Asymptomatic Viral Gastrointestinal Infection: The Missing Link?

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abstract
We present the case of an 8-month-old boy who presented with apparent life-threatening events later characterized as seizures in clusters. A total of 14 apneic episodes were observed within 24 hours before loading the patient with phenobarbital at which point the seizures stopped. There was no obvious explanation for his seizures. EEG revealed midline interictal discharges; MRI-head was normal; and all other investigations were normal. The patient’s stool was sent for virology with the clinical suspicion of benign infantile seizures associated with mild gastroenteritis (BISMG) despite lack of gastrointestinal symptoms. A small round virus was found. His clinical course followed the same progression as typical BISMG. This begs the question whether it is possible for virus in the stool to cause an asymptomatic gastrointestinal infection with its only clinical manifestation as seizures. We conclude that it may be possible for BISMG to present without gastrointestinal symptoms. As well, BISMG may be an unrecognized cause of apparent life-threatening events and should be considered in the differential diagnosis. Pediatrics 2014;133:e1–e4

Abbreviations
ALTE—apparent life-threatening event
BISME—benign focal epilepsy in infancy with midline spikes and waves during sleep
BISMG—benign infantile seizures associated with mild gastroenteritis
CSF—cerebrospinal fluid

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We describe a case of afebrile infantile seizures manifested in clusters associated with an asymptomatic presence of small rounded virus in stools. We review the literature on benign infantile seizures associated with mild gastroenteritis (BISMG): We discuss how these seizures may be an unrecognized cause of an apparent life-threatening event (ALTE). We finally debate why this case is worthy of consideration and the implications of doing so in practice expanding the criteria of BISMG and the investigations of ALTE.

CASE SUMMARY

A previously healthy 8-month-old boy was brought to the children’s emergency department with clusters of apneic episodes. The first episode was witnessed at home while the patient was initiating sleep: his lips and oral cavity turned blue and he was hypotonic. The episode lasted 15 seconds. The patient was alert afterward. Four more similar episodes occurred before emergency medical services arrived. In hospital, 9 more episodes were witnessed through the night. Other features during episodes included normal heart rate and oxygen desaturation below 85% prompting supplemental oxygen delivery. There was no fever, vomiting, diarrhea, or cough. The patient maintained normal fluid intake throughout. There were varying accounts of posture and movements during his events: tonic posturing, eye deviation to both left and right, head deviated to the right, hyperextended left leg, and right leg clonic. One episode featured a prolonged period of decreased awareness afterward. The rest of the episodes were shorter than 30 seconds, without subsequent decreased level of consciousness noted.

The patient had eczema, rhinitis and chronic cough, and wheezing. He was on daily fluticasone 1 puff twice daily and salbutamol 1 puff 3 times per day, as well as hydrocortisone 2.5% topical twice daily. Infection risk included a 2-year-old sister at home with diarrhea the night before the episodes. Immunizations were up to date.

On examination, vital signs were normal and the patient was alert, afebrile, and euvoletic. Growth parameters were all >90th percentile. Neurologic examination was normal. The only positive findings included expiratory wheeze, early 1/6 systolic murmur, and dermatitis on the chin and anterior chest. Investigations included postevent capillary blood gas, complete blood cell count, electrolytes, serum urea nitrogen, and creatinine. All were normal. Urine and blood cultures were negative. Nasopharyngeal aspirate for pertussis and parapertussis was negative. Electrocardiogram was normal. A lumbar puncture was deferred. EEG captured midline interictal discharges (Fig 1). The patient was suspected to have benign focal epilepsy of infancy. Due to seizure frequency and desaturations associated with events, the patient was loaded with phenobarbital intravenously (20 mg/kg) and maintained on it (5 mg/kg per day). The events subsided. Stool was sent for virology. “Small, round virus” (equivalent to small round structured virus) was identified (Fig 2). BISMG was diagnosed.

A brain MRI was normal. The patient was discharged 3 days later. He never developed diarrhea afterward and did not have any further seizures. He stayed on single antiepileptic drug maintenance due to parents’ demands. A follow-up EEG done 14 months later was normal and antiepileptic drug was weaned without seizure reoccurrence at 6 months follow-up.

FIGURE 1
EEG trace revealing midline spike (arrow).
Benign Infantile Seizures Associated with Mild Gastroenteritis

Clinical Features

BISMG has been described in patients 6 months to 5 years old with a peak incidence in the second year of life. It has been defined as 1 or more seizures with the following features and associated symptoms:

- Seizures occurring over a 24- to 48-hour period and often in clusters of various forms in the same patient, an unusual finding in other epilepsies;
- Diarrhea with or without vomiting, usually preceding the seizures by a day or more, or appearing up to 24 hours after the onset of seizures;
- Previously healthy infant with no family history of epilepsy and no previous seizures or head trauma;
- Afebrile patient without moderate to severe dehydration, electrolyte abnormalities, decreased level of consciousness or focal neurologic signs, and negative blood and cerebrospinal fluid (CSF) cultures.
- As well, it has been proposed that there should be no EEG or neuroimaging abnormalities, but these criteria have been subsequently questioned when abnormalities were in fact reported in some cases. The virus most often associated with BISMG is rotavirus, but norovirus, small round structured virus, and others have been reported. Prognosis is favorable. In recent reviews, it has been recommended not to even initiate maintenance antiepileptic therapy for 2 main reasons: the apparent ineffectiveness of the medications at aborting seizures acutely in hospital and, more importantly, the benign course reported in the vast majority after the initial episodes.

Etiology

The exact pathogenic mechanism is not known but some evidence has emerged from stool samples isolating rotavirus. CSF samples have revealed viral RNA or specifically viral protein 7, which has been demonstrated in animal models to have an affinity for neurons and to disrupt axonal transport. This likely causes an imbalance of excitatory neurotransmitter stimulation and also may decrease gabaergic inhibitory activity and thereby lower the seizure threshold. The elevated CSF nitric oxide level found in BISMG suggests a reflexive vasodilatory response in the presence of inflammation. Case reports have demonstrated transient neuroimaging abnormalities without clinical evidence of encephalopathy, also suggesting a mild inflammatory response. Elevated CSF carnitine levels have been measured in these patients, suggesting dysfunction of the blood-brain-barrier. Furthermore, it has been proposed that there is an underlying susceptibility to infection in the developing brain of the infant given the age distribution in BISMG. Mild, diffuse self-resolving encephalitis would be in keeping with the clinical findings of mixed seizure types and focal origins suggesting multiple transient foci and overall susceptibility of an inflamed developing brain to seize.

APPARENT LIFE-THREATENING EVENT

An ALTE is defined as a witnessed episode in a child involving some combination of apnea, color change, significant change in muscle tone, choking, or gagging. The incidence of ALTE in a large review was described as 2.27% of hospitalized children. The major causes of ALTE identified were gastroesophageal reflux disease, lower respiratory tract infection, and seizures. Nevertheless, infants presenting with an ALTE who subsequently appear well often undergo monitoring and investigations to no avail: in that same review, 23% of ALTEs were reported as “diagnosis unknown” upon discharge. As well, it is well known that seizures in infancy may present as apneic spells and should be considered when investigating ALTE.

DISCUSSION

New presentations of afebrile seizures in infancy may be associated with acute processes, or they may be the harbinger of epileptic syndromes. Patients presenting with an ALTE are monitored and investigated cautiously to rule out underlying life-threatening pathology. In ALTE and afebrile seizures, if a benign cause is identified, it can provide much reassurance to the families and limit the harms of excessive investigation and treatment, as well as the distress associated with seizures and the label of “epilepsy.” This is a unique case in that the patient displayed most of the clinical features of BISMG without the associated gastroenteritis, with other compelling characteristics as well: the patient fit the demographics at 8 months old with no other obvious seizure-provoking characteristics; there was a sick-contact at
home in an infant sister with diarrhea at close proximity to the events; the episodes presented in clusters in a 24-hour period with apparent mixed seizure types, and the patient had a prompt recovery and benign course after the events. Yet how can this be BISMG without the diarrhea? It would be unusual to send stool for virology without symptoms of gastroenteritis and was carried out in this case on the basis of the presumption that diarrhea may ensue after the seizures as has been reported, which nevertheless it did not do in this case.

It is also important to recognize that another benign infantile syndrome is on the differential diagnosis, benign focal epilepsy in infancy with midline spikes and waves during sleep (BISME). In our case, the EEG pattern found during sleep is characteristic of that found in BISME.\textsuperscript{9–10} However, the same finding has been reported in febrile seizures and a nonepileptic event suggesting it is not unique to BISME.\textsuperscript{9} Regardless, the management and prognosis is the same as BISMG and thus further differentiation with BISMG is unnecessary.

This case opens up a heretofore uncharted domain: the possibility of seizures as the sole manifestation of a gastrointestinal virus. Viruses are never normal flora; nevertheless, a small proportion of asymptomatic subjects are found to have transient viruses in stools.\textsuperscript{11–13} Thus, it is possible to have virus in stool without diarrhea. Furthermore, it is known that a virus can be found in stool while causing distant effects without local gastrointestinal symptoms; for example, poliovirus.\textsuperscript{14} Case-control studies investigating an association between ALTEs and viruses in stool would be helpful in suggesting a causal relationship.\textsuperscript{15}

This case also suggests a broader approach to presentations of ALTE: is it possible that more seizures are going unnoticed? Although it is recommended to consider seizures with all presentations of ALTE in infants, standard practice involves an interictal EEG, which oftentimes may be normal. The majority of interictal EEGs in BISMG are also found to be normal, catching ictal EEG abnormalities only rarely.\textsuperscript{12,4} Without the diarrhea or interictal EEG abnormalities, there may be no good findings to rely on to suspect seizures and BISMG. Thus, case-control studies investigating an association between ALTEs and viruses in stool would be helpful in suggesting a causal relationship. Thus, this case raises the possibility of including BISMG in the differential diagnosis of confirmed seizures and even perhaps ALTEs and investigating for it in those settings.

REFERENCES

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