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## Benign afebrile cluster convulsions with gastroenteritis: an observational study

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### Abstract

**Background:** The occurrence of afebrile seizures in association with viral gastroenteritis, without dehydration or electrolyte imbalance, is virtually unknown outside Asia. They are reported to have a benign prognosis and not to require specific investigations or therapy.

**Methods:** We report the occurrence of such afebrile convulsions in association with viral gastroenteritis without dehydration or electrolyte imbalance, over a 3-year period, in a cohort of 14 British children.

**Results:** The children (5 males and 9 females, 10 Caucasians and 4 Asians) were aged 9 to 60 months (median 14.5 months). All 14 had a normal neurological examination and normal serum biochemistry. Twelve children had generalised seizures and 2 had, in addition, absence seizures. The number of seizures per child ranged from 1 to 8. Most convulsions were short with 85.7% of children having the longest seizure not longer than 4 minutes. The longest duration for a seizure was 10 minutes and occurred in 2 children. Convulsions did not recur after the first day in 10 children, 3 children had recurrences the second day and one child on the fourth day. No convulsions recurred after 4 days.

Cerebrospinal fluid studies, computed tomography and electroencephalogram (EEG) were performed on two children who had prolonged seizures and the results were normal. No pathogenic bacteria were grown in any of the stools. Enzyme immunoassay detection of Rotavirus in the stools was positive in 7 of the 10 children where it was tested. All 14 children recovered spontaneously within a few days. On long-term follow of up to 31 months (median 16 months), none had further convulsions and all had normal development milestones.

**Conclusions:** Afebrile seizures in association with viral gastroenteritis do also occur outside Asia. Recognition of this entity should lead to reassurance of the parents. As in previously published series, investigations such as lumbar puncture, neuroimaging and EEG are usually normal and may not be necessary in most cases. Likewise, published data indicate that long-term anticonvulsant therapy is not usually warranted and the prognosis seems to be reassuring.

## Background

Febrile seizures are common in children between the age of 6 months and 6 years and carry a benign prognosis. In contrast, the occurrence of afebrile convulsions in a child usually necessitates investigations to identify the etiology and estimate the prognosis. Recurrences usually lead to anticonvulsant therapy. In addition to the parental anxiety generated and the unpleasantness and cost of investigations, the potential side effects of anticonvulsants have to be carefully weighed for each individual child.

The occurrence of afebrile seizures in association with viral gastroenteritis, without dehydration or electrolyte imbalance, is virtually unknown outside Asia and is not mentioned in any recent American or British pediatric textbook. They are reported to have a benign prognosis and do not require specific investigations or therapy.

## Methods

The occurrence of afebrile convulsions in association with viral gastroenteritis in a cohort of 14 patients in the United Kingdom, over a 3-year period, is described and the literature is reviewed.

Over a 3-year period, the records of all children below 16 years of age discharged from our hospital with a diagnosis of afebrile convulsions and gastroenteritis or acute diarrhea were reviewed. Informed consent for inclusion was waived by our hospital ethical review committee as the study was only descriptive, no specific investigation or therapy were being tested, all patients were managed as per our department clinical guidelines and all cases were anonymised before analysis.

## Results

Over a 3-year period 14 children (5 males and 9 females, 10 Caucasians and 4 Asians) aged 9 to 60 months (median 14.5 months) were admitted to hospital for afebrile seizures of new onset, in association with gastroenteritis. All had normal development milestones, no significant past medical problems and no medication history. There was no history of head trauma or drug ingestion. Prior to admission, no children had a history of antiemetics or loperamide therapy, and only oral rehydration solution therapy had been administered at home. None was reported to be febrile before or during the seizure which precipitated admission. On admission, they all had a normal neurological examination including mental status, blood pressure and funduscopy were normal and none had signs suggestive of non-accidental injury. None had clinical signs of exceeding 5% dehydration at presentation. All children remained afebrile throughout their hospital stay, even when further convulsions developed while in hospital.

There was a marked seasonal distribution of the cases as all occurred between the months of November and May, peaking between March and May (35% occurred between November and February and 65% between March and May). No cases occurred between June and November. Diarrhea occurred either the same day as the seizure in 6 children, or preceded it by a median of 1 day (maximum 4 days) in the 8 others. Twelve out of the 14 children (86%) had generalised seizures and 2 children (14%) had, in addition, absence seizures of the petit mal type. The number of seizures per child ranged from 1 to 8 (median 1 seizure). Most convulsions were short with 85.7% of children having the longest seizure not longer than 4 minutes. The longest duration for a seizure was 10 minutes and occurred in 2 children (14%).

Convulsions did not recur after the first day in 10 children (71%). Three children (21%) had recurrences the second day and one child on the fourth day. No convulsions recurred after 4 days. The duration of diarrhea ranged from 2 to 7 days (median 4 days) and the highest number of daily stools ranged from 2 to 14 (median 5 stools). Although none of the children had clinical evidence of more than 5% dehydration, 4 children required intravenous fluids because of vomiting and inability to tolerate oral fluids, while all other 10 children were managed with maintenance oral rehydration solution and antidiarrheic diet.

All 14 children had normal full blood count, blood film, serum urea, creatinine, electrolytes, glucose, calcium and magnesium levels. A urine toxicology screen was carried out in 8 children and was negative. The stools of all children were tested for pathogenic bacteria but no *Salmonella*, *Shigella*, or *Campylobacter* species were grown. Enzyme immunoassay detection of Rotavirus in the stools was positive in 7 (63.7%) of the 10 children where it was tested, but was not tested in 4 children.

Two children who had recurrent seizures lasting 10 minutes underwent further investigations. Their cerebrospinal fluid (CSF) was clear, with a normal opening pressure, normal white cell count, glucose and protein levels, with no organisms on Gram stain, sterile bacterial and viral cultures and negative polymerase chain reaction (PCR) testing for Rotavirus. They had a normal electroencephalogram (EEG) and cranial computed tomography on day 2 and their toxicology screen negative. They were initially administered anticonvulsant therapy (Phenobarbital and Valproate) but this was discontinued within one week. No other children required anticonvulsant therapy. There was no association between age, gender, duration or severity of the diarrhea on one hand and the number or the duration of seizures on the other hand

( $p > 0.05$ ). There was a significant association between the severity and the duration of the seizures ( $P < 0.05$ ).

When followed up from 6 to 31 months (median 16 months), none of the 14 children had recurrences of convulsions and their developmental milestones remained normal.

## Discussion

Convulsions may occur during a diarrheic illness. Children may develop febrile seizures if fever accompanies the diarrhea. Sometimes afebrile seizures may occur in association with dehydration, electrolyte imbalance, hypoglycemia or hypocalcemia complicating acute gastroenteritis. Encephalopathic manifestations may also occur in association with hemolytic-uremic syndrome following a prodromal diarrheic illness. In addition, encephalopathy may be associated with *Campylobacter* [1], *Shigella* [2] or non-typhoidal *Salmonella enteritis* [3]. In contrast, the occurrence of afebrile seizures during viral gastroenteritis without dehydration or electrolyte imbalance is little known in Western countries, is not reported in any recent American or British pediatric textbooks, and, to our knowledge, this cohort is the first to be reported outside Asia. Since the first reports in 1993, most reported cases have been published from Japan [4-8], Taiwan [9-12], and Hong Kong [13]. Their occurrence is not rare as shown in a study of 63 children with acute convulsions, where fits with gastroenteritis were the predominant causes in children aged 25–36 months and the second cause in 85% of those aged 13–24 months. [12]

Benign convulsions with mild gastroenteritis could be defined as seizures accompanying symptoms of gastroenteritis without clinical signs of dehydration or electrolyte derangement and with a body temperature less than 38.0°C before and after the seizures, in children without meningitis, encephalitis, encephalopathy or apparent history of epilepsy. [8] They may occur between the age of 3 months to 52 months (mean 20 months) [8,9], even with mild diarrhea, without electrolyte imbalance, dehydration and fever. Eighty per cent of cases occur between December and March, reflecting the winter prevalence of gastroenteritis, like in our series. [9] The average reported interval between the onset of gastroenteritis and that of seizures is 2.3 days (range 1–6 days) [8], although up to 40% may have a convulsion before the onset of gastroenteritis, similar to our findings. [5] Children may develop 1 to 7 short (less than 5 minutes) generalized seizures, tonic-clonic (65% of cases), tonic (25%), and clonic (10%). [8,9] Two or more convulsions may develop in 75% of cases. [8,9] Although seizures are mostly brief and often repetitive, occurring in clusters. In 60% of cases, the seizure type may alternate during an episode between generalized and partial seizures. [5]

Full blood count, serum glucose, calcium, creatinine, electrolyte levels, cerebrospinal fluid (CSF) examinations and cultures for bacteria and viruses have been reported to be always normal, although a few reported cases had rotavirus detected in the CSF suggesting encephalitis. [6,7,10,14,15] Although the electroencephalogram (EEG) after the seizures is usually normal in most reported cases, it may be transiently abnormal in some. [10] Computed tomography is normal as well in most published cases, although non-specific hypodense areas or edema suggestive of encephalitis have occasionally been reported. [6]

When administered, anticonvulsant therapy is ineffective in 58% of reported cases. [8] Follow-up EEGs, performed from 4 to 11 months after onset of seizure, are always normal in published cases. [10] Psychomotor development remains normal in all reported children after six months to four year follow up, without any recurrence of convulsions. [5,8-11]

Rotavirus is found in the stools of 54% of published cases. [9,10] The risk of seizure with diarrhea is reported to be the highest when rotavirus is the offending organism, with the relative risk of developing a seizure with a rotavirus enteritis being 2.3 when compared to negative culture, and 1.8 when compared to bacterial enteritis. [13] Small round structured virus (SRSV) has also been found in stools of some patients. [7]

The pathophysiology of afebrile seizures in gastroenteritis is not fully understood. Encephalitis following hematogenous rotavirus invasion of the central nervous system is suggested by reverse transcription polymerase chain reaction detection of Rotavirus RNA in the throat, blood and cerebrospinal fluid, and anti-rotavirus IgG in the cerebrospinal fluid of only some affected children. [6,7,14], 10 Some studies have suggested that common peptide hormones between the brain and the gastrointestinal tract, associated with spontaneous electrical epileptogenic activity and lowered seizure threshold in some adults, may be a contributing factor to the occurrence of afebrile convulsions during gastroenteritis. [14] Carnitine concentrations in CSF, usually 10% of that in the serum, are increased 2 to 3-fold in some reported cases, suggesting blood-brain barrier damage resulting in increased blood-brain barrier permeability and CNS carnitine accumulation. [16]

Without a clear pathophysiology explaining the association between the uncommon afebrile seizures and the much more common viral gastroenteritis in young children, it remains possible that chance alone may lead some children who develop seizures to have a concomitant common viral illness. However, this seems unlikely, as

illustrated by the previous series published in Asian countries, describing this as a new and separate entity. In addition, it is hard to believe that, if chance alone explained the association between seizures and a very common viral infection highly prevalent outside Asia as well, this association would not have been reported earlier in non-Asian countries as well. Furthermore, estimating the incidence rate of rotavirus gastroenteritis at 0.55 to 0.63 case/person/year [17,18], equivalent to an incidence rate of 0.010 to 0.0121 case/person/week (0.55/52 weeks = 0.010; 0.63/52 weeks = 0.0121), for all 390 children under 5 years of age admitted to our hospital in the same period with any type of seizure (febrile or not, including even children with known epilepsy or neurologic disease), the calculated expected number to develop a coincidental convulsion the same week with an episode of gastroenteritis was 3.9 to 4.7 (390 × 0.010 = 3.9; 390 × 0.0121 = 4.7), significantly less than the 14 reported cases (incidence rate ratio = 0.28, 95% confidence intervals 0.07 to 0.91, p = 0.02). If only neurodevelopmentally normal children with a first afebrile seizure were included in these calculation, the resulting expected number with concomitant gastroenteritis would have obviously been even less, making therefore a chance association very unlikely.

## Conclusions

This report agrees with previous studies that afebrile seizures related to acute gastroenteritis constitute a benign condition and carry an excellent prognosis. Recognition of this entity should lead to reassurance of the parents. Investigations such as lumbar puncture, neuroimaging and EEG may not be necessary in most cases and anticonvulsant therapy not always warranted. This report also confirms the findings of previous studies that the prognosis seems to be reassuring.

## Competing interests

None declared.

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