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Original article

Reversible splenial lesion syndrome in children with benign convulsions associated with mild gastroenteritis: A retrospective study of five cases

Lihua Jiang, Shanshan Mao, Jialu Xu, Feng Gao *

Department of Pediatric Neurology, The Children's Hospital, School of Medicine, Zhejiang University, 3333 Binsheng Road, Hangzhou, Zhejiang 310051, China

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Abstract

Objective: To assess the clinical and imaging features of reversible splenial lesion syndrome (RESLES) with benign convulsions associated with mild gastroenteritis (CwG) in children.

Patients and methods: We retrospectively reviewed the clinical course, blood and stool examinations, cerebrospinal fluid (CSF) examination, magnetic resonance imaging (MRI), electroencephalography (EEG) findings, therapy and prognosis of five children with RESLES associated with CwG.

Results: Five previously healthy patients, four girls and one boy, with mean age 26.4 ± 8.1 months, had clusters of general tonic-clonic or clonic seizures within the first two days of gastroenteritis. Rotavirus antigen was positive in the stool of one case. Interictal EEG was normal except in one case, which showed occipital slow wave. The initial MRI was performed within five days of onset, four patients had an isolated lesion in the splenium of the corpus callosum (SCC), and one patient had lesions extending outside the SCC that involved the genu of the corpus callosum. The follow-up MRI was performed 10–15 days after onset, and all lesions had completely disappeared. All patients were treated with antiviral, rehydration and anticonvulsant therapy in the acute phase. They had good prognosis and normal psychomotor development, with no neurological sequelae after 26–30 months of follow-up.

Conclusions: CwG and RESLES can coexist in young children. The patients present with clusters of general tonic-clonic or clonic seizures in the acute phase. Brain MRI shows focal lesion in the SCC with high signal intensity on T2-weighted and FLAIR sequences. It has good prognosis and excessive treatment is not necessary.

Keywords: Benign convulsions; Mild gastroenteritis; Corpus callosum; Magnetic resonance imaging; Child

1. Introduction

Viral gastroenteritis is highly prevalent in infants and young children worldwide. It is characterized by vomiting, watery diarrhea and occasionally fever, and the most common cause is rotavirus and norovirus [1]. Recently, two complications of central nervous system, benign convulsions associated with mild gastroenteritis (CwG) and reversible splenial lesion syndrome (RESLES), were reported in association with viral gastroenteritis [2,3]. However, concurrent CwG and RESLES have been rarely reported [4,5]. In the present study, we retrospectively reviewed five patients with RESLES in 233 patients diagnosed as CwG in our institute between September 2015 and August 2016.

* Corresponding author.
E-mail address: epilepsy@zju.edu.cn (F. Gao).

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We analyzed the clinicoradiological features and the outcome of the five patients in order to increase awareness of these complex complications.

2. Patients and methods

The study obtained approval from the ethics committee of Children's Hospital of Zhejiang University, and written informed consent was obtained from the guardians of all patients. We retrospectively reviewed 233 patients diagnosed as CwG at our institute between September 2015 and August 2016. The diagnostic criteria of CwG as follows:(1) afebrile convulsions associated with symptoms of gastroenteritis in previously healthy infants and young children aged between 6 months to 3 years; (2) without or with mild dehydration (less than 5% of body weight); (3) seizures often occurring in clusters; (4) laboratory examinations of serum electrolytes, blood glucose and cerebrospinal fluid (CSF) are usually normal; (5) interictal electroencephalogram (EEG) shows no paroxysmal discharge; and (6) always has a good prognosis without sequelae [2,4–6].

Except for 22 patients whose guardians refused MRI examination, MRI routinely was performed for the other 211 patients. RESLES was diagnosed based on the following criteria: (1) patients presented with or without neurological deficits; (2) MRI could detect a reversible lesion in the splenial with or without extracallosal lesions; (3) the lesions either disappeared or significantly improved during follow-up [6–8]. Patients with concomitant CwG and RESLES were included in the study. Those with gastroenteritis associated with clinical signs of moderate and severe dehydration, electrolyte imbalance, hypoglycemia, CSF abnormalities and positive stool culture of enteropathogenic bacteria were excluded. Patients with history of epilepsy, neurological abnormalities or delayed psychomotor development were also excluded.

The data of the clinical features at the onset, semiology, blood and stool examinations, CSF examination, MRI, EEG and treatment were collected.

3. Results

3.1. Clinical characteristics

Five patients, 4 female and 1 male, showed RESLES among 211 children diagnosed with CwG. The incidence of RESLES in CwG was 2.3% (5/211). All patients were previously healthy with no history of neurological disease and psychomotor development abnormality. The patient characteristics are listed in Table 1. The mean age was 26.4 ± 8.1 months. All 5 patients had vomiting and watery diarrhea at onset, of which 3 had short-term fever. Vomiting persisted for 1–2 days, and diarrhea resolved in about a week. They had seizures within the first 2 days of gastroenteritis. The seizures were in clusters and occurred in a 24-hour episode, at a frequency of 2–5 times. Seizure duration was several minutes, no status epilepticus was observed in these cases. The types of convulsions were general tonic-clonic or clonic seizures. Neurological examination was normal in all patients. No other clinical manifestations of encephalitis or encephalopathy, such as delirium and consciousness disturbance, were observed.

3.2. Laboratory examinations and EEG findings

Rotavirus antigen was positive in the stool of one out of five cases. All patients had negative bacterial stool cultures. All cases underwent interictal EEG. Only one child had occipital slow wave.

3.3. MRI findings

Initial MRI was performed within five days (range 3–5 days) after the onset of early symptoms. Four patients had an isolated lesion in the SCC. One patient had lesions that extended beyond the SCC and involved the genu of the corpus callosum. All lesions were characterized by high signal intensity on FLAIR and T2-weighted sequences, and minimal reduction on T1-weighted sequences (Fig. 1). The follow-up MRI examinations were performed 10–15 days after onset, which showed that the lesions had completely resolved.

3.4. Treatment and follow-up

All patients were treated with ribavirin (3–5 days) and rehydration for viral gastroenteritis and mild dehydration. Anticonvulsants were administered in the acute stage. Two patients received diazepam, while two others received phenobarbital. Another patient was first treated with diazepam and then phenobarbital because of repeated convulsions. After follow-up for 13–16 months, all children demonstrated normal psychomotor development with no neurologic sequelae.

4. Discussion

In this series, all patients shared the same clinical characteristics with CwG. Rotavirus and norovirus are the two most common viruses that cause CwG [1,2]. However, only one of our patients had positive rotavirus antigen in the stool. Due to limitations of the experimental conditions, we did not examine other enteroviruses. Given that CwG is benign and rarely results in unprovoked seizures later in life [9,10], anticonvulsants were only administrated in the acute stage. Phenobarbital has been shown to be more effective in controlling seizures than diazepam [9]. In our series, one patient received phenobarbital with no convulsion recurrence

Table 1
Clinical, EEG and MRI findings in patients presenting with CwG associated with RESLES.

Case	Age (M)	Sex	Clinical manifestations	Rotavirus	CSF	Na (mmol/l)	Therapy	Inter-ictal EEG	MRI		Follow-up MRI	
									Initial MRI (Scan date in relation to onset of gastroenteritis)			
1	36	F	Vomiting, watery diarrhea, fever, cluster generalized tonic-clonic afebrile seizures on the second day, 4 brief seizures	–	N	141	Ribavirin, rehydration, diazepam	Normal	5d	Band shaped lesion SCC and genu of CC	11d	N
2	14	F	Vomiting, watery diarrhea, fever, cluster generalized clonic afebrile seizures on the first day, 3 brief seizures	–	N	140	Ribavirin, rehydration, phenobarbital	Normal	5d	Oval shaped lesion SCC	10d	N
3	28	M	Vomiting, watery diarrhea, cluster generalized tonic-clonic afebrile seizures on the second day, 5 brief seizures	–	N	144	Ribavirin, rehydration, phenobarbital	Normal	5d	Oval shaped lesion SCC	15d	N
4	30	F	Vomiting, watery diarrhea, cluster generalized tonic-clonic afebrile seizures on the first day, 2 brief seizures	–	N	137	Ribavirin, rehydration, diazepam	Normal	3d	Oval shaped lesion SCC	10d	N
5	24	F	Vomiting, watery diarrhea, fever, cluster generalized clonic afebrile seizures on the second day, 4 brief seizures	±	N	139	Ribavirin, rehydration, diazepam, phenobarbital	Occipital slow wave	3d	Oval shaped lesion SCC	12d	N

Abbreviations: F = female, M = male, EEG = electroencephalogram, CSF = cerebrospinal fluid, SCC = splenium of corpus callosum, CC = corpus callosum, N = normal, Na = serum sodium, M = months.

after diazepam failed to control the seizures. Some clinicians also recommended one-day treatment with carbamazepine or lidocaine [5,10]. The mechanisms underlying CwG are not fully understood. Since CwG is only observed in young children, it is proposed that immaturity of brain function in these children probably plays a major role [11]. Viral fragments or RNA have been found in the cerebrospinal fluid (CSF), so CwG was thought to be a form of encephalitis caused by enterovirus infection [12]. In patients with rotavirus CwG, nitric oxide (NO) levels in both serum and CSF were much higher than in patients with purulent meningitis and encephalitis, which indicated that NO may have a pathophysiological role in CwG [13]. Some investigators suggested that CwG is a marginal syndrome or continual spectrum of benign infantile convulsions [11].

RESLES is rare, which is characterized by reversible SCC abnormalities, and is associated with several disorders of varied origin, including infection, hyponatremia, high-altitude cerebral edema, seizures and antiepileptic drug withdrawal, and metabolic disturbances [6,14–20]. According to MRI features, it could be classified into two types: type 1, damage limited to the SCC; type 2, damage spread to the entire corpus callosum or adjacent white matter or both [8]. Case 1 was type 2, while the rest were type 1. Transient signal changes in the corpus callosum appeared within five days of onset and completely disappeared in less than 15 days. No patient developed neurological sequelae in the follow-up.

Although RESLES due to rotavirus infection has been widely reported, it is rarely seen in cases with CwG [3,17,21]. Kato et al. described nine Japanese cases of transient SCC lesions occurring during a rotavirus infection, all of which had encephalopathic patterns such as alterations in consciousness or abnormal behavior, and only one had clinical features consistent with CwG [22]. Natsume et al. reported two cases of transient SCC lesions in children with CwG, but no other neurological symptoms except seizures in acute gastroenteritis [5]. Jang YY et al. reported a case of a Korean girl with rotavirus-associated CwG demonstrating a reversible SCC lesion [4]. She only had two episodes of brief generalized tonic-clonic seizure with mild acute gastroenteritis. Our cases had no other neurological abnormalities except seizures. Thus, CwG patients with RESLES may or may not have manifestations of encephalitis/encephalopathy other than seizures.

The exact pathophysiological mechanism of RESLES remains unclear. It has been supposed that transient SCC lesions likely reflect rapidly resolving intramyelinic edema or the influx of inflammatory cells [19,23]. Seizures impair glucose availability that results in reversible failure of cellular fluids regulation at the splenium [15,24]. Acute infection activated the immune system and elevated inflammatory cell infiltration or proinflam-

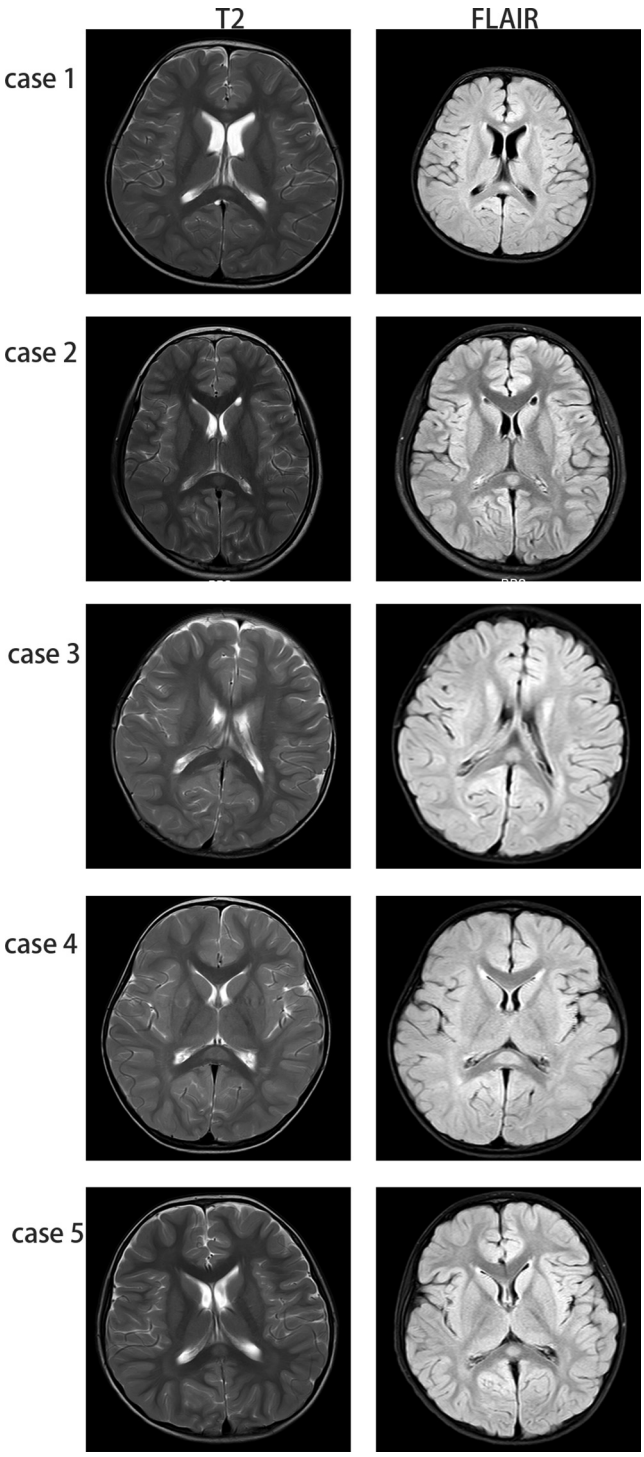

Fig. 1. Axial T2-weighted images (T2) and FLAIR-weighted images (FLAIR) of the initial stage in all five cases. Case 1 showing focal lesions in the splenium of the corpus callosum and corpus callosum with hyperintense on T2 and FLAIR. The other 4 cases showing ovoid lesion in the splenium of the corpus callosum with hyperintense on T2 and FLAIR in the splenium of the corpus callosum.

matory cytokines, which can lead to reversible cytotoxic edema of the SCC [15].

The five patients were all treated with ribavirin as short-term antiviral therapy, which was immediately stopped after the diagnosis was confirmed. Ribavirin is not only ineffective against enterovirus but also may produce serious side-effects, such as hemolysis, cardiopulmonary dysfunction, and severe allergic reactions [25,26]. Ribavirin treatment in our cases was inappropriate. These patients had a good prognosis without special treatment such as glucocorticoids and intravenous immunoglobulin, which is in consistent with previous reports.

5. Conclusions

CwG and RESLES can coexist in young children with acute viral gastroenteritis. Both syndromes have a benign course with good prognosis. The exact pathophysiological mechanism remains unknown. Early identification of these entities in children can avoid unnecessary treatment.

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