

SUPPLEMENT – ITALIAN LEAGUE AGAINST EPILEPSY

Recommendations for the management of “febrile seizures”

Ad hoc Task Force of LICE Guidelines Commission

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SUMMARY

Febrile seizures are the most common seizure disorder in childhood, affecting 2–5% of children. Simple febrile seizure is defined as a short (<15 min) generalized seizure, not recurring within 24 h, that occurs during a febrile illness not resulting from an acute disease of the nervous system in a child aged between 6 months and 5 years, with no neurologic deficits and no previous afebrile seizures. These recommendations address the instructions for management of the first febrile seizures, giving criteria for hospital admission,

diagnosis, differential diagnosis, and treatment of a prolonged seizure. The authors stressed the benign prognosis of the majority of cases and the risk factors for recurrence of febrile seizures and appearance of epilepsy later on. Both continuous and intermittent anticonvulsant therapy are efficacious in preventing single febrile seizures, but side effects may be so important to overcome the benefits. These treatments are indicated in very selected patients.

KEY WORDS: Seizures, Fever, Pediatric, Guidelines, Epilepsy, Management.

I. DEFINITIONS

1.1. Simple febrile seizure

A short generalized seizure, of a duration of <15 min, not recurring within 24 h, occurring during a febrile episode¹ not caused by an acute disease of the nervous system, in a child aged 6 months to 5 years, with no neurologic deficits (i.e., with no pre-, peri-, or postnatal brain damage, with normal psychomotor development, and with no previous afebrile seizures) (American Academy of Pediatrics 1996, 1999; Fukuyama et al., 1996). Fever may

not be detected before the seizure, but it must be present at least in the immediate postacute period (American Academy of Pediatrics 1996, 1999; Fukuyama et al., 1996) and be the symptom of a pediatric disease.

1.2. Complex febrile seizure

A focal, or generalized and prolonged seizure, of a duration of greater than 15 min, recurring more than once in 24 h, and/or associated with postictal neurologic abnormalities, more frequently a postictal palsy (Todd’s palsy), or with previous neurologic deficits (American Academy of Pediatrics 1996; Berg & Shinnar, 1996; Knudsen, 2000). It should be underscored that the child presenting with a prolonged seizure stopped with anticonvulsive therapy (i.e., diazepam) before the 15th minute should be classified within this group (Berg & Shinnar, 1996; Knudsen, 2000).

Should the complex febrile seizure (CFS) be characterized by a duration of more than 30 min, or by shorter serial seizures, without consciousness being regained at the

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¹Note: The minimum level of thermal increase to diagnose “fever” has changed in time, and varies according to the scientific societies and the measuring methods: at present, the American Academy of Pediatrics considers as “fever” any increase of the body’s external temperature over 38°C.

interictal state, the disorder is named febrile status epilepticus (O'Donohoe, 1992; Knudsen, 2000).

1.3. Differential diagnosis

Differential diagnosis should include some nonepileptic paroxysmal disorders:

- (1) Syncope during febrile states (Stephenson, 1978; Carroll & Brookfield, 2002).
- (2) Abnormal motor manifestations: shuddering, dystonic seizures (Stephenson, 1978; Carroll & Brookfield, 2002).

2. CRITERIA FOR HOSPITAL ADMISSION

2.1. Simple febrile seizures

2.1.1. First episode

Age >18 months: If the patient is clinically stable, with no signs or symptoms requiring diagnostic investigations, admission is unnecessary and parents should be adequately educated (American Academy of Pediatrics, 1996) (*class of evidence I*).

Age <18 months: Admission should be envisaged, and observation is recommended for the possible performance of lumbar puncture (see point 3.1) (American Academy of Pediatrics, 1996; Carroll & Brookfield, 2002) (*class of evidence I*).

2.1.2. Already diagnosed simple febrile seizures

Admission is unnecessary; parents' education must be verified (American Academy of Pediatrics, 1996; Fukuyama et al., 1996) (*class of evidence I*). It should be underscored, however, that a history of simple febrile seizure (SFS) does not exclude that the ongoing seizure may be the symptom of another disease, such as an infectious disease of the central nervous system (CNS).

2.2. Complex febrile seizures

Admission is recommended for observation (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991) because of the wide variability of conditions underlying this event (*class of evidence I*). A febrile seizure stopped with pharmacologic therapy within the first 15 min should be considered, in terms of admission indications, as a CFS.

2.3. Febrile seizure in children without a reliable familial context

Admission is recommended (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991) (*class of evidence I*).

3. DIAGNOSIS

Diagnosis is essentially based on physical examination and history taking (see definition) (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991; American Academy of Pediatrics, 1996; Fukuyama et al., 1996) (*class of evidence I*).

3.1. Simple febrile seizures

3.1.1. Routine laboratory tests

Not recommended. The decision on whether or not to perform these tests should exclusively aim at identifying the cause of fever (American Academy of Pediatrics, 1996) (*class of evidence I*).

3.1.2. Routine electroencephalogram

Not recommended because of limited diagnostic value in a child with a first SFS (American Academy of Pediatrics, 1996; Dunlop & Taitz, 2005; Hampers et al., 2006) (*class of evidence I*).

3.1.3. Routine neuroimaging

Not recommended (American Academy of Pediatrics, 1996; Dunlop & Taitz, 2005; Hampers et al., 2006) (*class of evidence I*).

3.1.4. Lumbar puncture

In the presence of meningeal signs: Must be performed (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991; American Academy of Pediatrics 1996; Carroll & Brookfield, 2002) (*class of evidence I*).

In patients under antibiotic treatment during the days before the seizure: It must be seriously considered, owing to the possible masking of meningitis signs and symptoms (*class of evidence I*).

In patients of age ≤18 months: The usefulness of routine lumbar puncture has been demonstrated (Carroll & Brookfield, 2002). However, at this age, clinical signs and symptoms for meningitis may be minimal. Careful observation of the patient for at least 24 h is thus necessary (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991; American Academy of Pediatrics, 1996) (*class of evidence I*).

In patients of age >18 months: Lumbar puncture should not be considered as a routine procedure, as the clinical signs of CNS infection are usually identifiable (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991; American Academy of Pediatrics, 1996; Carroll & Brookfield, 2002) (*class of evidence I*).

3.2. Complex febrile seizure

3.2.1. Search for fever etiology

Is recommended (American Academy of Pediatrics, 1996) (*class of evidence I*).

3.2.2. Performance of blood chemical tests

Possible performance of blood chemical tests in relation to clinical conditions (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991) (*class of evidence I*).

3.2.3. Search for a possible underlying brain lesion

Is recommended in order to differentiate the symptomatic forms from those based on a genetic predisposition.

3.2.4. Electroencephalogram

Is recommended, as early as possible, owing to the high diagnostic value it may have for some viral encephalitis.

3.2.5. Neuroimaging

Computed tomography (CT) scan and/or nuclear magnetic resonance (NMR) are highly recommended (Maytal et al., 2000) (*class of evidence II*).

3.2.6. Lumbar puncture

It has to be considered for all patients with a suspected CNS infection (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991) (*class of evidence I*).

4. TREATMENT

4.1. Treatment of simple febrile seizures

It consists of pharmacologic treatment of possible prolonged seizures, and in the prevention of possible recurrences. In most cases, SFS spontaneously ceases within 2–3 min, and does not require treatment. Occasionally SFS may last longer than 3 min; in these cases, pharmacologic treatment is recommended.

4.1.1. Treatment of a prolonged seizure in a hospital setting

- (1) Remove airway obstruction.
- (2) Prepare a venous access.
- (3) Monitor vital parameters (heart rate, breath frequency, blood pressure, SaO₂).
- (4) Administer oxygen, if necessary (SaO₂ <90%).
- (5) Administer intravenous bolus of diazepam at a dose of 0.5 mg/kg (Fukuyama et al., 1996), at a maximum infusion speed of 5 mg/min, and suspend it when the seizure stops; the dose may be repeated, if necessary, after an interval of 10 min (it should be noted that diazepam takes approximately 10 s to reach an efficacious

concentration in the brain, even with intravenous administration) (O'Donohoe, 1992; Dooley, 1998; Tassinari et al., 1998) (*class of evidence I*). Other benzodiazepines, such as lorazepam, are equally efficacious.

- (6) Monitor Base-Excess and blood glucose (Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association, 1991; Terndrup, 1998).
- (7) If the seizure does not stop, ask for a specialist's advice (anesthesiologist, neurologist) for treatment.

4.1.2. Treatment of a prolonged seizure in a home setting

See paragraph 5.4 of the section "Essential Issues for Health Education to Families."

4.1.3. Prevention and recurrence risk

The general risk of febrile seizure recurrence is estimated at around 30–40% (Knudsen, 2000). The risk factors for recurrence, similar for simple and CFS (Offringa et al., 1994), are:

- (1) Early age of onset (<15 months) (Offringa et al., 1994; Berg et al., 1997; Knudsen, 2000)
- (2) Epilepsy in first-degree relatives (Berg et al., 1997; Knudsen, 2000)
- (3) Febrile seizures in first-degree relatives (Offringa et al., 1994; Berg et al., 1997; Knudsen, 2000)
- (4) Frequent febrile illness (Offringa et al., 1994; Knudsen, 2000)
- (5) Low temperature at the onset of the febrile seizure (Offringa et al., 1994; Berg et al., 1997)

Recurrence frequency is 10% in patients with no risk factors; 25–50% in the presence of 1–2 risk factors; 50–100% in the presence of 3 or more risk factors (Knudsen, 2000). The risk of epilepsy is estimated at around 1–1.5% in patients with SFS (Sapir et al., 2000), only slightly higher than incidence in the general population, which is approximately 0.5%. The risk of epilepsy in subjects with CFS is, instead, estimated between 4 and 15% (Berg & Shinnar, 1996; Sapir et al., 2000).

There is no evidence for therapies to prevent subsequent epilepsy (Baumann & Duffner, 2000; Knudsen, 2000). Several studies, including meta-analyses (Rantala et al., 1997; American Academy of Pediatrics, 1999; Baumann & Duffner, 2000), have demonstrated that continuous administration of phenobarbital and valproic acid is efficacious in preventing SFS recurrence. There are, however, contraindications for administration of these drugs, namely potential side effects, which risk overcoming the benefits of treatment (Sulzbacher et al., 1999). Poor compliance has been described in case of continuous treatment with phenobarbital or valproic acid.

Even intermittent rectal or oral diazepam prophylaxis (Rosman et al., 1993; Fukuyama et al., 1996; Verrotti et al.,

2004; Pavlidou et al., 2006), administered at the onset of fever, is efficacious in preventing recurrences. However, even in this case, side effects are unavoidable (transient mild ataxia, hyperactive behavior, or lethargy; in rare cases respiratory depression, bradycardia, or hypotension).

Therefore, given the benign prognosis of SFS, which does not cause permanent damage and tends to spontaneously remit with age, and the potential side effects of anticonvulsive therapy, prophylaxis for SFS recurrences are not recommended (Fukuyama et al., 1996; Rantala et al., 1997; American Academy of Pediatrics, 1999; Baumann & Duffner, 2000; Knudsen, 2000) (*class of evidence I*). In a restricted group of patients with SFS for whom the seizures are considered as “unacceptable” because of their high frequency, prophylaxis may be indicated. Two possible scenarios should, therefore, be considered (Fukuyama et al., 1996; American Academy of Pediatrics, 1999):

A) *Patients with one or more SFS episodes and reliable parents:* Active surveillance, following the principle of “wait and see” (Fukuyama et al., 1996); in these cases it is recommended that administration of anticonvulsive therapy be avoided; give parents exhaustive information, including instructions on diazepam administration in the event of prolonged seizures (see section 5); and monitor the natural evolution of seizures (*class of evidence I*).

B) *Patients with at least one of the following conditions:*

- (1) Frequent seizures in a short period of time (3 or more in 6 months, 4 or more in one year);
- (2) History of seizures longer than 15 min, or requiring pharmacologic therapy to be stopped;

In these cases intermittent therapy (Rosman et al., 1993; Verrotti et al., 2004; Pavlidou et al., 2006), that is, rectal administration (first choice), or oral administration of diazepam, can be considered as an emergency measure and administered, at the onset of fever, at a dose of 0.4–0.5 mg/kg, to be repeated a second time if fever persists after 8 h. Typically diazepam administration should be limited to two doses, although specific clinical conditions may require a third dose after at least 24 h from the first administration (Fukuyama et al., 1996) (*class of evidence II*). It should be noted that febrile seizures occur, in 98% of cases, within the first 24 h from the onset of fever; it is, therefore, not justified to extend therapy administration after this period. In case of failure, and, in particular, when parents are unable to promptly recognize the onset of fever, continuous anticonvulsive therapy with phenobarbital or valproic acid may be used (Fukuyama et al., 1996). Phenobarbital should be administered at a dose of 3–5 mg/kg/day in 1–2 intakes. Valproic acid should be administered at a dose of 20–30 mg/kg/day, in 2–3 intakes. Valproic acid is to be preferred, as phenobarbital may provoke, among its various side effects, attention deficit, hyperactivity,

and cognitive impairment (Sulzbacher et al., 1999). Carbamazepine and phenytoin have proved to be inefficacious (American Academy of Pediatrics, 1999; Baumann & Duffner, 2000).

4.2. Treatment of CFS

As described in section 3.2, the term CFS indicates entities with variable etiology, semiology, and prognosis. A CFS may, in fact, result from an acute disorder of the CNS, be the onset of specific epileptic syndromes (e.g., Dravet syndrome), or simply be a prolonged febrile seizure, with the same prognosis as SFS. Therefore, treatment depends upon the etiologic and nosographic picture, and is not dealt with in these guidelines. In case of ongoing CFS, instructions under points in sections 4.1.1 and 5.4 must be considered.

5. ESSENTIAL ISSUES FOR HEALTH EDUCATION TO FAMILIES

5.1. Describe in as much detail as possible the features of febrile seizures

Incidence, relation with age, recurrence rate, incidence in relative absence of brain damage, difference from epilepsy, risk of subsequent epilepsy, prognosis for socio-behavioral development, benign evolution. This will allow parents to easily accept not to treat.

5.2. Instruct on the need of appropriateness of anticonvulsive therapy, when prescribed, including the relevant side effects.

5.3. Verify that the instructions for fever control are well understood

There is actually no evidence that the use either of antipyretics medications, even increasing the number of administrations, or methods for reducing fever will reduce the frequency of seizures (Schnaiderman et al., 1993; American Academy of Pediatrics, 1999; Knudsen, 2000) (*class of evidence I*). It is, however, important to reduce the patient’s discomfort.

5.4. Education on how to manage possible recurrences

- (1) Remain calm, no panic;
- (2) Loosen the child’s clothing, especially around the neck;
- (3) If the child is unconscious, place the child in the lateral decubitus position, to avoid inhalation of saliva or vomitus;
- (4) Do not force opening of the mouth;
- (5) Observe the type and duration of the seizure;
- (6) Do not give any drugs or fluids orally;
- (7) Administer rectal diazepam 0.5 mg/kg, in case of prolonged seizure lasting over 2–3 min. (Diazepam with

- rectal administration takes approximately 3 min to reach an efficacious concentration in the brain.);
- (8) In any event, contact the family pediatrician, or other practitioner;
 - (9) A medical intervention is necessary in the following cases:
 - a. Seizures of a duration >10 min or not remitting after treatment,
 - b. Recurrent seizures,
 - c. Focal seizures,
 - d. Presence of prolonged consciousness disorder, and/or postictal palsy (Fukuyama et al., 1996).

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