

Syndromes at risk of status epilepticus in children: genetic and pathophysiological issues

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ABSTRACT – Status epilepticus (SE) is a medical emergency with increased risk of morbidity and mortality in all age groups. Recent research has identified a variety of new genes implicated in disorders with severe epilepsies as a prominent feature. Autoimmune mechanisms have also been recently recognised as a cause of epilepsies with SE as a characteristic symptom. Knowledge about the aetiology potentially underlying SE may help to guide diagnostics and eventually influence treatment decisions. This review recapitulates, in brief, the risk of SE in specific clinical settings, provides an overview of paediatric epilepsy syndromes more commonly, or by definition, associated with SE, and summarizes some recent research data on genetic defects and disease mechanisms implicated in the pathogenesis of epilepsies frequently accompanied by SE.

Key words: status epilepticus, prolonged seizures, childhood, etiology, classification, genetics

Status epilepticus (SE) is a medical emergency with increased risk of morbidity and mortality in all age groups. The glossary of descriptive terminology for ictal semiology by the International League Against Epilepsy (ILAE) defines SE as either a seizure which shows no clinical signs of terminating after a period of time corresponding to the duration of the great majority of seizures of that type in most patients, or recurrent seizures without resumption of baseline central nervous system function interictally (www.ilae.org/Visitors/Centre/ctf/glossary.cfm). Traditionally, SE has been defined as a seizure or series of seizures lasting longer than 30 minutes (Berg *et al.*, 2004), while the term “prolonged seizures” has been

used by several authors with slightly different definitions for seizures lasting more than five, but less than 30 minutes (Shinnar, 2007). It has been proposed using more recent guidelines that seizures lasting for 5 minutes or more are classified as SE, as most seizures last less than 5 minutes; seizures that last longer often do not cease spontaneously and irreversible neuronal damage and pharmacoresistance may occur within 30 minutes of seizure activity (Brophy *et al.*, 2012). However, this view is still a matter of debate (Shinnar *et al.*, 2001; Beran, 2008). In this review, we will adopt the traditional SE definition, whereas seizures lasting for more than 5, but less than 30, minutes will be connoted as prolonged seizures.

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Generalised convulsive SE is characterised by rhythmic jerking of all extremities and profound mental impairment (Brophy *et al.*, 2012). Epilepsia partialis continua can be delineated from this form of status, since motor epileptic seizures are restricted to certain parts of the body (e.g. face, hands) and recur every few seconds or minutes for extended periods (more than one hour) (Cockerell *et al.*, 1996; Bien and Elger, 2008). The term non-convulsive SE describes continuous seizure activity observed on electroencephalography (EEG), but without clinical findings associated with generalised convulsive SE (Brophy *et al.*, 2012). In this form of status, seizure symptomatology is usually subtle and the semiological spectrum highly variable (Jirsch and Hirsch, 2007).

Apart from duration and semiology, SE can also be classified by its underlying aetiology. Some epileptic encephalopathies are, by definition, associated with SE, while prolonged seizures or SE are characteristic features of several epilepsy syndromes manifesting during infancy and childhood. New genetic techniques have identified a variety of new genes implicated in disorders with severe epilepsies as a prominent feature (Lemke *et al.*, 2013). Autoimmune mechanisms have been recently recognised as potential causes of epilepsies. In some of these disorders, SE or prolonged seizures represent characteristic clinical symptoms (Davis and Dalmau, 2013).

Data on the recurrence risk of SE is important, since such information may influence therapeutic considerations. Knowledge about the aetiology potentially underlying SE may help to guide diagnostics and eventually influence treatment decisions. This review recapitulates, in brief, the risk of SE in specific clinical settings, provides an overview about paediatric epilepsy syndromes associated with SE, and summarizes some recent research data on genetic defects and disease mechanisms implicated in epilepsies frequently accompanied by SE.

Risk of SE and/or prolonged seizures in specific clinical settings

Risk of SE and prolonged seizures in children with febrile convulsions

More than 25% of children with febrile convulsions will experience at least one prolonged seizure lasting longer than 10-15 minutes. Febrile seizures with focal onset show a tendency to be prolonged (Berg *et al.*, 1990). Recent results of the FEBSTAT study team revealed further factors that increase the risk of prolonged febrile convulsion and febrile SE: a preceding febrile convulsion occurring at an unusually young age (<12 months), low tempera-

ture, longer duration of fever, female sex, a positive first-degree family history of febrile convulsions, and structural temporal lobe abnormalities (Hessdorfer *et al.*, 2013).

Risk of SE and prolonged seizures in children with a first unprovoked seizure

In a prospective study by Shinnar and colleagues encompassing 407 patients, the first seizure lasted 5 minutes or more in 50%, 10 minutes or longer in 29%, more than 20 minutes in 16%, and 30 minutes or longer in 12% of cases. Seizures of partial onset had an increased tendency to be prolonged, compared to generalised seizures (20% vs. 6% with seizures >30 minutes, respectively) (Shinnar *et al.*, 1990; Shinnar *et al.*, 1996; Shinnar *et al.*, 2000; Shinnar *et al.*, 2001; Shinnar, 2007). Aetiology and age were not factors influencing seizure duration. Altogether, the authors concluded that two distinct subgroups of patients exist. One group, comprising about 75% of children, has seizures of short duration, while the other, consisting of approximately 25% of patients, shows a propensity for prolonged seizures. Mean seizure duration in the latter group was 30 minutes. Notably, the recurrence risk of seizures was not influenced by the duration of the first unprovoked seizure, although subjects with prolonged first seizures were more likely to suffer further prolonged seizures (Shinnar, 2007).

Risk of SE in children with new-onset epilepsy

A population-based study from Finland in which 150 children with new-onset epilepsy for more than 30 years were followed, found that 27% of these patients suffered at least one SE. Of these children, 90% presented with a status within the first two years, and 73% within the first year after the diagnosis of epilepsy was established (Sillanpää and Shinnar, 2002). Risk factors for SE included young age and remote symptomatic aetiology. In children with a preceding SE, the risk of further prolonged seizures was increased by about 50%. Of note, the occurrence of a SE did not negatively affect the long-term prognosis of affected individuals (Sillanpää and Shinnar, 2002).

Epileptic encephalopathies with propensity for prolonged seizures or SE

Early myoclonic encephalopathy (EME)

EME is a rare epileptic entity with neonatal onset. Erratic and massive generalised or focal myoclonus in developing parts of the body is the clinical hallmark.

Persisting myoclonus during sleep is also characteristic. The jerks are extremely frequent and may even be continuous. Typically, the EEG shows a suppression-burst pattern. The aetiology is heterogeneous. Many patients suffer from autosomal recessive metabolic defects, such as non-ketotic hyperglycinaemia. Some authors count the Hanefeld variant of Rett syndrome with early-onset seizures amongst this entity. Partial seizures and spasms are observed during the later part of the course. Prognosis is dismal (Pavone *et al.*, 2012).

Early infantile epileptic encephalopathy (EIEE or Ohtahara syndrome)

EIEE is mainly caused by cortical malformations and, less frequently, by metabolic disorders. In some cases, defects in the *ARX*- or *STXBP1* genes may be detected (*table 1*). Single or serial tonic seizures, focal motor seizures, and generalised tonic-clonic seizures prevail. Single spasms last up to 10 seconds, and the intervals between spasms range from 9 to 15 seconds. As in EME, background EEG is characterised by a suppression-burst pattern. Surviving infants are usually quadriplegic and present with severe intellectual disability (Ohtahara and Yamatogi, 2003; Beal *et al.*, 2012).

West syndrome

West syndrome is characterised by the clinical triad of infantile spasms, developmental regression, and hypsarrhythmia. Spasms, lasting 2-5 seconds may occur in clusters of up to 100 every 5-30 seconds (Plouin *et al.*, 1993). Tuberous sclerosis, congenital or acquired cerebral lesions, congenital infections, and rarely metabolic disorders are causative (Paciorkowski *et al.*, 2011). Recently, genetic defects in the genes *ARX*, *CDKL5*, *SCN8A*, *STXBP1*, *DNM1*, and *GABRB3* have been reported in some of the patients (*table 1*).

Malignant migrating partial seizures in infancy

The disease manifests from the first week of life to seven months of age. After an initial period lasting from a few days to months with relatively rare partial seizures that frequently have a motor or tonic component, seizure frequency dramatically increases and ictal semiology becomes highly polymorphous (Hahn *et al.*, 2007). Typically, duration of seizures is between one and four minutes, but in some patients they may last significantly longer and evolve into tonic status epilepticus (Coppola, 2009). With time, head growth becomes arrested. Over the years, the epilepsy wanes. In some cases, retigabine has been

surprisingly effective for some time. Defects in *KCNT1* are detectable in about 50% of cases (Barcia *et al.*, 2012) (*table 1*).

Dravet syndrome (or severe myoclonic epilepsy of infancy)

Dravet syndrome is characterised by onset of seizures in a febrile context within the first year of life in hitherto normally developed children. Prolonged unilateral seizures, often alternating in side, are generally the first type of seizures encountered. Frequent febrile status, myoclonic seizures, atypical absences, and later also focal seizures are characteristic. Valproate, topiramate, benzodiazepines, bromides, stiripentol, and a ketogenic diet are effective. However, save for rare exceptions, children do not become seizure-free for longer periods. Defects in *SCN1A* (up to 85% of cases), *SCN1B*, *SCN2A*, *PCDH19* and recently *CHD2* have been detected (Suls *et al.*, 2013).

Lennox-Gastaut syndrome (LGS)

LGS frequently follows West syndrome or other infantile epileptic encephalopathies. In many cases, cortical malformations are detectable. Atypical absences, sometimes lasting hours, non-convulsive status epilepticus, and tonic status epilepticus are common features. Defects in the genes *SCN8A*, *STXBP1*, *DNM1*, and *GABRB3* were recently recognised in some “idiopathic” cases with and without preceding West syndrome (Epi4K Consortium, 2013).

Continuous spike and waves during slow-wave sleep and related encephalopathies

Atypical benign partial epilepsy (ABPE) is defined by seizures evocative of benign epilepsy with centro-temporal spikes (BECTS) in conjunction with atonic seizures and atypical absences. The EEG shows focal sharp waves as in BECTS, but with exceptional pronounced activation during sleep. Generalised seizures tend to be prolonged and may last for hours or days. A status of atypical absences/and or subtle myoclonic atonic seizures has been reported in up to 40% of children. As in BECTS, prognosis with respect to epilepsy is usually favourable, but some patients may be left with persistent mental deficits (Hahn, 2000).

Patients with epileptic encephalopathy and continuous spike and waves during slow sleep (CSWS) typically have relatively rare, mainly nocturnal, seizures in combination with a continuous bioelectrical status recorded on EEG due to drowsiness throughout all non-REM sleep stages. Major neurocognitive deficits

Table 1. Targets for genetic workup in children with prolonged seizures or status epilepticus.

<i>ADSL</i>	Adenylosuccinate lyase deficiency is a rare cause of a severe epileptic encephalopathy starting within the first few days of life. Therapy resistance and SE are common (Jurecka <i>et al.</i> , 2008).
<i>ALDH7A1</i>	Mutations result in pyridoxine-dependent seizures. Affected children usually present with SE early after birth, but sometimes distinctly later (Oliveira <i>et al.</i> , 2013).
<i>ARX</i>	Defects are associated with a variety of cortical malformations (e.g. lissencephaly), additional organ manifestations, and intractable neonatal seizures in boys (Mirzaa <i>et al.</i> , 2013).
<i>FOLR1</i>	Folate receptor defects are associated with neurological regression, movement disorder, hypomyelination on MRI and sometimes severe epilepsy. The disorder is rare, but potentially treatable (Steinfeld <i>et al.</i> , 2009).
<i>FOXP1</i>	Mutations, deletions, or duplications may produce a congenital form of Rett syndrome in females and also in males, sometimes associated with severe epilepsy or atypical West syndrome (Guerrini and Parrini, 2012).
<i>GABRG2</i>	Deleterious defects may result in Dravet syndrome, while missense mutations cause milder phenotypes within the spectrum of idiopathic generalised epilepsies (Huang <i>et al.</i> , 2012).
<i>GAMT</i>	Cerebral creatine deficiency syndrome due to GAMT deficiency may result in epileptic encephalopathies including Lennox Gastaut syndrome. The disorder is partially treatable (Mikati <i>et al.</i> , 2013).
<i>GRIN2A</i>	Mutations are related to a spectrum of epilepsies ranging from Rolandic epilepsy to Landau-Kleffner syndrome or CSWS (Lesca <i>et al.</i> , 2013; Lemke <i>et al.</i> , 2013; Dimassi <i>et al.</i> , 2014).
<i>KCNQ2</i>	Dysfunction of this ion channel causes benign familial neonatal seizures. Recent research revealed that the phenotype is much broader, and that defects in this gene accounts for about 10-15% of neonatal epileptic encephalopathies (Weckhuysen <i>et al.</i> , 2013).
<i>KCNT1</i>	Defects result in malignant migrating partial seizures in infancy or severe autosomal dominant frontal lobe epilepsy (Barcia <i>et al.</i> , 2012).
<i>KCTD7</i>	Mutations cause an autosomal recessive progressive myoclonus epilepsy of early childhood onset with refractory epilepsy (Van Bogaert <i>et al.</i> , 2007).
<i>PLCB1</i>	Homozygous defects are a rare cause of malignant migrating partial seizures in infancy (Poduri <i>et al.</i> , 2012).
<i>PNKP</i>	The gene product is implicated in a DNA repair mechanism. Recessive mutations result in microcephaly, early-onset intractable seizures, and developmental delay (Shen <i>et al.</i> , 2010).
<i>TREX1</i> <i>RNASEH2A</i> <i>RNASEH2B</i> <i>RNASEH2C</i> <i>SAMHD1</i>	Defects in these genes account for the majority of cases with Aicardi-Goutières syndrome (Aicardi <i>et al.</i> , 1993-2013).
<i>SCN1A+B</i> <i>SCN2A</i> <i>SCN8A+9A</i> <i>CHD2</i> <i>SYNGAP1</i>	Mutations in one these genes may lead to infantile epileptic encephalopathies which range from Dravet syndrome to Ohtahara syndrome (Carvill <i>et al.</i> , 2013).
<i>PLCB1</i> <i>SLC25A22</i>	Defects may result in infantile epileptic encephalopathy with suppression-burst pattern on EEG (Pavone <i>et al.</i> , 2012).
<i>SPTAN1</i>	Mutations may cause West syndrome with cerebral hypomyelination (Saitou <i>et al.</i> , 2010).

are frequent. In some patients with acquired epileptic aphasia (Landau-Kleffner syndrome), seizures reminiscent of BECTS are observed, while the EEG pattern during sleep frequently parallels the continuous spike-wave activity recorded in CSWS (Dalla Bernadina *et al.*, 2002). Recently, mutations in the gene *GRIN2A*, encoding the $\alpha 2$ subunit of the *N*-methyl-D-aspartate (NMDA)-selective glutamate receptor, have been reported in patients affected by BECTS, ABPE, LKS, and CSWS (Lemke *et al.*, 2013; Lesca *et al.*, 2013; Dimassi *et al.*, 2014).

Autoimmune-mediated encephalopathies

Autoimmune mechanisms are increasingly recognised to play a causative role in the development of epilepsy in adults and children. Antibodies can be directed against intracellular structures or neuronal surface antigens. Autoimmune encephalopathies may manifest without underlying malignancies or present as paraneoplastic syndromes. In encephalopathies with paraneoplastic aetiology, anti-Hu antibodies are frequently associated with seizures, epilepsy partialis continua, and SE (Davis and Dalmau, 2013). Antibodies directed to the GABA(B) receptor are observed in cases with limbic encephalitis with early and prominent seizures (Lancaster *et al.*, 2010). About 70% of patients with antibodies directed against the NR1 subunit of the *N*-methyl-D-aspartate receptor develop seizures and/or SE. Approximately 40% of cases manifest before the age of 18 years. Seizures or SE are the presenting sign in about 30% of these children. An underlying ovarian teratoma is detected in 50% of female patients older than age 12 years. Steroids, immunoglobulin, plasma exchange, and tumour removal, if indicated, are recommended as first-line therapies. Recovery is slow and may take many months, but most patients remain free of seizures (Davis and Dalmau, 2013).

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), formerly named Hashimoto's encephalopathy, may manifest acutely or insidiously with impairment of consciousness, frequently evolving into coma. The disease also occurs in children. Patients may show a variety of additional neurological and/or psychiatric symptoms. Seizures and SE complicate the course in about 70-90% of subjects (Castillo *et al.*, 2006).

Rasmussen encephalitis is a rare and severe immune-mediated brain disorder that results in unilateral hemispheric atrophy with progressive neurological dysfunction and intractable seizures. Typically, seizures start during childhood, and difficult-to-treat focal motor seizures or epilepsy partialis continua are a constant feature of the disease. Hemispherectomy is still the only effective therapy, achieving seizure freedom in 62.5 to 85% of patients (Bien *et al.*, 2005).

Hemiconvulsion-hemiplegia-epilepsy syndrome (HHE) and febrile infection-related epilepsy syndrome (FIRES)

HHE and FIRES are rare childhood epilepsy syndromes that share an occurrence of refractory SE during or after fever, without evidence of central nervous system infection (Nabbout, 2013).

HHE is characterised by definitive hemiparesis following a prolonged unilateral febrile seizure in children usually before four years of age. Epilepsy, often of a complex-partial type, sets in a few months later, and cognitive sequelae are frequent. Longitudinal neuroimaging demonstrates unilateral cerebral swelling, increased signal intensity on T2 weighted images, and decreased water diffusion in DWI within the first two weeks after the febrile convulsion. Such alterations resolve by 3-4 weeks, when an extensive and progressive cortical and subcortical atrophy becomes obvious (Welcker *et al.*, 2013).

FIRES is characterized by the development of seizures in healthy children during or a few days after a non-specific febrile infection. Seizures rapidly worsen and evolve into status epilepticus, followed by pharmacoresistant epilepsy and severe mental deficits (van Baalen *et al.*, 2010).

The pathogenesis of HHE and FIRES has not been resolved, but it has been hypothesized that both entities share a common pathophysiology based on a vicious cycle in which inflammation-induced seizures evolve into status, which then enhances inflammatory pathways and ensures that they remain active (Nabbout *et al.*, 2011; Nabbout, 2013).

Recent genetic findings in epilepsies associated with prolonged seizures and SE

Whole-exome sequencing, single nucleotide array analysis, and gene panel diagnostics are new powerful techniques that have facilitated our understanding of the genetics of epilepsies manifesting in childhood (Lemke *et al.*, 2013). Application of these methods has broadened the phenotypic spectrum of some epilepsy syndromes, and has identified new genes involved in their pathogenesis. *Table 1* summarizes some recently identified genes related to more severe forms of epilepsy. □

Disclosures.

None of the authors has any conflict of interests to declare.

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