

# Syndromes with very low risk of acute prolonged seizures

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**ABSTRACT** – The provision of rescue medication is an important component in the treatment of epilepsy. An intervention within five to ten minutes in the case of an acute prolonged seizure may preserve the patient from status epilepticus (SE). However, the risk of convulsive SE (CSE) differs markedly between patients depending on individual factors. This report summarizes the literature on risk factors for CSE in children with epilepsy and adolescents, and discusses the hypothesis that some electroclinical syndromes engender a very low risk of CSE. The most important risk factor for SE is the history of a previous event. The longer a patient lives without SE, the lower the risk will be. CSE occurs significantly less frequently in idiopathic epilepsies compared to epilepsies with symptomatic or unknown aetiology. It is very rarely observed in patients with (non-encephalopathic) idiopathic generalised epilepsies, *i.e.* childhood absence epilepsy or juvenile myoclonic epilepsy. However, non-compliance or inappropriate treatment may trigger CSE in these syndromes. A very low risk can be assumed for children with Rolandic epilepsy, while CSE occurs in a considerable percentage of patients with Panayiotopoulos syndrome. Although the risk of CSE in otherwise normal children with cryptogenic focal epilepsy is uncertain, it is presumably low under successful continuous medication. In conclusion, the choice for or against the prescription of rescue medication remains an individual decision. Consequently, for several electroclinical syndromes, a *per se* provision of rescue medication does not appear justified.

**Key words:** childhood, status epilepticus, electroclinical syndrome, idiopathic epilepsy, rescue medication

After an initial unprovoked seizure, the incidences of acute prolonged seizures and status epilepticus (SE) are 47/100,000 children/year and 27/100,000 children/year, respectively (Eriksson *et al.*, 2005). More than 15% of children with epilepsy will experience at least one episode of SE (Fountain, 2000). Generalised tonic-clonic seizures (GTCS) are usually short in duration. In the case of a seizure lasting more than 10 minutes, there is a high risk of evolution leading to convulsive

status epilepticus (CSE) (Lowenstein *et al.*, 1999; Eriksson *et al.*, 2005). SE is defined by a seizure duration of longer than 30 minutes and is associated with numerous risks, including mortality (Eriksson *et al.*, 2005). Acute prolonged seizures are typically not self-limited and require treatment. Most acute prolonged seizures do not occur in the hospital, but in different situations of daily life (Alldredge *et al.*, 2001). The incidence of CSE can be reduced by an effective

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treatment in the pre-hospital phase (Eriksson *et al.*, 2005; Chin *et al.*, 2008). Besides the benefit for the patient him/herself, the reduction of hospital admissions can help to save costs (Lee *et al.*, 2013).

Although different forms of effective drugs are available, the question arises as to whether rescue medication should be prescribed to each and every patient with epilepsy. The risk of acute prolonged seizures and CSE varies between different electroclinical syndromes and depends on other individual factors. Many patients may not require a provision of rescue medication because of a very low risk of CSE. Major arguments for not prescribing rescue medication in these cases may be the necessity to reduce costs and the possible negative psychosocial effects for patients. The fact that a patient must carry rescue medication on his person on a daily basis serves to remind patients, and their parents, of the fact that they have epilepsy. The continuous concern may influence the interaction with caregivers, and the psychosocial development of patients may be impaired in cases with an otherwise excellent prognosis.

The epidemiological studies on SE and prognosis in childhood epilepsy typically do not report on acute prolonged seizures, since this is a more recently used term. Therefore, this review focuses on the risk factors for CSE. In summary, careful recommendations are given regarding individual constellations in which there seems to be no necessity of providing rescue medication to a child with epilepsy.

## Sources of evidence and their limitations

Prospective studies that include children with a first unprovoked seizure or new-onset epilepsy are the gold standard. They provide data on risk factors, type, frequency, timing, recurrence, and outcome of SE in patients with epilepsy (Wirrell *et al.*, 1995; Wirrell *et al.*, 1996; Shinnar *et al.*, 1997; Shinnar *et al.*, 2001; Sillanpää and Shinnar, 2002; Berg *et al.*, 2004; Stroink *et al.*, 2007; Callenbach *et al.*, 2009; Camfield and Camfield, 2009; Wirrell *et al.*, 2011; Camfield and Camfield, 2012). Prospective studies that include patients with a first episode of SE of any aetiology provide less convincing information regarding risk factors in patients with pre-existing epilepsy (DeLorenzo *et al.*, 1995; Cascino *et al.*, 1998; Chin *et al.*, 2006; Hesdorffer *et al.*, 2007). However, risk factors for recurrence and outcome can also be analysed appropriately using these types of studies. At a lower level of evidence, important information arises from retrospective studies that usually include hospital-based cohorts with SE or different types of epilepsy (Loiseau *et al.*, 1983; Deonna *et al.*, 1986; Loiseau *et al.*, 1995;

Ferrie *et al.*, 1997; Novak *et al.*, 1997; Caraballo *et al.*, 2000; Genton *et al.*, 2001; Larch *et al.*, 2009).

Prospective studies on the prognosis of childhood epilepsies and SE frequently do not differentiate between various forms of SE, *i.e.* CSE, non-convulsive SE (NCSE), myoclonic SE (MSE), and others. Of even greater importance is the fact that electroclinical syndromes are usually not discriminated. There is a lack of information regarding the time of occurrence of SE in relation to antiepileptic treatment. SE may occur before initiation of treatment, under continuous treatment, when changing drugs, or after stopping the therapy. Information about non-compliance, inappropriate medication, or other trigger factors is almost always lacking. Finally, the studies do not provide any information on the usage of rescue medication which may theoretically lower the rate of SE in epilepsy patients. Some of the retrospective studies on patients with specific epileptic syndromes provide more details on these important factors. Therefore, they should be considered when trying to answer the question about the necessity of rescue medication. However, the variation in syndrome definitions constitutes a major shortcoming of all these studies. To give an example, Valentin *et al.* (2007) compared the application of the 1989 ILAE definition of childhood absence epilepsy with the 2005 ILAE Task Force proposal. The more strict criteria of the 2005 proposal allowed the classification of CAE for only 30 of 44 children who had been previously diagnosed with CAE. A difference is presumed regarding prognosis and the risk of generalised tonic-clonic seizures (GTCS).

## Epilepsy in patients with a first SE and SE in patients with epilepsy

About one third of patients who present with a first episode of SE have a history of previous unprovoked seizures or pre-existing epilepsy (Hauser *et al.*, 1997). While Chin *et al.* (2006) found that 7.4% of patients under 15 years of age had an epilepsy diagnosis, this proportion was 38% in patients <16 years in the Richmond population (DeLorenzo *et al.*, 1995). Of the patients with a first unprovoked SE, 25.5% were found to have epilepsy in the Rochester population (Cascino *et al.*, 1998).

Fountain (2000) reported a risk of SE of at least 15%, in patients with epilepsy. In the Connecticut study, SE occurred in 9.1% of children before epilepsy was diagnosed (Berg *et al.*, 1999). After the diagnosis was made, SE occurred in 9.5% (Berg *et al.*, 2004). In patients from the Dutch population, the risk of SE was 9.5% within a five-year follow-up period (Stroink *et al.*, 2007). A higher risk of 27% was reported for the Finish population (Sillanpää and Shinnar, 2002). Camfield and

Camfield reported at least one SE in 20% of otherwise normal children from Nova Scotia with focal epilepsies (2012).

SE is the initial event in 6.5-12% of children presenting with a first unprovoked seizure or a new-onset epilepsy (Shinnar *et al.*, 1990; Hauser *et al.*, 1997; Berg *et al.*, 1999; Shinnar *et al.*, 2001; Berg *et al.*, 2004; Camfield and Camfield, 2012; Stroink *et al.*, 2007). A recurrence of SE can be expected in about one third of the patients (Berg *et al.*, 2004; Stroink *et al.*, 2007).

### Risk factors for SE in children with epilepsy

The most important risk factor for SE is the presence of SE in the past (Shinnar *et al.*, 1996; Novak *et al.*, 1997; Hesdorffer *et al.*, 1998; Shinnar *et al.*, 2001; Sillanpää and Shinnar, 2002; Berg *et al.*, 2004; Stroink *et al.*, 2007). Berg *et al.* reported a cumulative probability of 32% for an episode of SE during eight years of follow-up in patients with a history of prior SE, compared to 7.2% in patients without (Berg *et al.*, 2004). The duration of the second seizure was highly correlated with the duration of the initial event (Shinnar *et al.*, 2001). Of 25 children who initially presented with SE for a duration of  $\geq 30$  minutes, the duration of the second seizure was  $\geq 10$  minutes in 44%,  $\geq 20$  minutes in 36%, and  $\geq 30$  minutes in 24%, respectively.

Other risk factors for SE comprise young age (Shinnar *et al.*, 2001; Sillanpää and Shinnar, 2002; Berg *et al.*, 2004), symptomatic aetiology (Shinnar *et al.*, 1997; Berg *et al.*, 2004; Chin *et al.*, 2006; Stroink *et al.*, 2007), non-idiopathic (cryptogenic) aetiology (Shinnar *et al.*, 1997; Berg *et al.*, 2004; Stroink *et al.*, 2007), history of febrile convulsions (Sillanpää and Shinnar, 2002; Stroink *et al.*, 2007), focal epilepsy (Berg *et al.*, 1999; Sillanpää and Shinnar, 2002), and prior craniotomy (Berg *et al.*, 1999). Although rarely mentioned, non-compliance is presumably another important risk factor (Fountain, 2000).

### Factors associated with a low risk of SE in epilepsy

The risk of SE is low in patients presenting with brief seizures at epilepsy onset (Shinnar, 2007). In 137 cases with an initial seizure duration  $\leq 10$  minutes, the second seizure lasted  $\geq 10$  minutes in 8%,  $\geq 20$  minutes in 4%, and  $\geq 30$  minutes in only 1% (Shinnar *et al.*, 2001). In the event that the first two years pass without SE, the risk of SE decreases markedly (Sillanpää and Shinnar, 2002; Hesdorffer *et al.*, 2007).

The relationship with antiepileptic treatment is another important factor. Stroink *et al.* (2007) observed

a recurrence of SE in 14 of 44 children (34%) within five years of follow-up. However, SE occurred in only 3 patients when the antiepileptic medication was continued unchanged. The antiepileptic medication had not yet been started or had already been stopped in 11 patients at the time of SE.

The risk of SE is much lower in patients with idiopathic epilepsies compared to other aetiologies. In the Dutch study, SE during the five-year follow-up period was observed only in patients with idiopathic epilepsy who had already experienced a SE as the initial event (Stroink *et al.*, 2007). In this cohort, the lowest rate of SE was found in patients with idiopathic epilepsy and without a history of febrile seizures. Comparably, the rate of SE in the Connecticut cohort was the lowest in patients with idiopathic epilepsy (4%) (Berg *et al.*, 2004).

A lower risk of recurrence in idiopathic cases was also found in studies on outcome after a first SE. A recurrence of SE was noted in only 4% of cases with idiopathic aetiology compared to 44% with remote symptomatic and 67% with progressive aetiology (Shinnar *et al.*, 1997).

### CSE in patients with (non-encephalopathic) idiopathic generalised epilepsy (IGE)

Shorvon and Walker reviewed the available data on this topic (2005) and stated: "Convulsive SE is surprisingly uncommon in IGE and much less common than in the secondary generalised or partial epilepsies. This point has been long established, although the older studies, which have given frequency figures, have generally failed to differentiate idiopathic and cryptogenic generalised epilepsies. The true frequency in IGE is, therefore, unclear; however, clinical experience suggests that tonic-clonic status is rare in IGE and also, when it does occur, there is usually a complicating factor such as drug withdrawal".

In a prospective cohort of patients presenting with new-onset epilepsy, 5.9% of the 136 children and adolescents with IGE experienced at least one SE (Berg *et al.*, 2004). The rate was 3.9% in 113 cases without initial SE. In the Dutch study, 3% of 204 children with IGE presented with SE at onset, but none of the remaining 198 patients experienced SE during the five years of follow-up (Stroink *et al.*, 2007). Therefore, the risk of SE appears to be low in IGE without initial presentation of SE.

In children with childhood absence epilepsy (CAE), the rate of patients with GTCS varies between 8 and 25% (Loiseau *et al.*, 1983; Loiseau *et al.*, 1995; Wirrell *et al.*, 1996; Callenbach *et al.*, 2009). In the Nova Scotia cohort, 9.7% of 72 children with CAE presented with

GTCS, and 4 experienced absence SE while on medication (Wirrell *et al.*, 1996). In contrast, this type of status occurred late in the course and after stopping medication in 5 of 6 patients with GTCS in the Dutch study (Callenbach *et al.*, 2009). Loiseau *et al.* (1983) also found that most GTCS in CAE occurred after 5 to 10 years, and the rate was 36% in 90 patients. In another cohort, Loiseau *et al.* (1995) found a difference in risk for GTCS depending on the age at onset of CAE. While the percentage of patients with GTCS was 16.2% in the case of onset under the age of 9 years, it increased to 43.7% in children with onset at 9 or 10 years of age. The total rate of GTCS was 25% in 52 patients. The rate of GTCS is much higher in patients with juvenile absence epilepsy (JAE). GTCS occurred in 79% of 62 patients in a study by Loiseau *et al.* (1995). Two of these patients experienced absence SE. Trinka *et al.* (2004) differentiated pyknoleptic ( $n=81$ ) vs. non-pyknoleptic ( $n=82$ ) absences and found rates of GTCS of 8.5 and 7.4%, respectively. Unfortunately, none of the studies provides information on the duration of GTCS in absence epilepsies. However, although absence SE may complicate CAE, no cases of CSE have been reported in these studies.

Camfield and Camfield (2009) analysed the long-term outcome in 24 patients with juvenile myoclonic epilepsy (JME) from Nova Scotia. All patients had at least one GTCS, since this was an inclusion criterion. The authors stated that at least 90% of patients with JME suffered from GTCS. Eight patients (3%) from this cohort presented with at least one episode of CSE during the 25-year follow-up period. Other studies did not report any cases with CSE with regards to generalised tonic-clonic seizures. Larch *et al.* (2009) noticed myoclonic SE (MSE) in 3% of 247 patients. The rate of patients with NCSE was 5.8 to 6.7% in other reports (Agathonikou *et al.*, 1998; Dziewas *et al.*, 2002). There is a belief that in JME, SE of any form is clearly associated with sleep deprivation, AED withdrawal, or inappropriate treatment (Genton *et al.*, 2000; Shorvon and Walker, 2005; Baykan *et al.*, 2013; Crespel *et al.*, 2013). Inappropriate treatment with carbamazepine, phenytoin, vigabatrin, or gabapentin can be the cause of SE in different forms of IGE (Panayiotopoulos *et al.*, 1997; Genton *et al.*, 2000; Dziewas *et al.*, 2002; Thomas *et al.*, 2006; Larch *et al.*, 2009).

### CSE in patients with idiopathic focal epilepsy

Deonna *et al.* (1986) reported on 107 neurologically normal children with partial epilepsy who were included in a retrospective, hospital-based study. Benign focal epilepsy was only diagnosed in patients with simple partial seizures that clinically presented

with a Sylvian onset (or component) or sensorimotor symptoms ( $n=38$ ). Patients with complex partial seizures were subsumed in a different group ( $n=31$ ). In 4 patients, the diagnosis of benign focal epilepsy was based only on the clinical symptoms, since the waking EEG showed non-specific pathology and no sleep recordings were available. Severe seizures were defined as SE and prolonged seizures with a duration >15 minutes or clusters, and these occurred in 24% of the 38 children, including 11% who presented with SE. The authors stated that, despite therapy, severe seizures occurred in one third of the patients. It remained unclear whether severe seizures were focal or secondary generalised, and whether the 4 patients with only non-specific EEG changes were affected. However, the general prognosis in this group was excellent for all patients, and only one child continued to have seizures after the age of 15 years. Berg *et al.* (2004) could not identify even a single patient with SE out of a group of 66 children with idiopathic partial epilepsy. The results from the Dutch cohort were similar, with no case of SE reported in 30 children with idiopathic localisation-related epilepsy (Stroink *et al.*, 2007). SE occurred in 3 of 42 children with Rolandic epilepsy from the Nova Scotia cohort (Wirrell *et al.*, 1995). However, atypical features were present in 2 of the children. Developmental delay was found in one child; the other presented with an abnormal EEG background activity and seizures which occurred only during the daytime. No information was provided regarding the relationship to time of diagnosis and antiepileptic treatment. The same group reported another study of 79 patients with Rolandic epilepsy (Peters *et al.*, 2001). Whereas 36 patients (46%) were not treated with antiepileptic drugs at any time, 43 (54%) were treated with antiepileptic drugs. The initial therapy was comprised of carbamazepine in 82%, phenobarbital in 12%, and clobazam in 7%. The treatment was changed in 28% of the patients. The rate of GTCS was 50% in the group without treatment, compared to 16% in treated patients. CSE was observed in only one case that was not treated with antiepileptic drugs. However, the long-term prognosis was excellent in both groups as well as in the patient with SE. In summary, CSE is a rare event in patients with classic Rolandic epilepsy. This appears to be particularly true for children treated with antiepileptic drugs.

The situation is completely different for children with Panayiotopoulos syndrome (PS), for whom the risk of CSE is high. In 113 children recruited from multiple centres, partial SE occurred in 44% (Ferrie *et al.*, 1997). An evolution with secondary generalisation (CSE) was observed in 16%. A prospective study from Argentina showed similar results (Caraballo *et al.*, 2000); 20 of 66 patients presented with partial SE, which led to secondary generalisation and evolved to CSE in 25%.

## SE in cryptogenic focal epilepsy

Wirrell *et al.* (2011) compared the outcome of 111 children with cryptogenic partial epilepsy (normal cognition in 66%, mildly delayed in 24%, and severely delayed in 10%) with 95 patients suffering from symptomatic partial epilepsy. Of the children with cryptogenic partial epilepsy, 14% initially presented with SE. After diagnosis, a first SE was observed in only 3.1% of the remaining patients. In contrast, 28% of the children with symptomatic partial epilepsy initially presented with SE, and a first SE during follow-up occurred in 43% of the remaining patients.

Camfield and Camfield (2012) identified 188 children under the age of 16 years with both normal IQ and neurological status, including 23 patients with Rolandic epilepsy. SE occurred in 39 patients, of whom 19 presented with an initial SE at the time of diagnosis. Twelve patients experienced multiple (2 to 10) episodes with SE. Of the 39 otherwise normal children with complex partial seizures reported by Deonna *et al.* (1986), 46% suffered from "severe seizures" (8% SE, 8% clusters, and 33% prolonged seizures >15 minutes). The rate of "severe seizures" in 36% was not significantly different in children with non-Rolandic simple partial seizures (12% SE, 16% clusters, and 16% prolonged seizures). However, the aetiologies in otherwise normal children with partial epilepsy were not reported for these studies and patients with structural lesions may have been included.

Stroink *et al.* (2007) identified initial presentation with SE in 15/70 patients (21.4%) with cryptogenic partial epilepsy in the Dutch study. A first SE occurred in only 2 of the remaining 55 children after a diagnosis of epilepsy had been established (3.6%). Berg *et al.* (2004) reported an initial SE in 7.7% of 221 children with cryptogenic partial epilepsy, and the first SE followed diagnosis in 7% of the remaining 199 cases.

Altogether, the incidence of SE in patients with cryptogenic partial epilepsy, or otherwise normal children with partial epilepsy, remains unclear.

## Conclusion

The question as to whether or not rescue medication should be prescribed for an individual patient depends on many factors. The risk of experiencing acute prolonged seizures and SE obviously influences this decision. This risk is low in children and adolescents with appropriately treated CAE or JME. Patients with

classic Rolandic epilepsy may not need rescue medication. The risk of SE is uncertain in otherwise normal children with partial epilepsy of unknown aetiology. However, it seems to be low in children who are seizure-free under continuous antiepileptic treatment and who have no history of previous SE.

Since even the rare event of a CSE may harm the individual patient, it is not possible to give a general recommendation for or against rescue medication based only on the syndrome diagnosis. The given infrastructure, such as the availability of ambulant emergency care and the distance to the next emergency room, is of great importance. The number of involved caregivers (for example, teachers) and their role in daily life may be important, since all of them should be advised on when and how to administer rescue medication to an individual child. Most importantly, the willingness of the properly-informed family itself is critical. Rescue medication may even be prescribed to a child with a very low risk of CSE. On the other hand, it may not be prescribed to another child with a comparably higher risk, whose parents may be less anxious and live close to the nearest emergency facility.

The most important risk factor for SE is the history of a previous event. Therefore, rescue medication is recommended for this subgroup of patients independent of the epilepsy syndrome.

Based on the available data, the following statements can be made:

- the risk of SE is low in patients who experienced initially brief seizures;
- most episodes of SE occur at epilepsy onset and within the first two years after diagnosis;
- the longer a patient lives without SE, the lower is the risk of experiencing SE;
- the risk of SE is low with continuous, appropriate and successful medication;
- the risk of SE is low in idiopathic generalised epilepsies. In appropriately-treated CAE and JME, the risk is very low;
- the risk of harmful CSE is very low in Rolandic epilepsy. In contrast, Panayiotopoulos syndrome frequently presents with CSE;
- the risk of CSE is uncertain in patients with cryptogenic partial epilepsies. However, it is much lower when compared in patients with symptomatic partial epilepsy. □

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