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ORIGINAL ARTICLE

Complex febrile seizures: Study of the associated pathology and practical use of complementary tests☆

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KEYWORDS
Complex febrile seizure;
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Abstract
Introduction: Although one third of febrile seizures are complex, a consensus has still not been reached on how to manage them, as is the case with simple febrile seizures. The objective of this study is to estimate the usefulness of complementary examinations and the risk of associated serious intracranial pathology.
Patients and methods: A retrospective review was conducted from 2003 until 2011 on patients from 6 months to 6 years presenting with a complex febrile seizure admitted to a tertiary care hospital, excluding the cases with previous neurological disease. Epidemiological and clinic variables were collected, as well as complementary tests and complications.
Results: We found 65 patients (31 females and 34 males), of whom 44 had repeated seizures in the first 24 hours, with 15 having focal seizures. The vast majority (90%) of the recurrences occurred before 15 hours. The mean age was 20.7 months and temperature was 39.1 ± 0.12 °C. None of the patients had severe intracranial pathology. The electroencephalogram gave no helpful information for the diagnosis. Neuroimaging was normal in all studied cases.
Conclusions: The incidence of complications in complex febrile seizure in our series did not justify the systematic admission or the systematic study with complementary tests when the neurological examination was normal. The routine electroencephalogram does not appear to be justified.

PALABRAS CLAVE
Crisis febril compleja;
Convulsiones;
Fiebre;

Crisis febriles complejas: estudio de la patología asociada y utilidad de las pruebas complementarias

Resumen
Introducción: Un tercio de las crisis febriles son complejas. Su manejo no ha suscitado un consenso como en el caso de las crisis febriles simples. El objetivo de este estudio es estimar

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Epilepsia;
Manejo

la rentabilidad de los exámenes complementarios y el riesgo de enfermedad intracraneal grave asociada.
Pacientes y métodos: Estudio retrospectivo desde el año 2003 hasta el 2011 de los pacientes ingresados en un hospital de tercer nivel con criterios de convulsión febril compleja de 6 meses a 6 años, excluyendo los casos con afección neurológica previa. De los pacientes seleccionados, se recogieron variables epidemiológicas, clínicas, pruebas complementarias y complicaciones.
Resultados: Se encontró a 65 pacientes (31 mujeres y 34 varones) de los cuales 44 tuvieron crisis repetidas en las primeras 24 h y 15 presentaron crisis focales. El 90% de la recurrencia ocurrió antes de 15 h. La edad media fue de 20,7 meses y la temperatura fue de 39,1 ± 0,12 °C. En ningún paciente se encontró afección intracraneal grave durante su ingreso. El electroencefalograma no ofreció información de ayuda para su diagnostico. La neuroimagen fue normal en todos los casos estudiados.
Conclusiones: La incidencia de complicaciones en la convulsión febril compleja en nuestra serie no justificó el ingreso ni el estudio sistemático con pruebas complementarias cuando la exploración neurológica era normal. El electroencefalograma de rutina no parece estar justificado.

Introduction

Febrile seizures are a common medical emergency and occur in 2-5% of children between 6 and 60 months of age.[1,2] Complex febrile seizures (CFS) are a type of febrile seizure defined by recurrence within the first 24 hours, duration of more than 15 minutes, or manifestation as a focal seizure with or without generalisation or with neurologic deficit following the seizure[2-5], and no previous history of afebrile seizure. The American Academy of Pediatrics has recently proposed a clinical practice guideline[2] on the evaluation and management of simple febrile seizures (SFS). However, it does not address consensus recommendations on the approach and management of CFS. Furthermore, the ILAE recommends admission of all patients with CFS[3,4], although the evidence in recent publications suggests that it is a questionable measure that uses considerable resources in relation to the benefits it provides.[6-8] The manifestation of a febrile seizure as a CFS has been associated traditionally with a higher risk for infectious intracranial pathology and increased risk of subsequent epilepsy[3,9,10], although there are studies that challenge these premises and conclude that it is inconsistent to associate organic lesions requiring urgent intervention or treatment with CFS when the examination of the CFS patient does not show positive findings.[7,8,11-13]

The objective of this study was to evaluate the usefulness of complementary examinations and the risk of severe intracranial pathology associated to CFS, and to review and discuss the relevant publications on the subject in order to create an updated practice protocol.

Materials and methods

We did a retrospective study from 2003 to 2011 of patients meeting CFS criteria who were seen at a tertiary hospital. The hospital protocol required admission of all CFS cases, which allowed us to evaluate their subsequent evolution. We included children 6 months to 6 years of age. We defined CFS as seizure with a rectal temperature of at least 38.3°C and accompanied by at least one of the following criteria: duration longer than 15 minutes, recurrence in less than 24 hours, and focal features or neurologic deficit following the seizure. Patients with a previous history of neurological disease were excluded. We collected subject data on the following epidemiological variables: age, sex, personal and family histories; clinical variables (mean temperature during the event, mean duration of seizure, number of seizures, time to onset of seizure, focal neurologic signs, type of CFS), complementary tests (acute phase reactants, lumbar puncture (LP)), complications, EEG, neuroimaging tests, and diagnosis associated to the fever. We did not consider the long-term follow-up because that was not the purpose of our study.

The collected data were analysed with the statistical software SPSS version 15.0 to calculate frequencies, the mean ± standard deviation of the quantitative variables, and the cumulative percentages of seizures.

We followed the ethical protocols established by our hospital to access data in medical records to prepare this publication aimed at informing the scientific community.

Results

A total of 65 patients met criteria for CFS at admission according to the traditional definition, of which 31 were female and 34 male with a mean age of 20.7 months (range 7 to 62 months). The mean temperature during the episode was 39.1°C with a standard deviation of 0.12. The mean duration of the seizure was 6.5 minutes, with a 0.7 minute standard deviation and a range of 1 to 30 minutes. The mean hospital stay was 4.6 ± 2.5 days. Mean time from onset of fever to seizure was 14.5 hours with a standard deviation of 14.8 hours and a range of 0.5-48 hours. In recurrent cases, most patients had only two seizures. Table 1 shows the distribution of the number of seizures. Out of the 55 cases

Table 1 Number of seizures per patient in cases of recurrent seizures.

Number of seizures	Cases
2	47
3	7
4	0
5	1

Table 2 Time to recurrence with the frequency distribution and cumulative percentage for 30 of the cases with recurrent seizures.

Time (h)	Frequency	Cumulative percentage
0.2	1	3.3
0.5	4	16.7
1	3	26.7
2	3	36.7
3	1	40
4	1	43.3
5	3	53.3
6	3	63.3
7	1	66.7
8	1	70.0
12	3	80.0
14	1	83.3
16	3	93.3
20	1	96.7
24	1	100
Total	30	100

where seizures recurred, we were able to record the time to seizure recurrence in 30 cases. Mean time to recurrence was 6.94 hours, with a standard deviation of 6.60. The time-to-recurrence frequencies are shown in Table 2.

Only one patient had an abnormal neurological examination with right-sided hemiplegia and facial paresis, which resolved in a few hours. The brain CT for this patient was normal.

A total of 44 patients only met the criterion of having more than one seizure within the first 24 hours (ranging from 2 to 5); 15 had focal activity alone or in combination with other CFS criteria, and in 10 the seizure lasted longer than 15 minutes. Fifteen patients met two or more criteria for CFS (Fig. 1).

With regard to individual histories, 15 of the patients had experienced CFS previously. Interestingly, 19 patients had a family history of at least one first-degree relative with SFS, one patient had a first-degree relative with CFS, and eight had a family history of epilepsy in relatives up to the second degree (Fig. 2).

We performed EEG on 62 patients, usually the day following admission, and found focal slow wave activity in 13 of them, which bore no relationship to clinical presentation in 10 cases, and was associated to a focal seizure in 3 cases. We found EEG alterations in 7 other patients: instability (theta range waves) over the vertex in three patients, instability over both temporal regions and the vertex in one; spike and

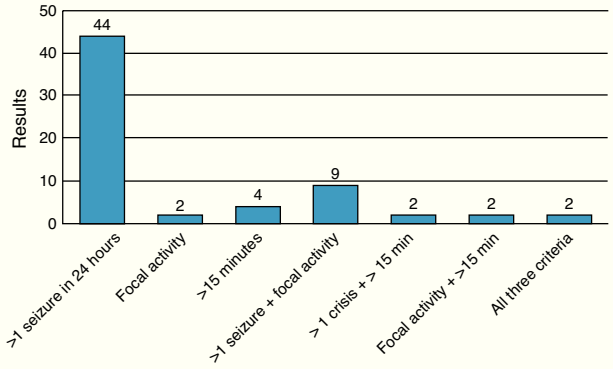

Figure 1 Number of cases associated to each type of CFS.

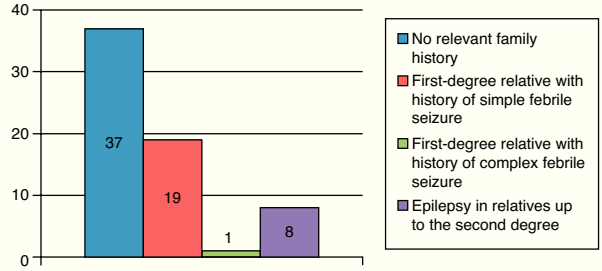

Figure 2 Family history associated to CFS.

slow wave discharges over the temporal region of the left hemisphere in one; predominant bilateral temporoparietal monotonous slow wave bursts in one, and, finally, paroxysmal spike-wave focal activity over the temporal region of the right hemisphere in one. The correlation between clinical symptoms and neuroimaging tests is shown in Table 3.

Analysis of acute phase reactant levels by means of the C-reactive protein (CRP) test was indicated in 44 cases. The mean result was 33.9 mg/l, with a standard deviation of 37.19 and a range of 2.8-146 mg/l. The cumulative percentage showed that 90% of cases had levels below 85 mg/l. Only 2 cases exceeded this figure, corresponding to one case of invasive acute gastroenteritis (AGE) and one of bacteraemia. Lumbar puncture was indicated in only 12 children, and no abnormalities were found. A neuroimaging procedure was performed in 34 children (brain CT or brain MRI), and only one of them showed a mild nonspecific subcortical atrophy that did not lead to any subsequent interventions.

The diagnosis associated to the fever was unspecified viral infection in 40 patients, streptococcal pharyngoamygdalitis in 7, acute otitis media (AOM) in 5, AGE in 6 cases, and urinary tract infection in 2 cases. Other diagnoses associated to fever were bacteraemia, varicella, pneumonia, and post-vaccination fever (Fig. 3).

In the subsequent evolution, only one out of all 65 children had an afebrile seizure within 12 months after the initial CFS. Among the patients who had EEG alterations, only the one who had monotonous bursts with bilateral temporoparietal predominance showed signs of mild cortical-subcortical atrophy in the brain CT. None of the 7 patients with EEG alterations had a recurrence in a minimum 12-month follow-up.

Table 3 Electroencephalogram alterations in children with CFS.

Electroencephalogram alterations	Total number of patients	Imaging test	Recurrence	Clinical focal criterion met
Theta range waves in vertex	3	No	No	No
Theta range waves over bilateral temporal region and vertex	1	No	No	No
Predominant bilateral temporoparietal slow wave activity	1	Brain CT: mild signs of cortical/subcortical atrophy	No	No
Slow wave discharges and spikes over temporal region in left hemisphere	1	Brain CT: normal	No	Yes
Focal paroxysmal spike-wave activity over the temporal region in the right hemisphere	1	Brain MRI: normal	No	Yes
Focal slow waves	13	Normal	In 8 cases	3

Brain MRI: brain magnetic resonance imaging; brain CT: brain computerised tomography.

Discussion

The ILAE[3] recommends admission and testing in cases of CFS based on the need to rule out infections of the central nervous system, organic lesions, metabolic disorders, or onset of an epileptic disorder, for which the patient must undergo costly and invasive tests in many instances. The usefulness of these tests has been questioned in several studies.[7,8,11-13] Indeed, the American Academy of Pediatrics recently revised the SFS protocol due to the restrictive nature of the recommendations made in the previous 1996 practice parameter[14], which current clinical practice had largely made obsolete. At present, in cases of SFS, a LP is recommended in infants younger than 12 months who have not been vaccinated against *Haemophilus influenzae* type b or *Streptococcus pneumoniae*, or when the immunisation status is unknown. This also applies to cases with prior antibiotic treatment.[2] Generally, SFS does not require assessment beyond the clinical examination. Specifically, it does not call for EEG, blood tests, or neuroimaging studies, unless otherwise indicated by the medical history or on examination.[1,2] Assessment of CFS probably does not diverge much from this approach. In our series, there were no subsequent complications during the follow-up period for a mean stay of 4.6 ± 2.5 days.

Whether a LP should or should not be done is one of the doubts that emerges in cases of CFS. Previous reviews have concluded that performing LP following an episode of CFS is unnecessary in children who do not show symptoms of meningitis[7,8] and that, instead, observation of the patients in the first hours is key to assess their evolution in the state of consciousness and/or the presence of meningeal signs.[11] In our series, LP was rarely indicated and even then it did not result in evidence of infection in any of the cases in which it was performed. We only found one case of serious bacterial infection, the diagnosis of which was based on clinical presentation and a raised CRP level of 146 mg/l.

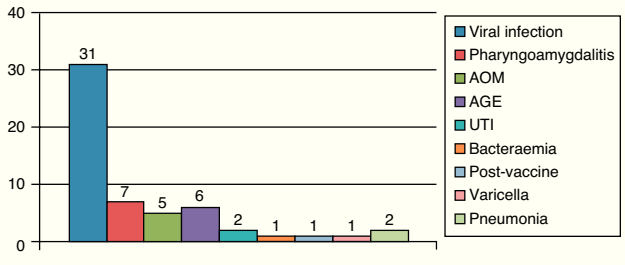

Figure 2 Diagnoses associated to CFS.

The neuroimaging study done in 34 cases of our series did not contribute any useful diagnostic information, consistent with findings in previously published studies.[12,13,15]

With regard to neurophysiological testing, the EEG only showed sharp epileptogenic paroxysms in two patients, in whom the neuroimaging study was normal. There was no correlation with subsequent epileptic activity, so it was not useful for managing the condition. This is consistent with other published studies, which have rarely found EEG alterations in children with CFS.[16] It is routine practice to perform an EEG in children with a first-time CFS, possibly due to the association found between this type of seizure and later development of epilepsy in prior studies.[3,17] Some studies have found a greater proportion of children with CFS than SFS who went on to develop epilepsy. More specifically, this was the case in children with CFS with focal features as opposed to recurrence in the first 24 hours or lasting longer than 15 minutes. With regard to early performance of EEG, as recommended by the ILAE[3], out of all the patients in the study only one had an afebrile seizure within 12 months of the CFS; this patient's EEG showed a mild nonspecific slowing of the normal background electrical activity. None of our patients' EEGs suggested a diagnosis of encephalitis, in which fever and persistent alteration in the level of consciousness are common presenting clinical features. Retrospective analysis revealed that the routine performance of early EEG was not useful, as the proportion of EEG alterations in children with CFS was low and similar to that found in children with SFS.[18,19] Consequently, it is

reasonable to delay EEG, as it has no bearing on urgent interventions or admission to the hospital.[9]

Time to seizure recurrence is an interesting and relevant finding regarding the practical question of how long patients should be observed following a CFS. In our series, there were no seizure recurrences after 24 hours, and the cumulative percentage reached 93% by 16 hours (Table 2).

Among the limitations of our study is the fact that it is a retrospective study based on a single centre. Its validity revolves around the acute illness associated to CFS during the hospital stay.

Based on our experience and the literature, we propose a revision of the practical approach to CFS. This includes aborting seizures lasting over 3 minutes. An appropriate medical history and physical examination must guide the choice of complementary tests to determine the cause of the fever so it can be managed adequately.

Cases of febrile seizures with focal features and full recovery do not seem to call for urgent neuroimaging investigation, although they should be referred to a specialist. A neuroimaging study is advisable in cases of persistent fever or neurologic deficit to determine the course of action according to the results. LP is indicated under the same conditions as in SFS.

Early neurophysiological studies do not seem to be justified by any of the factors that define a seizure as complex, nor by a higher or lower rate of recurrence, as long as the seizures continue to meet the criteria for a febrile seizure. Therefore, these studies are not an admission criterion.

To conclude, we would like to underscore that the incidence of complications in CFS does not seem to justify routine assessment by means of complementary tests when the examination is normal. Admission for observation for at least 24 hours in the emergency department seems an appropriate location for CFS, space permitting. Although our conclusions are consistent with what has been previously published, similar studies are needed to support them.

Conflicts of interest

The authors declare having no conflicts of interest.

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