a temperature to 39°C and had a generalised tonic-clonic seizure lasting 2 min. Shortly after the seizure he developed diarrhoea. He remained drowsy and his conscious level fluctuated over the next few hours with Glasgow Coma Scale between 8 and 14/15.

INVESTIGATIONS

Blood investigations were essentially normal for all four cases, other than raised C-reactive protein in cases two and three (38 and 86 mg/l, respectively), and mildly raised lactate and reduced bicarbonate in cases one and two (state what these were as you refer to them later in the discussion). Blood cultures were negative in all cases other than case three, in whom α -haemolytic streptococcus was grown (considered likely to be a contaminant).

Lumbar puncture was successfully undertaken in all cases except case two, in whom it failed. In the three cases where cerebrospinal fluid (CSF) was available it was normal, with negative bacterial culture and negative herpes simplex virus PCR. Rotavirus detection in CSF was not available at our institution.

Case 1 had an electroencephalogram (EEG), which was normal. Cases 2 and 3 had a normal CT brain, and case 4 had a normal MRI brain.

All four cases had stool positive for rotavirus by ELISA.

TREATMENT

All four cases were commenced on intravenous ceftriaxone and this was continued for between three and seven days, with the addition on intravenous aciclovir in cases two, three and four. Case two also received azithromycin. Cases two and three were treated with phenytoin, with case two also requiring lorazepam for initial seizure control.

OUTCOME AND FOLLOW-UP

All four children quickly improved over a matter of days, and were discharged home without medication. At follow-up at 6 weeks, all the children were well, with no further neurological episodes.

DISCUSSION

Rotavirus is the commonest cause of severe gastroenteritis in childhood, isolated from up to 40% of children with acute diarrhoea.¹ Infection is most common between the ages of 6 and 24 months, with 1 in 50 children in the European Union admitted to hospital with the disease by the age of five.² In the UK, the highest incidence of rotavirus gastroenteritis is in late winter and spring, which is when the cases described here all presented.³

Although the clinical course of rotavirus infection in children is usually relatively benign, complications following infection have been reported, including neurological manifestations. A retrospective analysis of 984 children

with community-acquired rotavirus gastroenteritis found that 3.6% of children developed seizures, and 1.3% developed encephalitis with an abnormal EEG.⁴ In a few reports in the literature rotavirus has been detected in the patient's CSF;^{5 6} however, in the majority this is negative, or as in our cases, unavailable.

The patients described here presented within a short space of time, all with neurological manifestations. This has not been previously been reported, and given the low rate of neurological complications must be considered unusual. This is not simply explained by increased incidence as the rate of rotavirus infection in the population at the time was not significantly higher than normal.³ It is possible that particular strains of rotavirus circulating in the population at any one time are more neurotropic than others. However, there is no published literature to suggest the patients with neurological complications of rotavirus cluster either geographically or in time.

The mechanisms by which rotavirus causes neurological complications are poorly understood. The occasional finding of rotavirus in the CSF suggests direct invasion of the neural tissues by the virus, and rotavirus infection of neurones has been demonstrated in vitro.⁷ However, the lack of evidence of rotavirus in the CSF in many cases of rotavirus-associated encephalitis suggests an alternative mechanism. Other possible mechanisms include toxins entering the bloodstream via intestinal epithelium damaged by rotavirus infection, or neurological complications being secondary to electrolyte disturbances commonly seen in gastroenteritis.⁵ While all of our cases had normal serum sodium and potassium, two of them had low bicarbonate and high lactate, which would support the latter theory.

A recently suggested pathogenic mechanism involves non-structural protein 4, one of the six non-structural proteins that make up part of the rotavirus particle.⁸ It is a viral enterotoxin, and in addition to contributing to diarrhoeal effects in the gut, it may be responsible for the neurological problems described.

This case series shows that infection with rotavirus can cause a range of neurological symptoms and signs and although these manifestations are rare, given the extremely high incidence of rotavirus infection this has important clinical implications. Three of the four children described here were started on aciclovir for possible encephalitis. Although this should remain standard practice as diarrhoea is a common childhood symptom, we suggest that in a child with neurological symptoms who improves rapidly, detection of rotavirus in the stool may assist clinicians in the decision to stop aciclovir early, especially if there is no CSF available.

Learning points

- ▶ Rotavirus is an extremely common infection in children, and usually benign.
- ▶ Neurological complications are rare, but because of the high incidence of infection, are important to remember as part of the differential diagnosis.
- ▶ The outcome from all these cases was very good.
- ▶ In a child with neurological symptoms who improves rapidly, the finding of rotavirus in the stool may assist in the decision to stop treatment early.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Van Damme P**, Giaquinto C, Huet F, *et al*. Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *J Infect Dis* 2007;**195**:S4–16.
2. **Soriano-Gabarró M**, Mrukowicz J, Vesikari T, *et al*. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J* 2006;**25**(1 Suppl):S7–S11.
3. Rotavirus laboratory reports of all identifications by month England & Wales, 1992–2009 [online]. Health Protection Agency Website. Available at http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733771737?p=1191942172772 (accessed 10 April 2009).
4. **Johansen K**, Hedlund KO, Zweyberg-Wirgart B, *et al*. Complications attributable to rotavirus-induced diarrhoea in a Swedish paediatric population: report from an 11-year surveillance. *Scand J Infect Dis* 2008;**40**:958–64.
5. **Goldwater PN**, Rowland K, Thesinger M, *et al*. Rotavirus encephalopathy: pathogenesis reviewed. *J Paediatr Child Health* 2001;**37**:206–9.
6. **Furuya Y**, Katayama T, Miyahara K, *et al*. Detection of the rotavirus a genome from the cerebrospinal fluid of a gastroenteritis patient: a case report. *Jpn J Infect Dis* 2007;**60**:148–9.
7. **Weclawicz K**, Svensson L, Kristensson K. Targeting of endoplasmic reticulum-associated proteins to axons and dendrites in rotavirus-infected neurons. *Brain Res Bull* 1998;**46**:353–60.
8. **Ramig RF**. Pathogenesis of intestinal and systemic rotavirus infection. *J Virol* 2004;**78**:10213–20.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Day TG, Jackson C, Bryant PA. Cluster of neurological manifestations of rotavirus infection in children. *BMJ Case Reports* 2012; 10.1136/bcr.04.2011.4134, Published XXX

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