Seizure 18 (2009) 686–689

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Benign infantile seizures with mild gastroenteritis: Study of 22 patients

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ARTICLE INFO

Article history:
Received 6 July 2009
Received in revised form 30 August 2009
Accepted 18 September 2009

Keywords:
Benign
Gastroenteritis
Infantile
Rotavirus
Seizures

ABSTRACT

Purpose: To analyze the electroclinical features, aetiology and outcome in patients with normal neurological examination and psychomotor development who presented seizures during a mild gastroenteritis (MG).

Patients and methods: Evaluation of the clinical charts of 22 patients who were assessed in the Neurology Department, Hospital Nacional de Pediatría Prof. Dr. JP Garrahan between 1999 and 2007.

Results: Twelve patients were boys and 10 were girls, the age of onset ranged from 5 to 26 months, and the median age was 10 months. Rotavirus antigen test in stool was positive in 9 of 18 studied patients. The seizures were brief, focal with secondary generalization in 15 patients (68.5%), apparently generalized in 5 (22.5%) and focal in two (9%). Seven of the patients (35%) had more than one seizure in 24 h. The interictal EEG was normal in all patients. Neuroradiological studies were performed in 19 patients with a normal result. No patient was put on long-term treatment with antiepileptic drugs. Four patients had subsequent mild gastroenteritis and two of them presented convulsions during the disease. After between 12 and 67 months of follow-up, all patients had normal psychomotor development and neurological examination.

Conclusions: In this study we confirmed the association of benign infantile seizures (BIS) and MG with or without rotavirus. The identification of this entity allows avoiding unnecessary complementary studies and treatment with antiepileptic drugs.

1. Introduction

The 2001 proposal of The Task Force on Classification and Terminology recognized the benign familial and non-familial infantile seizures among the epileptic syndromes.[1] However, the latest report of the ILAE Classification Core Group considered that both groups (familial and non-familial) are identical—they have similar age at onset, as well as similar clinical and electrophysiological features. They differ only in the family history and represent a unique syndrome: benign infantile seizures (BIS).[2–5]

In Japan, Morooka[6] described the first patients with BIS associated with MG. These previously healthy infants, aged 6 months to 3 years, presented apparently generalized, afebrile, isolated or in cluster seizures. The laboratory examinations including blood glucose, serum electrolytes, and cerebrospinal fluid as well as the interictal electroencephalograms (EEGs) were normal.

After this first report, more than 60 Japanese cases with BIS and MG were reported.[7–11] In the last 15 years, nine series of patients have been described. The patients were of different ethnic origin, and presented similar electroclinical features and outcome.[12–19]

BIS occur in infants during the course of a mild gastroenteritis. Rotavirus was positive in stools in more than 50% of the reported patients. The ictal electroencephalographic records in patients with BIS and MG showed a focal origin with or without secondary generalization.[20–23]

The aim of this study is to analyze the clinical, electroencephalographic, etiologic and evolutive features of infants with normal neurologic examination and psychomotor development who presented seizures during the course of a mild gastroenteritis.

2. Patients and methods

The clinical charts of 22 infants with convulsions associated with mild gastroenteritis studied in the Neurology Department of the Children Hospital Prof. Dr. JP Garrahan between 1999 and 2007 were assessed.

We have considered the following inclusion and exclusion criteria.

Inclusion criteria: patients aged 2–36 months, with normal psychomotor development and neurologic examination who presented focal seizures with or without secondary generalization,

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doi:10.1016/j.seizure.2009.09.006

Table 1
Clinical, electroencephalographic and evolutive features of 22 patients with BIS and MG.

Patient	Sex	Age at onset (months)	Present age (months)	Rotavirus	Semiology of the seizure	Frequency and duration of the seizures	Interictal EEG	Ictal EEG	Evolution
1	F	5 m	17 m	+	Head deviation, generalized hypertonia seizures	Cluster (three brief seizures)	Normal	No	Normal psychomotor development
2	M	23 m	45 m	–	Apparently generalized tonic–clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
3	M	9 m	23 m	–	Apparently generalized clonic seizures	Cluster (two brief seizures)	Normal	No	Normal psychomotor development
4	F	9 m	26 m	–	Apparently generalized tonic seizures	Cluster (four brief seizures)	Normal	No	Normal psychomotor development
5	M	6 m	73 m	+	Fixed gaze, head deviation seizures	Isolated brief	Normal	No	Repeated gastroenteritis without seizures
6	F	8 m	44 m	–	Fixed gaze, generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
7	M	12 m	33 m	+	Head deviation, generalized clonic seizures	Isolated intermediate	Normal	No	Normal psychomotor development
8	M	10 m	29 m	+	Apparently generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
9	F	18 m	30 m	–	Loss of visual contact, cyanosis and generalized clonic movements	Isolated brief	Normal	No	Repeated gastroenteritis with similar seizures
10	M	9 m	23 m	+	Fixed gaze, oculocephalic deviation, generalized clonic seizures	Isolated Intermediate	Normal	No	Normal psychomotor development
11	F	20 m	71 m	–	Oculocephalic deviation, generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
12	M	26 m	75 m	–	Fixed gaze, oculocephalic deviation	Cluster (four brief seizures)	Normal	Yes (posterior rhythmic slow waves)	Normal psychomotor development
13	M	9 m	23 m	+	Fixed gaze, cyanosis, generalized clonic seizures	Isolated Intermediate	Normal	No	Repeated gastroenteritis with similar seizures
14	F	8 m	28 m	–	Oculocephalic deviation followed by generalized clonic seizures	Isolated Intermediate	Normal	No	Normal psychomotor development
15	F	5 m	18 m	+	Fixed gaze cyanosis generalized clonic seizures	Cluster (two brief seizures)	Normal	No	Repeated gastroenteritis without seizures
16	M	11 m	59 m	+	Cephalic deviation follow by generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
17	F	21 m	60 m	–	Fixed gaze, cyanosis follow by generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
18	M	14 m	48 m	+	Fixed gaze and cephalic deviation follow by generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
19	M	17 m	35 m	–	Apparently generalized tonic seizures	Isolated intermediate	Normal	No	Normal psychomotor development
20	M	10 m	22 m	–	Fixed gaze follow by generalized clonic seizures	Isolated brief	Normal	No	Normal psychomotor development
21	F	18 m	30 m	–	Apparently clonic generalized seizures	Isolated intermediate	Normal	No	Normal psychomotor development
22	F	11 m	34 m	–	Apparently generalized clonic seizures	Cluster (three brief seizures)	Normal	No	Normal psychomotor development

Abbreviation: F, female; M, male.

and seizures with apparently generalized onset, during the course of a gastroenteritis associated or not with rotavirus infection.

Exclusion criteria: patients with gastroenteritis associated with clinical signs of dehydratation, electrolytic derangement, hypoglycaemia, and cerebrospinal fluid abnormalities. Those patients with stool positive culture of enteropathogenic bacteria were also excluded.

Other exclusion criteria were history of febrile or afebrile seizures, neurological abnormalities, and delayed psychomotor development.

Age at onset, semiology, frequency of the seizures and recurrence during further episodes of gastroenteritis were evaluated. Personal and family history, physical and neurological examination were also taken into account.

Hemogram, serum electrolyte, acid base status, blood glycaemia, uraemia, presence of rotavirus antigen in stool and stool culture were investigated.

3. Results

We included 24 patients who presented seizures associated with mild gastroenteritis between 5 and 26 months of age. The median age was 10 months. Thirteen of the patients were male and 11 were female. Two of them presented perinatal antecedents: one girl required 3 days of phototherapy for jaundice, and a boy presented a transient respiratory distress of the newborn. One patient had family history of BIS and two of febrile seizures.

All of them presented seizures within the first 5 days of the onset of gastroenteritis. Rotavirus antigen was positive in stools in 9 of 18 studied cases.

Seizures were focal with secondary generalization in 15 patients (68.5%), apparently generalized in 5 (22.5%), and focal in only 2 cases (9%). The duration of the seizures was less than 2 min in 17 (77.5%) patients and within 2 and 5 min in the other 5 cases (22.5%). Seven of the patients (35%) presented more than one convulsion in 24 h (cluster seizures); the remaining presented only isolated seizures.

The interictal EEG was normal in all the cases. In only one patient with grouped seizures an ictal electroencephalogram was performed and left rhythmic slow waves were observed. A cerebral CT scan was performed in 14 patients, and cerebral MRI was performed in nine patients. The neuroimaging studies showed no abnormalities. In Table 1, we show the clinical, electroencephalographic and evolutive features of our series of patients.

Antiepileptic drugs (AEDs) were administered in six patients during the seizure, three of them received benzodiazepines and two fenitoin, only one of them received phenobarbital. No patient was put on chronic treatment with AEDs.

The follow-up was between 12 and 67 months, media 38 months. Four of the patients presented further episodes of gastroenteritis, two of them presented convulsions with similar features during the episode.

In the last control, all the patients presented normal neurological examination and psychomotor development.

4. Discussion

Our series of patients shows electroclinical and evolutive features similar to the reported cases.[7–19,24]

- Normal psychomotor development.
- Age at onset between 5 and 26 months (peak of more frequent presentation 10 months).
- Focal seizures with or without secondary generalization.
- The seizures can occur grouped or in clusters.
- Normal interictal EEG.
- Clinical findings of gastroenteritis.
- Frequent association with rotavirus.
- The recurrence of the seizures during further episodes of gastroenteritis is rare.
- Benign course.

The BIS associated with MG are characterized by focal brief seizures that can rapidly have secondary generalization. It is usually difficult, both for parents and physicians, to recognize the focal origin of the episodes.

A recent report described a boy who presented MG associated with rotavirus and seizures, the interictal EEG performed after the seizures showed bilateral independent temporo parietal sharp waves.[25] The EEG performed 10 days after the seizures was normal. Both ictal and interictal EEG show that the posterior cerebral area is more frequently affected.[5]

The seizures occur within the first 5 days of the onset of the MG. In those patients who repeated seizures during further episodes of MG, the seizures had similar clinical features to that of the first episodes.

The seizures are brief and they do not recur. In the presence of a new episode of MG, the recurrence of the seizure is not frequent. Therefore a chronic treatment with AED is not indicated. Nevertheless, if we take into account that the seizures can be in cluster, treatment with antiepileptic drugs could be useful. In these cases, we indicate the usual doses of benzodiazepines during the cluster. In this situation treatment with phenytoin or phenobarbital is not recommended.

It has been excluded that the hydroelectrolytic and metabolic disturbances cause the seizures in these group of patients. The presence of a direct effect that the virus has in the brain function is the most probable cause of the seizures. Several authors have sustained this hypothesis because of the presence of positive rotavirus PCR in CSF in the affected patients.[14,26–28] The inoculation of the virus in monkeys brain caused neurologic alterations and infectious histologic reaction.[29] Other hypothesis to take under consideration is a remote effect of the virus in the brain. Increased levels of nitric oxide in CSF were found in patients with seizures associated with rotavirus when they were compared with a control group including children who had febrile seizures or meningitis. These patients presented significantly lower values.[30] It is possible that seizures are caused because of toxic effects of nitric oxide in the brain. Rotavirus can affect cerebral and intestinal calcium mobilization, it can also generate fluctuation in calcium channels and a neurotransmission derangement.[31] Other hypothesis considers that rotavirus affects both intestinal and brain proteic synthesis which contributes with an increased epileptic activity secondary to a lower excitatory neuronal threshold.[32]

Infants infected with Norwalk virus who presented mild gastroenteritis associated with convulsions, which were grouped in some cases, have been reported.[33]

Table 2 shows familial and non-familial BIS and related syndromes. Is noteworthy that familial and non-familial BIS represent one of the more frequent epileptic syndromes in infants.[5] The acknowledgment of the BIS and related syndromes that have a

Table 2
Familial and non-familial benign seizures and related syndromes.

Familial forms
Benign familial neonatal–infantile seizures
Benign familial infantile seizures and paroxysmal choreoathetosis
Benign familial infantile seizures and familial hemiplegic migraine
Non-familial form
Benign infantile seizures with mild gastroenteritis
Benign partial epilepsy in infancy with middle spikes and spike-wave during sleep

benign course allows us to avoid unnecessary studies and the prescription indication of an intensive treatment.

Seizures can occur together with diarrhoea: infants can have febrile seizures if fever is associated in other cases, afebrile seizures are secondary to dehydratation, electrolytic or metabolic derangements. In the course of an uremic haemolytic syndrome, clinical features of an encephalopathy can appear. Encephalophatic features can also occur when the gastroenteritis is caused by campylobacter, shigella or salmonella.

We stress the importance that paediatricians recognize BIS associated with MG. This will lead to the avoidance of unnecessary studies and treatment. Irrational use of AEDs in the initial period and chronic treatment with AEDs. Although most of the patients with rotavirus infection and SNC manifestations have had a complete recovery, exceptionally they can present a not so good evolution. Furthermore, the use of vaccination against rotavirus would be of help in avoiding gastrointestinal, metabolic and neurologic complications and would reduce the cost of hospitalization and treatment. Iturriza-Gómara et al.[35] characterized the genes VP7 y VP4 in a patient with gastroenteritis caused by rotavirus. This can be useful in the determination of the real incidence of these entity in paediatric population.

5. Conclusions

Our patients presented brief seizures that in some cases were grouped. The age of more frequent presentation was 10 months of age (range 5–26 months), in all the cases the seizures were associated with MG. In approximately 50% of the patients rotavirus was identified.

The use of benzodiazepines during the acute phase may be necessary in patients with grouped seizures. Chronic treatment with AEDs is not indicated.

All the patients presented a normal psychomotor development in their evolution; four of them repeated a similar mild gastroenteritis in their evolution, two of which associated with seizures that had similar features to that of previous events.

The patients presented well-defined electroclinic and evolutive clinical features similar to that of familial and non-familial BIS. If our group of patients correspond to a variant of BIS or to symptomatic seizures in relation with rotavirus is to be determined.

Irrespective to the nosological location of this entity, we believe that it is very important to recognize it in order to avoid complementary studies and unnecessary treatment with antiepileptic drugs.

Disclosure

All co-authors have had a significant role in designing, executing, and/or analyzing data from the study, and/or in writing the manuscript, and they have seen and approved the final version of the paper and accept responsibility for the data presented.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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