Prolonged Epileptic Seizures: identification and treatment

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What is more harmful, seizures or epileptic EEG abnormalities? Is there any clinical data?

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ABSTRACT – Cognitive impairment is a common and often devastating co-morbidity of childhood epilepsy. While the aetiology of the epilepsy is a critical determinant of cognitive outcome, there is considerable evidence from both rodent and human studies that indicate that seizures and interictal epileptiform abnormalities can contribute to cognitive impairment. A critical feature of childhood epilepsy is that the seizures and epileptiform activity occur in a brain with developing, plastic neuronal circuits. The consequences of seizures and interictal epileptiform activity in the developing brain differ from similar paroxysmal events occurring in the relatively fixed circuitry of the mature brain. In animals, it is possible to study interictal spikes independently from seizures, and it has been demonstrated that interictal spikes are as detrimental as seizures during brain development. In the clinic, distinguishing the differences between interictal spikes and seizures is more difficult, since both typically occur together. However, both seizures and interictal spikes result in transient cognitive impairment. Recurrent seizures, particularly when frequent, can lead to cognitive regression. While the clinical data linking interictal spikes to persistent cognitive impairment is limited, interictal spikes occurring during the formation and stabilization of neuronal circuits likely contribute to aberrant connectivity. There is insufficient clinical literature to indicate whether interictal spikes are more detrimental than seizures during brain development.

Key words: interictal spikes, cognition, learning, memory

Cognitive impairment is a devastating co-morbidity of childhood epilepsy. Many parents and clinicians consider the cognitive impairment associated with childhood epilepsy to be far more impairing than the seizures. While the primary determinant of cognitive outcome in childhood epilepsy is aetiology, there is increasing evidence that seizures and interictal EEG abnormalities contribute to cognitive impairment. A critical question is which is more detrimental, the seizures or the interictal abnormalities? Answering this question is fundamental to our therapeutic approach to children with epilepsy.

It is often difficult to differentiate the adverse cognitive effects of interictal spikes (IIS) from those of seizures since typically they occur together. Additionally, teasing out the effects of the seizures and IIS from the aetiology can be difficult. In animal studies, one can induce

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seizures, IIS, or both, in the normal brain, allowing investigation into the biological mechanisms underpinning cognitive impairment due to seizures or IIS. For the most part, in animals studies of recurrent seizures, the seizures are brief (<5 minutes in duration). In this review, pertinent animal data will first be briefly discussed laying the groundwork for the human studies.

Animal data

Recurrent seizures

There is now a substantial literature showing that recurrent seizures in the developing brain can result in long-term adverse consequences. Rat pups subjected to a series of recurrent brief seizures during the first weeks of life have considerable cognitive impairment including deficits of spatial cognition based on the Morris water maze (Holmes *et al*., 1998; Huang *et al*., 1999; Liu *et al*., 1999; Karnam *et al*., 2009a; Karnam *et al*., 2009b) and delayed non-match-to-sample task, a spatial memory test in which animals have to remember which of two levers to press to obtain a food award (Kleen *et al*., 2011a), impairment of auditory discrimination (Neill *et al*., 1996), altered activity level (Karnam *et al*., 2009a), and reduced behavioural flexibility (Kleen *et al*., 2011b). Recurrent early-life seizures also result in a number of physiological changes including a persistent decrease in GABA currents in the hippocampus (Isaeva *et al*., 2006) and neocortex (Isaeva *et al*., 2009), enhanced excitation in the neocortex (Isaeva *et al*., 2010), impairment in spike frequency adaptation (Villeneuve *et al*., 2000), marked reductions in after-hyperpolarising potentials following spike trains (Villeneuve *et al*., 2000), impaired long-term potentiation (LTP) (Karnam *et al*., 2009a), enhanced short-term plasticity (Hernan *et al*., 2013), alterations in theta power (Karnam *et al*., 2009b), and impaired place cell coherence and stability (Karnam *et al*., 2009b).

Despite the detrimental effects of early-life seizures on cognitive function, recurrent brief seizures during the first two weeks of life do not result in cell loss (Holmes *et al*., 1998; Liu *et al*., 1999; Riviello *et al*., 2002). However, seizures in immature rats can result in synaptic reorganisation, as evidenced by CA3 sprouting (Holmes *et al*., 1998; Huang *et al*., 1999; Sogawa *et al*., 2001; Huang *et al*., 2002) and decreased neurogenesis (McCabe *et al*., 2001).

To determine the relationship between age at seizure onset and cognitive outcome, Karnam *et al*. (2009a) induced 50 brief seizures using flurothyl, an inhaled convulsant, in rat pups between postnatal day (P) P0-10 or P15-P25. The seizures in the rats were characterised by clonic activity followed by tonic extension with a total duration of <5 minutes. Rats were studied as adults in the Morris water maze, radial-arm water maze, open field, and active avoidance test. To assess synaptic strength and network excitatory and inhibitory function, animals were evaluated with long-term potentiation (LTP) and paired-pulse facilitation/inhibition. Compared to controls, both groups of rats with recurrent seizures were impaired in spatial memory in both water maze tests and had altered activity in the open field. Rats with recurrent flurothyl seizures had impaired LTP but showed no deficits in paired-pulse facilitation or inhibition. The cognitive deficits did not vary as a function of age during which time the seizures occurred.

Whereas recurrent brief flurothyl-induced seizures in immature rats result in cognitive impairment, recurrent seizures in adult animals, in which the neuronal circuitry is relatively fixed, appears to result in fewer deficits. Investigators have examined the effect of kindling on spatial memory in animals which were studied after or during kindling using both the radial arm maze and water maze. The timing of the kindling stimulations determines type of deficit. If the kindling stimulation is given prior to the learning trial there is impaired performance (McNamara *et al*., 1992; Robinson *et al*., 1993; Gilbert *et al*., 2000), whereas kindling immediately after the learning trial impaired retention (Gilbert *et al*., 1996). Whether kindling has long-term effects on learning is not clear; some authors report impairment following hippocampal kindling (Leung *et al*., 1990; Leung and Shen, 1991) while other authors report no long-standing effects (McNamara *et al*., 1992). While Lin *et al*. (2009) found that recurrent flurothyl-induced seizures over 11 days in adult rats lead to progressive impairment in a spatial hidden goal task, full recovery did occur.

In the majority of studies, recurrent seizures have been induced in normal rats. However, in children, seizures do not occur in the "normal brain". The assumption that seizures induced in the normal and pathological brain have similar effects may be erroneous. Lucas *et al*. (2011) found that seizures induced in rat pups with malformations of cortical development, but without seizures, had severe spatial cognitive deficits based on the water maze. When the rat pups were subjected to recurrent flurothyl-induced seizures and tested at 25 days of age (immediate post-weaning), there was a worsening of performance. In contrast, in animals tested during adolescence, there was no longer an additional adverse effect of seizures. The authors also investigated whether the severity of the structural abnormality and seizures impacted brain weight, cortical thickness, hippocampal area, and cell dispersion area. Early-life brief seizures did not have a significant impact on any of these parameters. These

observations indicate that the major factor responsible for the cognitive impairment in the rats with cortical dysplasia was the underlying brain substrate, not the seizures.

Interictal spikes

In adult rats, IIS have been shown to result in task-specific cognitive impairment. Using a within-subject analysis to analyse how IIS might independently affect memory processing in the hippocampus, Kleen *et al*. (2010) studied rats that developed chronic IIS following intrahippocampal pilocarpine in a hippocampal-dependent operant behaviour task, the delayed match-to-sample test. Hippocampal IIS that occurred during memory retrieval strongly impaired performance. However, IIS that occurred during memory encoding or memory maintenance did not affect performance in those trials. IIS were most dysfunctional when hippocampal function was critical, during the active engagement of neurons involved in performing the task.

Single-cell firing patterns have been investigated following IIS in mature rodents. There is a sustained reduction of action potentials in the hippocampus for up to two seconds following IIS. Furthermore, when occurring in flurries, IIS can reduce action potential firing for up to six seconds (Zhou *et al*., 2007). The widespread inhibitory wave immediately after IIS can also reduce the power of gamma oscillations and other oscillatory signals in the hippocampus (Urrestarazu *et al*., 2006). Since oscillations are closely coupled with ongoing learning and memory function (Halasz *et al*., 2005), this disruption in oscillations likely contributes to cognitive deficits.

In addition to causing transitory cognitive impairment, IIS during early brain development may have long-term adverse effects on the developing neural circuits. In studies of the effects of IIS on network development, IIS were elicited by either penicillin (Baumbach and Chow, 1981; Crabtree *et al*., 1981) or bicuculline (Ostrach *et al*., 1984; Campbell *et al*., 1984) through focal application on the striate cortex of rabbits. IIS were elicited for 6-12 hours following each drug application which was given daily from P8-9 to P24-30. Despite frequent IIS, none of the rabbits had behavioural seizures. In single-unit recordings from the lateral geniculate nucleus, superior colliculus, and occipital cortex ipsilateral to the hemisphere with IIS, there was an abnormal distribution of receptive field types, whereas normal recordings were found from the contralateral hemisphere. Remarkably, this finding was age-dependent. Adult rabbits with similarly induced IIS during adulthood had normal disruption of receptive field types, highlighting an additional vulnerability of critical developmental periods to cumulative IIS effects over time.

To determine the long-term effects of IIS on executive function, Hernan *et al*. (2014) studied the effects of IIS in the prefrontal cortex. P21 rat pups received intracortical injections of bicuculline into the prefrontal cortex while the EEG was continuously recorded and the animals were tested as adults for short-term plasticity. At the time the adults were tested, IIS were no longer present. IIS resulted in a significant alteration in short-term plasticity bilaterally in the prefrontal cortex. In a delayed non-match-to-sample task, the rats showed marked inattentiveness without deficits in working memory. Rats also demonstrated deficits in sociability, showing autism-like behaviour. The study showed that early-life focal IIS in the prefrontal cortex have long-term consequences for cognition and behaviour at a time when IIS are no longer present. This study also showed that focal IIS during development can disrupt neural networks, leading to long-term deficits and thus may have important implications in attention deficit disorder and autism.

Generalised and multifocal IIS have also been elicited in young rats with flurothyl (Khan *et al*., 2010). Rat pups were given a low dose of flurothyl for four hours for a period of ten days during continuous EEG monitoring. Rats developed IIS without seizures while age-matched controls under similar testing conditions showed few IIS. When rats were tested as adults, there was impairment in reference memory in the probe test of the Morris water maze, reference memory impairment in the four-trial radial-arm water maze, and impaired LTP. Early-life IIS also resulted in impaired new cell formation and decreased cell counts in the hippocampus, indicating a potential mechanism in which IIS during development can produce cumulative lasting effects in addition to any dynamic disruptions.

Lessons from the animal data

Animal data indicates that recurrent seizures and IIS can result in adverse effects on cognition. Both seizures and IIS can result in transient cognitive impairment. In the case of seizures, the transient cognitive impairment occurs during the seizure and postictal period, whereas IIS specifically alters the neural circuits involved in that process, stressing the importance of matching the affected neural substrate with a cognitive test that assesses its intrinsic function. The IIS must occur at a particular moment in cognitive processing such that the process is vulnerable to disruption.

Both seizures and IIS in the immature brain can have permanent adverse effects on cognition that extend

well beyond the time when the seizures and IIS have stopped. Both seizures and IIS appear to be deleterious when they occur in the developing brain, relative to the fully mature neural network.

Human data

Seizures

Animal data would predict that recurrent seizures in the immature brain, particularly if very frequent, would result in cognitive impairment. This appears to be the case in children. In general, childhood epilepsy carries a significant risk for a variety of problems involving cognition. The distribution of IQ scores of children with epilepsy is skewed toward lower values (Farwell *et al*., 1985; Neyens *et al.,* 1999), and the number of children experiencing difficulties in school because of learning disabilities or behavioural problems is greater than in the population without epilepsy (Williams *et al*., 1998; Sillanpaa *et al*., 1998; Wakamoto *et al*., 2000; Bailet and Turk, 2000). Predictors of poor cognitive outcome include a high seizure frequency (Hermann *et al*., 2008) and long duration of the epilepsy (Farwell *et al*., 1985; Seidenberg *et al*., 1986).

However, many children that develop epilepsy appear to have cognitive deficits that precede the onset of the seizures, suggesting that aetiology of the seizures, and not the seizures themselves, are responsible for the impaired cognition (Berg *et al*., 2004; Fastenau *et al*., 2009; Jackson *et al*., 2013). Most children with epilepsy maintain stable IQ scores. However, there is evidence that some children with epilepsy have delayed mental development (Neyens *et al*., 1999) or even have progressive declines of IQ on serial intelligence tests over time (Bourgeois *et al*., 1983; Berg *et al*., 2004).

In a community-based cohort, 198 children, aged <8 years with new-onset epilepsy, were followed prospectively and reassessed using the Wechsler Intelligence Scales for Children (WISC) 8-9 years later (Berg *et al*., 2012). The authors found that pharmacoresistant epilepsy was associated with an 11.4-point lower full scale IQ. It was found that in the absence of pharmacoresistance, age was not associated with cognitive scores. Although the initial level of adaptive function on the Vineland Adaptive Behavior Scale (VABS) was correlated with later cognitive function, it did not account for the impact of pharmacoresistance on later function. The impairment observed in the children with pharmacoresistant epilepsy involved multiple cognitive subdomains of the WISC, in particular verbal comprehension and perceptual organisation.

In the case of temporal lobe epilepsy in children, increasing duration of epilepsy is associated with declining performance across both intellectual and memory measures (Hermann *et al*., 2002). In a study of 46 children and adults (age range: 14-59 years) with temporal lobe epilepsy, a cognitive trajectory that differed from age- and sex-matched healthy controls was reported (Hermann *et al*., 2006). Adverse cognitive outcomes were observed in approximately a quarter of the patients, particularly in memory.

Animal data would also suggest that epilepsy onset in early childhood is detrimental. Indeed, predictors of cognitive impairment in children with epilepsy include early onset of seizures (Huttenlocher and Hapke, 1990; Glosser *et al*., 1997; Bulteau *et al*., 2000; Bjornaes *et al*., 2001; Hermann *et al*., 2002; Cormack *et al*., 2007), particularly during the neonatal period (Glass *et al*., 2009). Studies have demonstrated correlations between IQ and age at onset in a variety of refractory childhood-onset epilepsies treated surgically (Vasconcellos *et al*., 2001; Jonas *et al*., 2004; Cormack *et al*., 2007; Vendrame *et al*., 2009; D'Argenzio *et al*., 2011) or pharmacologically (O'Callaghan *et al*., 2011). Investigators have demonstrated that earlier intervention, especially for seizures beginning in infancy, results in better developmental outcomes and the ability to rebound after surgery (Jonas *et al*., 2004; Freitag and Tuxhorn, 2005; Loddenkemper *et al*., 2007).

Children with epileptic encephalopathies have cognitive impairment at the onset of epilepsy and also have significant declines over time. The epileptic syndromes in which psychomotor deterioration occurs exhibit an early age at onset. Such syndromes include early infantile epileptic encephalopathy with suppression-burst (Ohtahara syndrome), early myoclonic encephalopathy, migrating partial epilepsy in infancy, infantile spasms (West syndrome), severe myoclonic epilepsy of infancy (Dravet syndrome), Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, continuous spike-wave discharges of slow wave sleep (CSWS), and Landau-Kleffner syndrome (LKS) (Genton and Dravet, 1997; Panayiotopoulos, 2002; Nabbout and Dulac, 2003).

While aetiology of the epilepsy undoubtedly plays a major role in cognitive development, early-life seizures independent of aetiology can lead to cognitive impairment (Glass *et al*., 2009; Korman *et al*., 2013). In a study of neuropsychological function in children with focal cortical dysplasia, Korman *et al*. (2013) found that age at onset of epilepsy and extent of the dysplasia each contributed independently to cognitive dysfunction. The authors suggested that early onset of epilepsy disrupts critical periods of development and leads to poor cognitive outcomes. Furthermore, it was concluded that a later age at onset of epilepsy would not be expected to mitigate deficits because of widespread pathology, nor would

a localised lesion be likely to mollify the developmental deficits resulting from an early age at epilepsy onset.

Interictal spikes

Animal studies would predict that IIS result in transitory cognitive impairment. IIS in humans can produce brief disturbances in neural processing, resulting in a phenomenon called "transitory cognitive impairment" (Binnie, 2003). Aarts *et al*. (1984) noted that IIS can briefly disrupt neural processes affecting function within the brain region where they occur. The authors analysed the effect of IIS on verbal or non-verbal short-term memory in patients with epilepsy but without overt clinical manifestations during these discharges, thus targeting the so-called "subclinical" manifestations of IIS. In right-handed individuals, the authors reported that right-hemisphere IIS were associated with errors in a non-verbal task whereas left-hemisphere IIS resulted mainly in errors in verbal tasks. EEG discharges interfered mainly when they occurred simultaneously with the presentation of the stimulus, corresponding to the encoding phase of the task. Shewmon and Erwin in a series of elegantly performed studies (Shewmon and Erwin, 1988a; Shewmon and Erwin, 1988b; Shewmon and Erwin, 1988c; Shewmon and Erwin, 1989) further localised the effect, noting that occipital IIS could disrupt visual perception. IIS in the occipital region caused transitory deficits with stimuli presented in the contralateral visual field. Deficits were most pronounced when the stimulus was presented during the slow wave following the IIS.

In a study of 10 adult patients with depth electrodes implanted into their hippocampi for preoperative seizure localisation, Kleen *et al*. (2013) recorded EEG during 2,070 total trials of a short-term memory task, with memory processing categorised into encoding, maintenance, and retrieval. The influence of hippocampal IIS on these processes was analysed and adjusted to account for individual differences between patients. Hippocampal IIS occurring in the memory retrieval period decreased the likelihood of a correct response when they were contralateral to the seizure focus ($p<0.05$) or bilateral ($p<0.001$). Bilateral IIS during the memory maintenance period had a similar effect ($p<0.01$), particularly with spike-wave complexes of longer duration ($p<0.01$). The results strengthen the view that IIS contribute to cognitive impairment in epilepsy depending upon when and where they occur. The results of this study confirmed an earlier study by Krauss *et al*. (1997) who found declines in working memory due to IIS.

Because of their frequent nature, IIS in benign epilepsy with centro-temporal spikes (BECTS) has generated considerable interest. The vast majority of studies have found that children with BECTS have a variety of cognitive impairments (Fonseca *et al*., 2007a; Danielsson and Petermann, 2009). Children with BECTS have been reported to have mild language defects, revealed by tests measuring phonemic fluency, verbal re-elaboration of semantic knowledge, and lexical comprehension (Riva *et al*., 2007; Verrotti *et al*., 2011), as well as impairment in non-verbal functions (Metz-Lutz *et al*., 1999; Metz-Lutz and Filippini, 2006). The cognitive profile of the deficits is related to the side of focus with non-verbal deficits significantly correlated with the lateralisation of the epileptic focus in the right hemisphere with verbal deficits observed with left hemisphere discharges. Frontal functions, such as attention control, response organisation, and fine motor speed, were impaired in the presence of active discharges independently of the lateralisation of the epileptic focus (Metz-Lutz *et al*., 1999; Metz-Lutz and Filippini, 2006). However, not all studies have shown consistent neuropsychological profiles in children with BECTS. Some of the variability in function may be explained by fluctuations in IIS frequency and cognitive performance. In a study of six children with BECTS, month-to-month marked fluctuations in cognitive abilities and frequency and location of IIS have been noted (Ewen *et al*., 2011).

Transitory cognitive impairment has been studied during IIS in children with BECTS using EEG and computerised neuropsychological testing with a word and pseudoword visual discriminating task (Fonseca *et al*., 2007b). A small percentage of children (15.4%) made a significantly greater proportion of errors during IIS than during IIS-free periods. Of interest, in this study, the IIS were inhibited by the task, likely due to increased alertness, in 20 of the 33 children.

Whether there is a relationship between the frequency of IIS and cognition is unclear; some authors report a relationship between the number of spikes (Filippini *et al*., 2013) and others report no such relationship (Fonseca *et al*., 2007a; Tedrus *et al*., 2010; Goldberg-Stern *et al*., 2010). In a study of IIS in 182 children with a variety of epilepsy syndromes, including BECTS, Ebus *et al*. (2012) calculated the IIS index using a 24-hour ambulatory EEG and compared the findings to neuropsychological tests. The IIS index was calculated in wakefulness and in sleep, as percentage of time in five categories (0%, <1%, 1-10%, ≥10-50%, and ≥50%). The group of patients with diurnal IIS in ≥10% of the EEG record showed impaired central information processing speed, short-term verbal memory, and visual-motor integration. This effect was observed independently of other EEG-related and epilepsy-related characteristics, as well as epilepsy syndrome diagnosis.

If IIS can cause cognitive impairment, it would be reasonable to consider suppressing the IIS with antiepileptic drugs. In a double-blinded, placebo-controlled, crossover study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo, or placebo followed by lamotrigine (Pressler *et al*., 2005). Global rating of behaviour significantly improved only in patients who showed a significant reduction in either frequency or duration of discharges during active treatment, but not in patients without a significant change in discharge rate. However, in a small study using sulthiame to treat the IIS in BECTS, it was found that children had a significant deterioration in their reading ability, despite a reduction in IIS frequency (Wirrell *et al*., 2008). A major obstacle to designing studies to treat IIS is the lack of well tolerated drugs that effectively suppress IIS.

Despite the impairment observed during the presence of active IIS, children with BECTS have no permanent effects of the IIS, with the vast majority of children having no residual cognitive impairment (Callenbach *et al*., 2010). However, two related conditions which appear to be a continuum of BECTS, LKS and CSWS, have a substantially worse prognosis (Halasz *et al*., 2005; Mikati and Shamseddine, 2005; Metz-Lutz and Filippini, 2006; Margari *et al*., 2012; Seegmuller *et al*., 2012).

LKS is a rare childhood disorder characterised by a loss or regression of previously acquired language and epileptiform discharges, involving the temporal or parietal regions of the brain (Landau and Kleffner, 1957; Cooper and Ferry, 1978; Hirsch *et al*., 1990; Beaumanoir, 1992). Although a considerable amount of variation exists in the disorder, the typical history is of a child developing an abrupt or gradual loss of language ability and inattentiveness to sound, with onset during the first decade of life. This interruption in communication skills is generally closely preceded, accompanied, or followed by the onset of seizures or an abnormal EEG, or both (Sawhney *et al*., 1988; Deonna, 1991). Receptive dysfunction, often referred to as verbal auditory agnosia (Rapin *et al*., 1977), may be the dominant feature early in the course of the disorder. In some children, the disorder progresses to a point at which the child cannot even recognise sounds. In addition to the aphasia, many of the children have behavioural and psychomotor disturbances, often appearing autistic.

The EEG in LKS typically shows repetitive spikes, sharp waves, and spike-and-wave activity in the temporal region or parietal-occipital regions, bilaterally. Sleep usually activates the discharge, and, in some cases, the abnormality is observed only in sleep recordings. Speech deficits in the syndrome may be explained by either disruption of normal connections or an excessive inhibitory reaction to epileptiform discharges. However, the severity of the aphasia does not always have a close correlation with degree of EEG abnormality (Foerster, 1977; Holmes *et al*., 1981) or clinical seizures (Landau and Kleffner, 1957). It has been suggested that the epileptiform activity is an epiphenomenon and simply is reflective of an underlying cortical abnormality (Lou *et al*., 1977; Kellermann, 1978; Holmes *et al*., 1981). Even if the EEG parallels speech recovery, this does not prove that epileptiform activity causes aphasia. It is also possible that the decreased epileptiform activity during speech recovery simply reflects resolving injury to the speech areas.

While steroid treatment and intravenous immunoglobulin have been shown to be effective in treating LKS (Mikati and Shamseddine, 2005), this could be used to treat the underlying cause of LKS, such as inflammation. However, there is limited data indicating that there is a direct relationship between IIS and language impairment. Subpial resection, which eliminates epileptiform activity in the receptive language cortex, has been shown to reduce IIS and resolve linguistic function in LKS (Grote *et al*., 1999; Castillo *et al*., 2008). Since subpial resection would not be expected to alter the underlying aetiology of LKS, the fact that the patients improve with a destructive surgical procedure would indicate that the epileptiform discharges contribute LKS.

A condition related to LKS is epilepsy with CSWS (Tassinari *et al*., 2000). The disorder has also been called *electrical status epilepticus during sleep* (ESES). The distinguishing feature of CSWS is the continuous bilateral and diffuse slow spike-wave activity persisting through all of the slow-wave sleep stages. The spike-wave index (total minutes of all spike-waves multiplied by 100 and divided by the total minutes of non-REM sleep without spike-wave activity) ranges from 85 to 100%. The cause of CSWS is unknown, but early developmental lesions play a major role in approximately half of the patients, and genetic associations have recently been described. Clinical, neurophysiological, and cerebral glucose metabolism data support the hypothesis that interictal epileptiform discharges play a prominent role in the cognitive deficits by interfering with the neuronal networks at the site of the epileptic foci but also at distant connected areas (Van, 2013). High-dose benzodiazepines and corticosteroids have been successfully used to treat clinical and electroencephalographic features (Sanchez Fernandez *et al*., 2013a; Sanchez Fernandez *et al*., 2013b). As with LKS, there is no definitive data that indicates that the EEG abnormalities are responsible for the cognitive impairment. However, as with LKS, children with CSWS typically do not improve unless there is a reduction of spike-wave discharges during sleep (Scholtes *et al*., 2005; Brazzo *et al*., 2012).

There also appears to be a link between IIS and autism. Studies examining the EEG of individuals with autistic spectrum disorder show a very high rate of IIS (Hashimoto *et al*., 2001; Kim *et al*., 2006; Parmeggiani *et al*., 2007). For example, Hughes and Melyn (2005) found abnormal EEGs with IIS in 75% of 59 children with childhood autism. Many children with ASD have IIS on their EEG but do not experience seizures (Kim *et al*., 2006). In children with ASD, the most common location of IIS is in the frontal region, suggesting that frontal dysfunctions are important in the mechanism of symptoms in autism (Hashimoto *et al*., 2001). The location of IIS in the frontal regions is of interest since one of the major abnormalities in children with ASD is a disturbance in executive control (Hughes *et al*., 1994; Hughes *et al*., 1997; Hughes *et al*., 1999). The prefrontal cortex is a critical structure likely to be involved in executive control (Bachevalier and Loveland, 2006; Dumontheil *et al*., 2008; Shalom, 2009).

In children with ASD, it is not clear whether epileptiform discharges contribute or cause ASD, or whether ASD is a disturbance of brain function and epileptiform discharges are a reflection of a dysfunctional brain. In this regard, the rodent data is of interest in view of the finding that IIS in the prefrontal cortex of rats results in ASD-like behaviour (Hernan *et al*., 2013).

Which is more harmful: interictal spikes or seizures?

There is now clear evidence that both seizures and IIS in immature rodents and children can result in cognitive impairment. The effects of both IIS and seizures in the immature brain are dependent upon brain maturation. In the fully developed brain, seizures and IIS result in temporary impairment and appear to have few long-term effects, whereas in the developing brain, both IIS and seizures have more profound effects.

Determining which is worse, seizures or IIS, is difficult to determine clinically since it is difficult to separate out the two. It is widely believed that frequent epileptiform events observed in children with epilepsy are capable of causing deleterious alterations in developing brain networks and are therefore associated with the high incidence of cognitive deficits and psychiatric comorbidities in these patients. □

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