

Review

Current understanding and neurobiology of epileptic encephalopathies

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ABSTRACT

Epileptic encephalopathies are a group of diseases in which epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. These impairments can worsen over time. This concept has been continually redefined since its introduction. A few syndromes are considered epileptic encephalopathies: early myoclonic encephalopathy and Ohtahara syndrome in the neonatal period, epilepsy of infancy with migrating focal seizures, West syndrome or infantile spasms, Dravet syndrome during infancy, Lennox-Gastaut syndrome, epileptic encephalopathy with continuous spikes-and-waves during sleep, and Landau-Kleffner syndrome during childhood. The inappropriate use of this term to refer to all severe epilepsy syndromes with intractable seizures and severe cognitive dysfunction has led to confusion regarding the concept of epileptic encephalopathy. Here, we review our current understanding of those epilepsy syndromes considered to be epileptic encephalopathies. Genetic studies have provided a better knowledge of neonatal and infantile epilepsy syndromes, while neuroimaging studies have shed light on the underlying causes of childhood-onset epileptic encephalopathies such as Lennox-Gastaut syndrome. Apart from infantile spasm models, we lack animal models to explain the neurobiological mechanisms at work in these conditions. Experimental studies suggest that neuroinflammation may be a common neurobiological pathway that contributes to seizure refractoriness and cognitive involvement in the developing brain.

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The concept of Epileptic Encephalopathy (EE) suggests that not only the seizures but also the epileptiform abnormalities themselves can have an impact on cognition and behavior, above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation), and that these impairments can worsen over time (Berg et al., 2010). In addition to the syndromes defined as EEs (Table 1), the encephalopathic effects of seizures and interictal epileptiform abnormalities may potentially occur in association with any form of epilepsy. However, the term ‘epileptic encephalopathy’ is often used inappropriately for all neurological diseases with severe features, such as intractable seizures and severe cognitive dysfunction. This might be due to the proportion of patients who do not fulfill the criteria for any currently defined epilepsy syndrome (Berg et al., 2010). We suggest that the use of the terms EE should be restricted to patients consistent with the above definition because this will affect the treatment choices.

Our understanding of the mechanisms of EE is currently limited. The involvement of ion channels, neurotransmission and synaptic function genes has been increasingly evoked. Other contributing factors, such as neuroinflammation, probably also play a role in the pathophysiology, and anti-inflammatory steroids have in fact been used as an effective treatment in most EEs (Gupta and Appleton, 2005; Arya et al., 2012). Neuroinflammation has been widely studied since its involvement in ictogenesis was first established (Vezzani et al., 2013). More recently, experimental studies also report a role of inflammation in the cognitive and behavioral comorbidities of epilepsy.

We believe that studying the specific electroclinical characteristics of EEs will help us to reach a better understanding of the effects of seizures on brain function and their potential to cause lasting deleterious changes in the developing brain. In this review, we describe current knowledge of the mechanisms underlying epilepsy syndromes considered EEs, and we describe the most recent data on the role of inflammation in cognition and behavior in addition to its effect on ictogenesis and epileptogenesis.

1. Neonatal epileptic encephalopathies

The recent report of the International League Against Epilepsy (ILAE) commission on classification and terminology (Berg et al., 2010) recognizes three neonatal electroclinical syndromes: Benign Familial Neonatal Epilepsy (BFNE), Early Myoclonic Encephalopathy (EME), and Ohtahara syndrome (OS). While BFNE is a self-limited form of epilepsy

associated in most cases with normal development, EME and OS are characterized by a severe disruption of cerebral functions associated with seizures, often intractable. The implementation of video-EEG monitoring in the Neonatal Intensive Care Unit has allowed for a better definition of the different electroclinical phenotypes of neonatal epilepsies. At the same time, significant advances in epilepsy genetics have led to the discovery of new genes in epileptic encephalopathies (*CDKL5*, *KCNQ2*, *KCNT1*).

EME and OS share an important feature: a burst-suppression pattern (BS) on EEG, although there has been much discussion concerning specific differences between the BS patterns of these two syndromes (Aicardi and Ohtahara, 2005). BS consists of short periods of high-voltage activity with mixed features including spikes and slow waves, without age-appropriate activity alternating with periods of marked background attenuation (Fig. 1). Although neonates presenting with BS may have different underlying etiologies (hypoxic-ischemic encephalopathy, congenital metabolic disorders, extensive brain malformation, gene mutation), the pathophysiology of BS is a fascinating question. Steriade and colleagues provided the first cellular data on the EEG BS pattern (Steriade et al., 1994). They showed that at the cortical level, EEG bursts are always associated with a phasic synaptic depolarizing intracellular potential, occasionally crowned by action potentials, in virtually all recorded neurons, while suppression epochs are due to the absence of synaptic activity among cortical neurons. Interestingly, in contrast to cortical neurons, only 60–70% of thalamic cells ceased firing and were completely silent during the suppressed periods of EEG activity. The remaining 30–40% of thalamic cells discharged rhythmic (1–4 Hz) spike bursts during the period of EEG silence. Their findings demonstrated a close correspondence between neocortical and thalamic activity. The bursts originated from thalamocortical cells with preserved oscillatory properties during periods of electrical silence in the neocortex (Steriade et al., 1994). Using Single-Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET), Hirose et al. showed interictal hypoperfusion/hypometabolism of bilateral basal ganglia, the thalami and the right parieto-occipital cortex in one case of EME (Hirose et al., 2010), suggesting that the EME may be characterized by functional deafferentation of the cortex from subcortical structures. An electrical source imaging study found that activity during the bursts was associated with coherent sources in the thalamus, brainstem and cortical regions, whereas suppression phases were associated with coherent sources only in the cortical regions, reflecting the complete deafferentation of cortical structures from subcortical ones (Japaridze et al., 2015). The immature connectivity and incomplete myelination of the neonatal brain may predispose it to effective deafferentation between cortical areas and between the cortex and sub-cortical structures (Dubois et al., 2014).

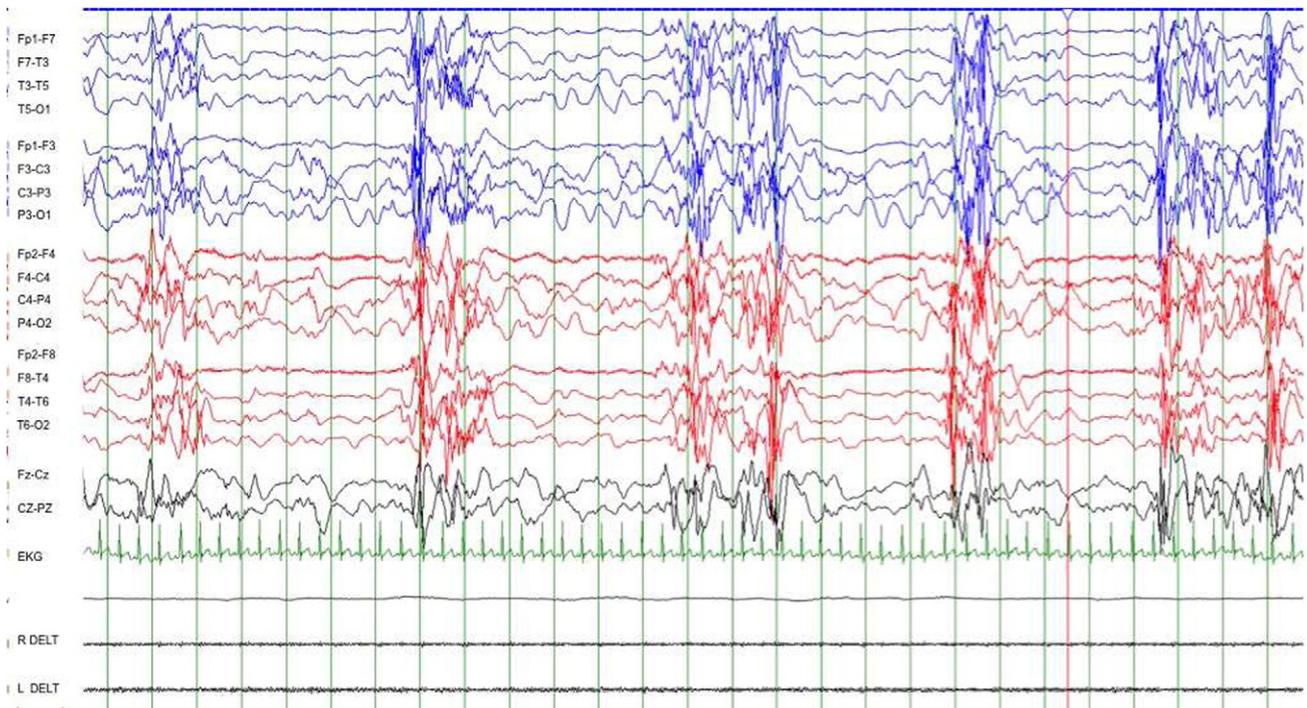
Many of the investigations regarding the pathophysiology of OS have been focused on genetic mutations. Mutations in the X chromosome-linked *Aristaless*-related homeobox gene (*ARX*) were initially reported in nine families with mental retardation (syndromic and nonspecific), various forms of epilepsy, including infantile spasms and myoclonic seizures, and dystonia (Stromme et al., 2002). Since then, several other mutations of the *ARX* gene have been reported (Fullston et al., 2010; Eksioğlu et al., 2011) and associated with a spectrum of phenotypes, ranging from OS (Giordano et al., 2010; Kato et al., 2010) to X-linked Infantile Spasms Syndrome (ISSX) (Stromme et al., 2002; Kato

Table 1

Electroclinical syndromes considered epileptic encephalopathies, arranged by age at onset.

Neonatal period
Early myoclonic encephalopathy
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Dravet syndrome
Childhood
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep
Landau-Kleffner syndrome

A



B

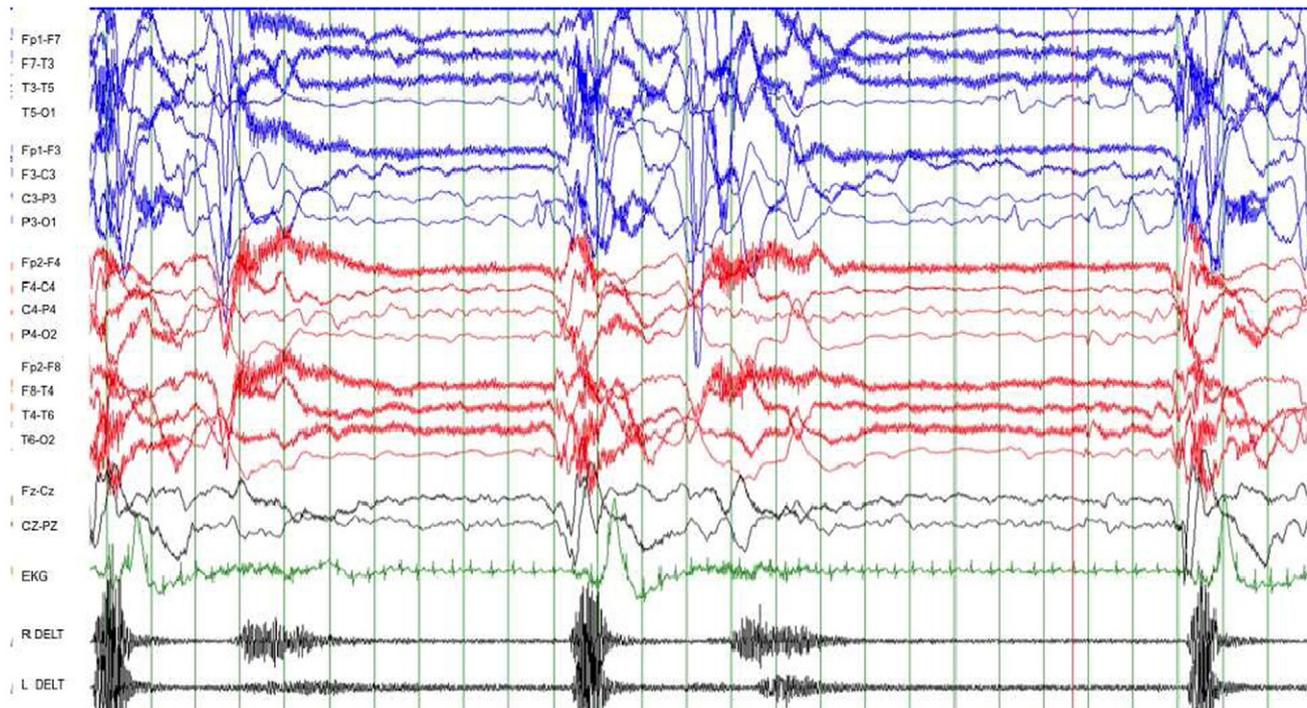


Fig. 1. A and B: Polygraphic EEG recording showing a burst-suppression pattern in a 4-week old infant with Ohtahara syndrome with *STXBP1* mutation, recorded during sleep (A) and wakefulness (B). The bursts consist of high-amplitude spikes and slow waves lasting 1–2 s and appearing synchronously over the two hemispheres, intermixed with periods of low-voltage activity. A cluster of tonic spasms during wakefulness is shown in (B), with the characteristic diamond shape of the EMG over the left and right deltoids associated with a diffuse high-amplitude slow wave on EEG and an altered respiratory pattern with chest movements occurring almost exclusively during the burst phase. The polygraphic recording demonstrates fragmentary low-amplitude myoclonic jerks involving both extremities and shifting randomly from one side to another. Gain 10 $\mu\text{V}/\text{mm}$; high-frequency filter, 60 Hz; paper speed, 15 mm/s.

et al., 2003). Animal models of ARX alterations (Colombo et al., 2007, Colasante et al., 2008, Friocourt et al., 2008, Marsh et al., 2009) have demonstrated neuron-specific ARX inactivation with the subsequent loss of function of GABAergic interneurons. Thus, an error of the

GABAergic system might play a critical role in the BS pattern in the case of ARX mutations. Interestingly, a similar unbalanced distribution of GABAergic interneurons between the striatum and the cerebral cortex has recently been demonstrated by post mortem neuropathological

investigations in an infant with neonatal-onset EE and BS, although an ARX mutation could not be demonstrated (Inoue et al., 2013).

Alternatively, the *in vivo* inhibition of the glutamate transporter in rat pups generates an abnormal EEG pattern close to BS, consisting of bilateral recurrent bursts of spikes alternating with periods of EEG silence (Milh et al., 2007). These animal data suggest that the deficient transport of glutamate may be a potential cause for early onset epilepsies with a BS pattern.

More recently, *de novo* mutations in the *STXBP1* (Syntaxin Binding Protein 1) gene – also known as Munch18-1 – have been found to be associated with OS (Saitou et al., 2008). This gene is considered a major cause of OS even though mutations in *STXBP1* have also been implicated in other early-onset epilepsies including West syndrome. A clear phenotype-genotype correlation has not yet emerged. *STXBP1*/Munch18-1 is a regulatory component of the SNARE (Soluble NSF attachment protein receptors) complex, which is involved in a late step of neuronal exocytotic fusion (Shen et al., 2007). Synaptic vesicle fusion is mediated by the concerted action of the two SNARE protein families, which play a major role in neurotransmitter release. Among SNARE proteins, syntaxin-1 is unique in including an N-terminal peptide (N-peptide) that binds to Munch18-1, and a large conserved H_{abc} domain that also binds to Munch18-1. The N-peptide and the H_{abc} domain of syntaxin 1 have distinct and independent roles in synaptic vesicle function, indicating that the complex domain structure of syntaxin-1 is required for its multifaceted role in different types of synaptic vesicle fusion (Zhou et al., 2013). Taken together, these studies shed light on the pathophysiology of OS, which, in the setting of normal brain architecture, could be related to altered neurotransmission.

Other genes have been reported as a cause for OS, including *KCNQ2*, *CDKL5*, and *KCNT1* (Pavone et al., 2012; Kato et al., 2013; Saitou et al., 2012). Diseases associated with these genes share with OS their age at onset, developmental delays, and intractability of the seizures. However, the recognition of distinct electroclinical phenotypes suggests that they represent specific etiology-related syndromes (Melani et al., 2011; Numis et al., 2014; Ohba et al., 2015).

1.1. *KCNQ2*-encephalopathy

Mutations in *KCNQ2*, encoding the voltage-gated potassium channel *K_v7.2*, were initially identified as the major cause of BFNE (Ronen et al., 1993; Singh et al., 1998). The *K_v7.2* channel underlies the muscarine-regulated M-current, a widely distributed slow-activating or non-activating current that plays a dominant role in modulating neuronal excitability by causing spike-frequency adaptation and setting the subthreshold membrane potential (Shah et al., 2008). Most *KCNQ2* mutations associated with BFNE result in mild or complete loss of function of the mutant allele, so that haploinsufficiency represents the major pathophysiological mechanism (Soldovieri et al., 2007; Soldovieri et al., 2014).

A remarkable twist in the *KCNQ2* story occurred with the report of *de novo* mutations in children with a severe epilepsy syndrome (Weckhuysen et al., 2012). This so-called “*KCNQ2* encephalopathy” is characterized by intractable seizures with a neonatal onset, associated with a severely abnormal interictal EEG pattern, either BS or multifocal epileptiform abnormalities, and severe developmental delays. More recently, several dozen patients have been reported. Since many of these patients were diagnosed well after the neonatal period, the electroclinical phenotype could not be differentiated from Early Myoclonic Encephalopathy (EME) or OS (Weckhuysen et al., 2012; Kato et al., 2013; Milh et al., 2013; Weckhuysen et al., 2013). Recent reports of patients diagnosed during the neonatal period have delineated a distinct neonatal electroclinical phenotype as well as a dramatic response to sodium-channel blockers (carbamazepine or intravenous phenytoin) (Numis et al., 2014). The onset of seizures almost always occurs during the first week of life. Seizure semiology consists of a tonic component with or without clonic jerking, often associated with autonomic features such as apnea and desaturation. Seizure frequency is high with 10 or

more seizures per day or even per hour. The seizures appear to be resistant to most treatments. However, in many cases, they tend to decrease in frequency or resolve after the first two years of life. The ictal EEG shows the onset of low-voltage fast activity over a single hemisphere followed by focal spike-and-wave complexes. While seizures are quite short in duration, the post-ictal phase is characterized by marked and prolonged diffuse voltage attenuation. The interictal EEG is characterized by multifocal epileptiform abnormalities, intermixed with random, asynchronous attenuations (Numis et al., 2014).

The fact that mutations in the same gene can give rise to either benign or severe epilepsies or development demonstrates the importance of *KCNQ2* in brain development, and suggests that the resulting potassium current may be differently affected in the two types of diseases. A functional study comparing the impact of mutations in *KCNQ2* found in children with BFNE and in children with *KCNQ2*-encephalopathy shows more dramatic functional deficits in channels carrying mutations associated with more severe epileptic phenotypes (Miceli et al., 2013). In order for the *KCNQ* channel to properly allow ion flow, all four gates of the tetramer must work in tandem. If one of the subunits has a mutation leading to electromechanical uncoupling or pore-blocking, the tetramer becomes non-conducting, despite 3 normal wild-type subunits. This dominant-negative effect is exhibited by many of the mutations leading to *KCNQ2* encephalopathy, with a pronounced loss of the M-current in the severe phenotypes (Orhan et al., 2014).

The severe phenotype seen in *KCNQ2* encephalopathy may be further explained by the separation of the mutated potassium channels from their usual axonal partner, the voltage-gated sodium channels. In a typical cell, ankyrin-G forms a submembrane framework that binds potassium and sodium channels together in the initial axon segment. The failure of the appropriate clustering of channels in the membrane can lead to abnormal excitability (Yue and Yaari, 2006; Soldovieri et al., 2007). This theory provides further grounds for the development of pharmacologic interventions that could reconnect or bind the channels together and prevent the excessive or sustained firing of action potentials seen with seizures. Finally, a recent work has revealed a previously unexplored level of complexity in pathogenic mechanisms. Indeed, some of the mutations stabilize the activated state of the channel, thereby producing gain-of-function effects, suggesting that changes in network interactions through these gain-of-function mutations, rather than in intrinsic cell properties, may be responsible for neuronal hyperexcitability (Miceli et al., 2015).

1.2. *CDKL5* encephalopathy

Seen most frequently in females (12:1 female to male ratio), the EE associated with *CDKL5* mutations is characterized by an early onset. This form of epilepsy was first identified in two females with severe intellectual disability and early-onset seizures (Kalscheuer et al., 2003). Patients have severe psychomotor impairment already evident at seizure onset, specifically hypotonia, poor visual fixation, and gaze avoidance. While these patients don't experience any true regression, they fail to develop verbal language and fine motor skills. In addition, a significant proportion of patients show a deceleration of head growth and some form of hand stereotypies. Epilepsy starts during the very first weeks of life, and while seizures are often intractable at onset, the interictal EEG can be normal (Bahi-Buisson et al., 2008b).

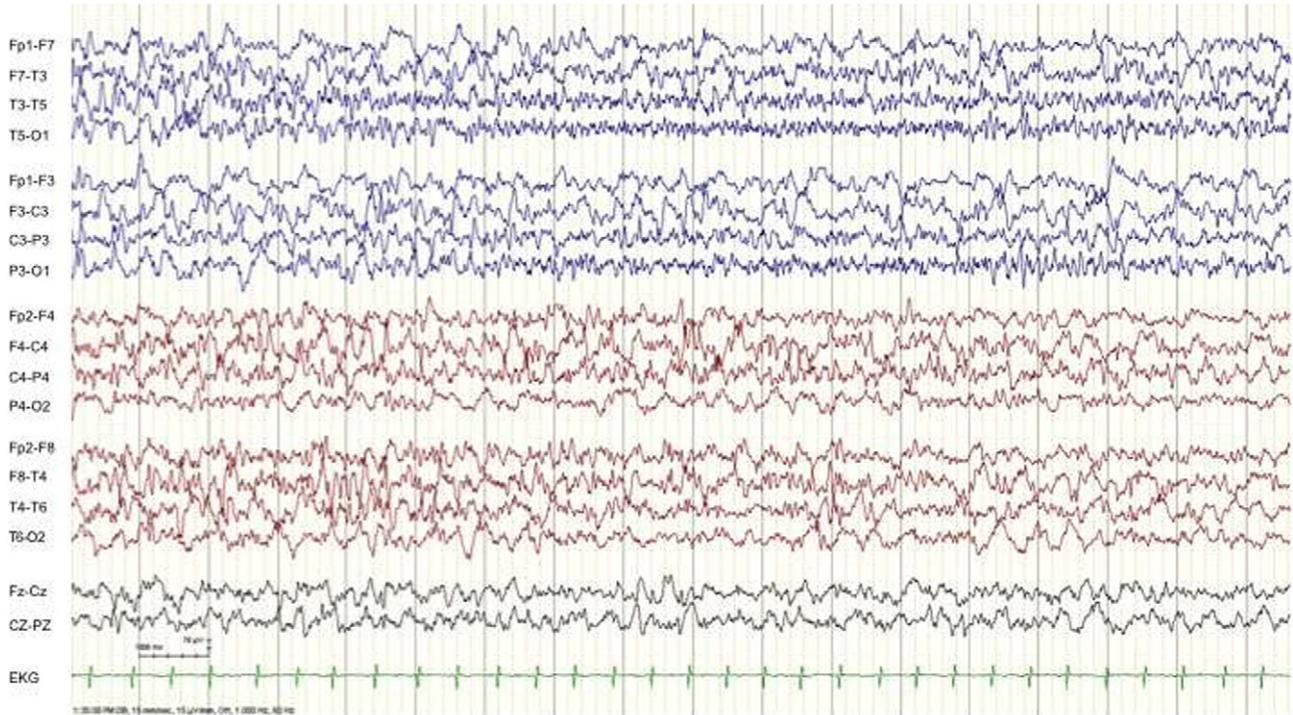
A three-stage electroclinical course has been described (Bahi-Buisson et al., 2008a). Initially, the affected individual has frequent, albeit brief, seizures. Some of these children show successful seizure control after several weeks to months, with some even achieving a seizure-free period. All patients at this stage already exhibit hypotonia and poor eye contact. Identifying this disorder in the very first weeks of life can be challenging. A distinctive seizure type, characterized by an initial tonic vibratory phase, followed by a series of spasms, and ending with bilateral myoclonic jerks, contributes to the delineation of the phenotype and allows for early recognition (Klein et al., 2011; Melani

et al., 2011). The second stage is characterized by the appearance of epileptic spasms with or without hypsarrhythmia. In the third stage, children suffer from severe refractory epilepsy with multiple seizure types, including tonic, myoclonic and spasms, occurring multiple times per

day. By this point, the interictal EEG is abnormal, with high-amplitude slow waves and bursts of spikes and polyspikes.

The *CDKL5* gene (cyclin-dependent kinase-like 5), also known as serine/threonine kinase 9 (STK9), is on the short arm of the X

A



B

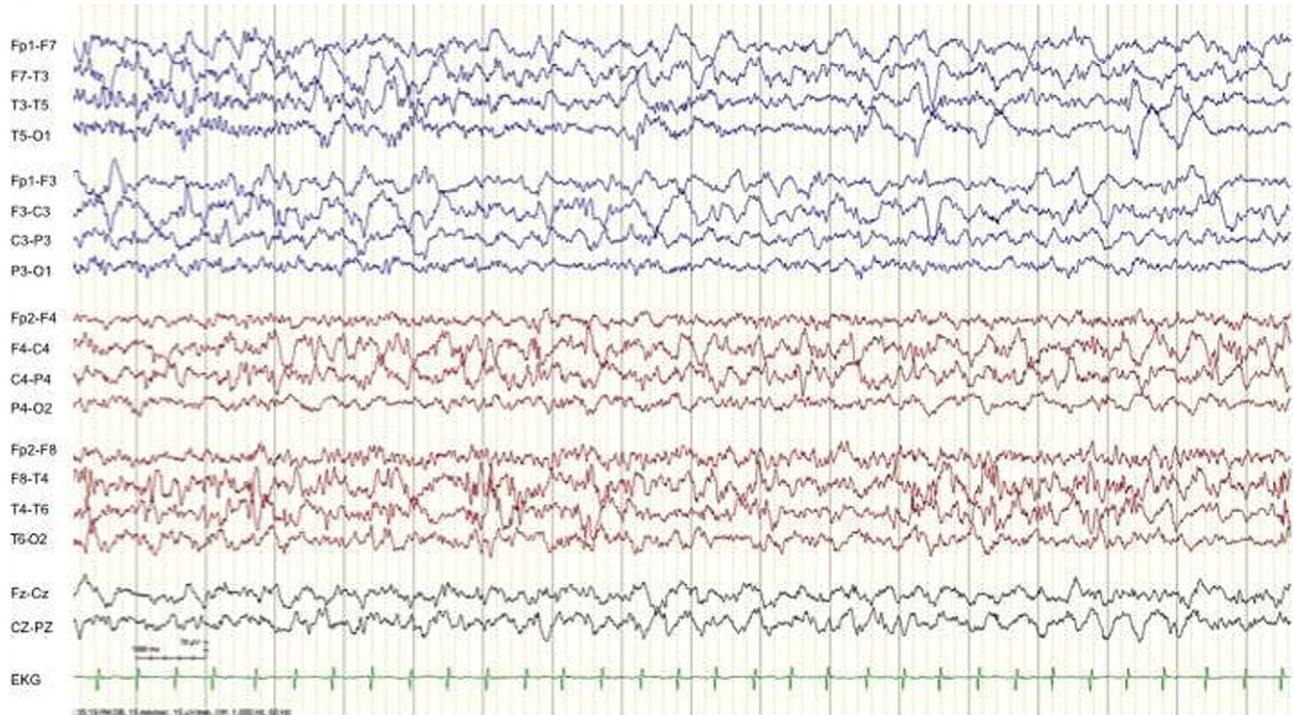
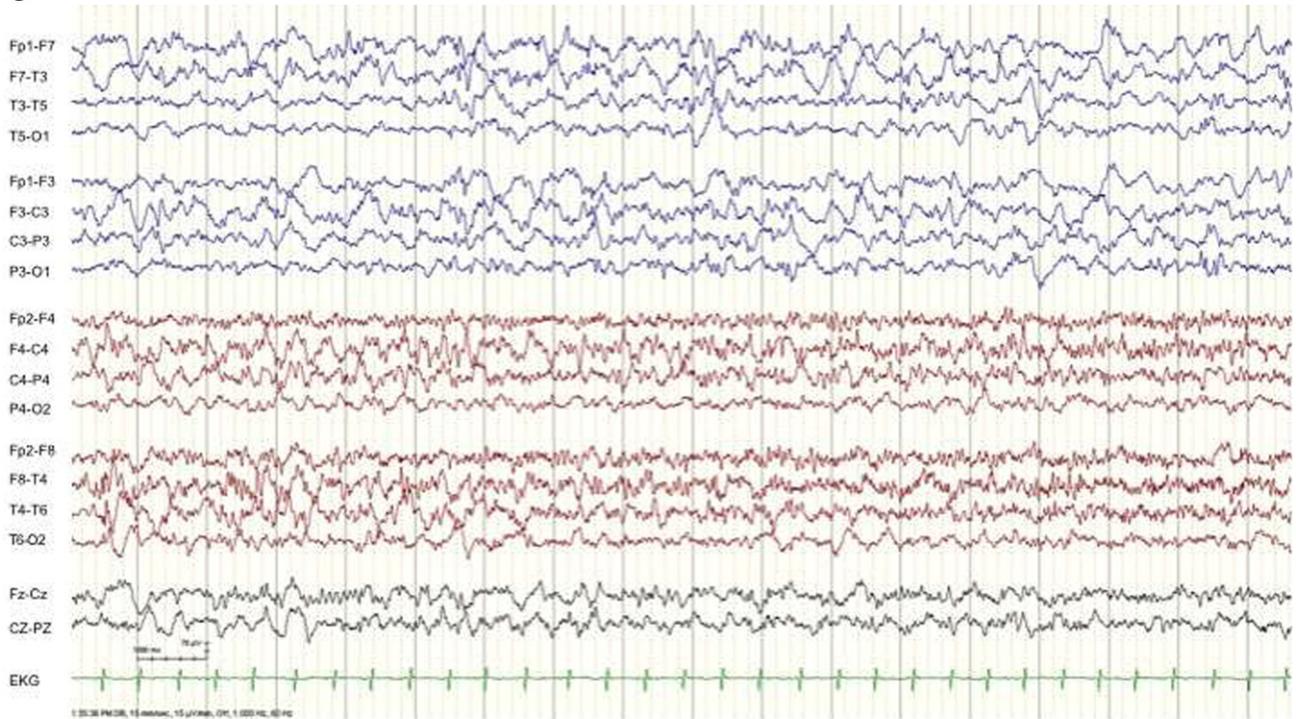


Fig. 2. (A–D) Ictal recording in a 2-month-old full-term infant with neonatal-onset epilepsy with migrating focal seizures and *KCNT1* mutation. Note the random onset of prolonged ictal discharges migrating from one hemisphere to the other. (A) A low-amplitude fast-activity seizure starts over the posterior regions of the left hemisphere, associated with a tonic right eye deviation; (B) simultaneous independent ictal discharges involving two different cortical regions: while the ictal discharge over the left posterior region is ending, another ictal discharge starts over the central-temporal regions of the right hemisphere; clinically, eyes are back to midline and there is no other evident clinical correlate; (C,D) The seizure over the left hemisphere is over, while the ictal discharge over the right hemisphere now involves the frontal-central-temporal regions, and is associated with a tonic left eye deviation. Gain 15 $\mu\text{V}/\text{mm}$, high-frequency filter, 60 Hz; paper speed, 15 mm/s.

C



D

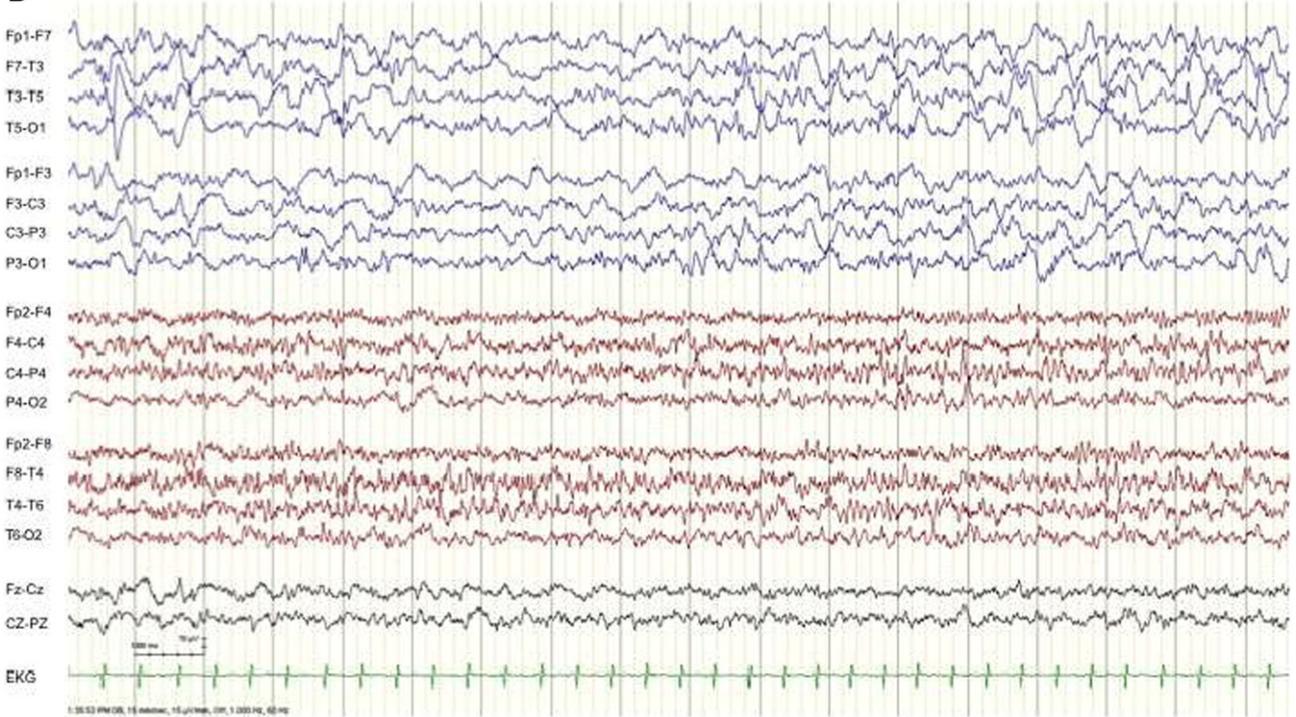


Fig. 2 (continued).

chromosome (Xp22). Several mutations and deletions have been found in the *CDKL5* gene, and as the clinical entity is more broadly recognized, some phenotypic variability is emerging (Bahi-Buisson et al., 2008b, Mei et al., 2010, Melani et al., 2011). There has not so far been any demonstration of an association between clinical severity and the nature or position of the mutations, although mutations affecting the catalytic domain tend to cluster in patients with more severe phenotypes.

The mechanism by which a mutation in the *CDKL5* gene leads to such a severe and early-onset EE is not yet fully understood. A function of the *CDKL5* protein is to add a phosphate group to specific positions on other proteins, and one of its major targets is MeCP2, known to be involved in neuronal function and synaptic maintenance. Another link stems from the finding that a specific gene in the green alga *Chlamydomonas* leads to a protein similar to the human *CDKL* protein

(Tam et al., 2013). This protein regulates appropriate flagellar length in the algal species, which is interesting in light of the fact that an increasing number of human diseases are being attributed to abnormal cilia (Badano et al., 2006). A *CDKL5* knockout (KO) mouse model has recently been described (Amendola et al., 2014; Fuchs et al., 2014). Behavioral analysis reveals that the constitutive KO model reproduces key features of the human disorder, including limb claspings, hypoactivity, and abnormal eye tracking. Investigations of the KO mouse have uncovered potential substrates for the *CDKL5*-associated encephalopathy, including reduced dendritic arborization of cortical neurons, decreased visual evoked responses, and alterations in Akt/rpS6 signaling pathways. Particularly interesting is the double dissociation of behavioral phenotypes resulting from a conditional KO of *Cdkl5* in glutamatergic cortical neurons and GABAergic forebrain neurons. These findings suggest that the behavioral deficits in *CDKL5* encephalopathy derive from the localized absence of the kinase in forebrain neurons, and that the limb control and eye tracking phenotypes depend on cortical motor and visual circuit defects. Although early-onset seizures are a key feature of *CDKL5* encephalopathy, this mouse model lacks spontaneous seizures or epileptiform activity. *CDKL5* possibly impacts the development of epilepsy in humans in a manner different from mice (Amendola et al., 2014; Fuchs et al., 2014). Researchers continue to explore these relationships and the role of seizures in the development of the encephalopathy.

1.3. Epilepsy of infancy with migrating focal seizures (EIMFS)

First described in 1995, EIMFS is characterized by polymorphous, migrating, almost continuous focal seizures associated with an arrest of development, resulting in profound disability (Coppola et al., 1995) (Fig. 2). Most affected infants start having seizures during the first few weeks of life and all start having seizures by six months of age (Cilio et al., 2008). Seizures are highly treatment-resistant. Ictal discharges

arise randomly from various areas of both hemispheres and migrate from one region to another, conferring the main feature and name to this syndrome. De novo *KCNT1* mutations have recently been identified in EIMFS (Barcia et al., 2012). *KCNT1* encodes a weakly voltage-dependent intracellular sodium-activated potassium channel. It is a member of the *Slo*-type subfamily of potassium channel genes, also known as Slack (sequence like a calcium activated potassium channel), and co-assembles with other *Slo* subunits (Kim et al., 2014). It is widely expressed in the nervous system and represents the largest known potassium channel subunit. Its activity contributes to the slow hyperpolarization that follows repetitive firing. Functional studies show that *KCNT1* mutations causing EIMFS are associated with a gain-of-function phenotype in vitro, leading to the constitutive activation of the sodium-activated potassium channel (Barcia et al., 2012). While this could account for the increased excitability and seizure phenotype, the severity of the developmental delay in children with EIMFS suggests an independent developmental role for this gene. In addition to regulating ion flux, a number of channels have non-conducting functions that regulate biochemical activities independent of ion flux (Kaczmarek, 2006; Fleming and Kaczmarek, 2009). This is likely to be the case for the *KCNT1* channel, which, in its C-terminal domain, interacts with a protein network including fragile X mental retardation protein (FMRP). *KCNT1* mutations may alter the conformation of the C-terminal region of the protein, impairing not only the gating of the channel but also its ability to interact with developmentally relevant proteins such as FMRP, and accounting for the severe developmental delay (Barcia et al., 2012).

2. West syndrome

West syndrome, or Infantile Spasms (IS), is one of the most common epilepsy syndromes in the first year of life, although the overall

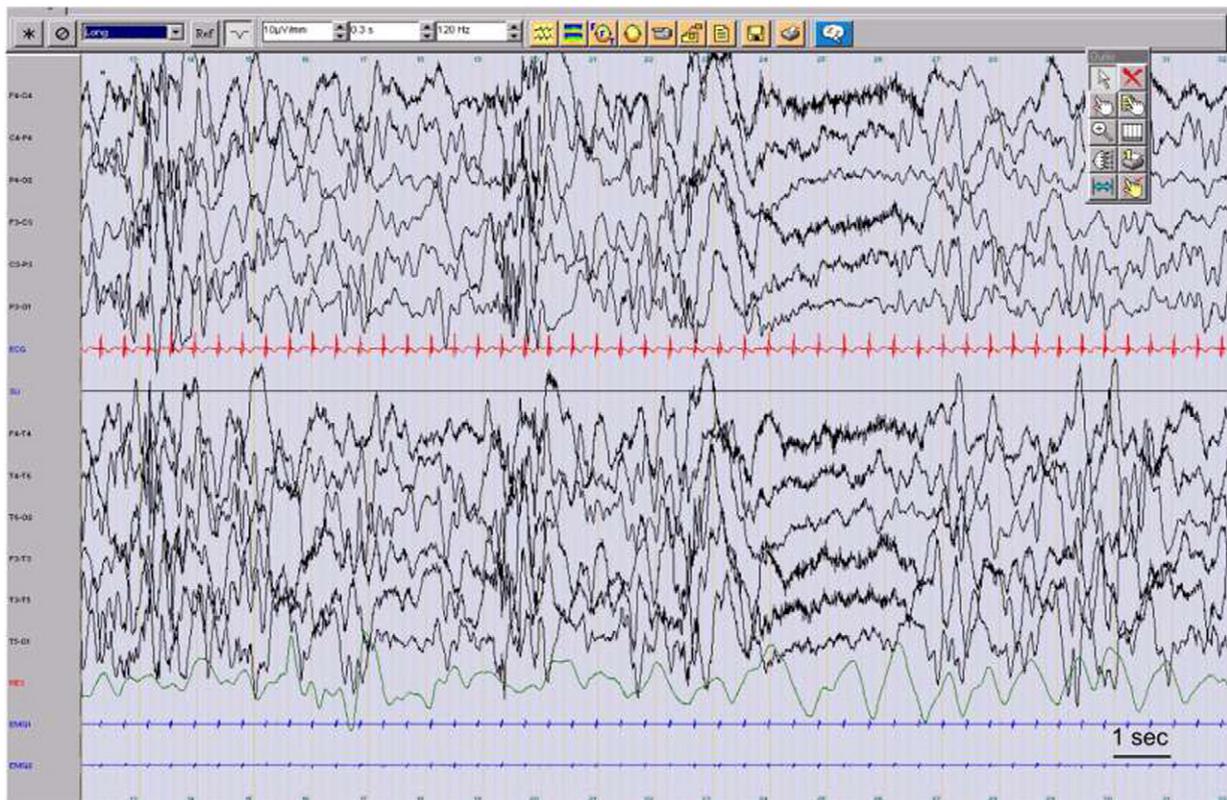


Fig. 3. EEG in a 6-month-old boy showing hypsarrhythmia consisting of diffuse high-voltage waves with a chaotic background of irregular, multifocal spikes and sharp waves, and asynchrony between the cerebral hemispheres. An electrodecrement is observed when an epileptic spasm occurs.

incidence is relatively low (1 in 2000). West syndrome is characterized by the association of epileptic spasms, psychomotor regression and a specific EEG pattern called hypsarrhythmia (Fig. 3). IS result from a whole range of causes comprising focal or multifocal, pre-, peri- or post-natal brain damage or malformation, or genetic predisposition, or can occur without evidence of any structural lesion (Dulac and Tuxhorn, 2005). This syndrome remains one of the most severe of infancy because of its important developmental implications. Children presenting with IS are at high risk of developing cognitive deterioration, which seems to be related to a persistence of epilepsy in the majority of cases (Koo et al., 1993; Rantala and Putkonen, 1999; Riikonen, 2004). Early and aggressive treatment is warranted, since early control of the epileptic spasms and resolution of the hypsarrhythmia seems to be associated with a higher chance of a normal cognitive outcome (Rantala and Putkonen, 1999; Auvin et al., 2012a).

While hormonal treatment (adrenocorticotrophic hormone (ACTH) or oral steroids) has been shown to be effective in more infants than vigabatrin, and result in the earlier resolution of spasms and hypsarrhythmia, the effect of these two options on long-term outcomes has not been established yet (Hancock et al., 2013). How ACTH controls IS is still unclear. A major hypothesis has centered on the ability of ACTH to reduce the endogenous synthesis of corticotrophin-releasing hormone (CRH), which when injected, produces severe seizures in immature rats (Brunson et al., 2001a; Brunson et al., 2001b). This theory does account for the time course of action of ACTH, the all-or-none response to treatment and is also supported by the findings of reduced ACTH and cortisol levels in the spinal fluid of patients with IS (Baram et al., 1992; Baram et al., 1995). One hypothesis is that ACTH may act, at least in part, via its effect on melanocortin receptors, independent of steroid release, and ACTH peptides fragments may function as agonists of these receptors without mediating steroidogenesis. To date, no clinical trial with such compounds has been undertaken. Another attractive idea is that ACTH could stimulate the synthesis of deoxycorticosterone (DOC), which is bioconverted to its tetrahydroxy derivative (THDOC), a potent agonist of the GABA-A receptor site (Reddy and Rogawski, 2002; Rogawski and Reddy, 2002). This theory is consistent with the therapeutic effects of vigabatrin on IS and support the current interest in ganaxolone, a neurosteroid derivative and highly selective agonist of δ -subunit-containing GABA-A receptors, which are extrasynaptic and mediate tonic inhibition (Kerrigan et al., 2000; Pieribone et al., 2007). None of the above mechanisms excludes the possibility that ACTH controls IS by modifying a wide range of cytokines (immunomodulation) (see Section 6).

Clinical studies have provided insights into the mechanisms underlying epileptic spasms. The most important challenge in clinical studies lies in the multiple variables that act as confounders (e.g. various etiologies of IS, different types and timing of treatment). For example, it is still not clear to what extent hypsarrhythmia itself contributes to the long-term cognitive deficits, or whether etiology plays the principal role in determining the long-term outcome. There is also a limited availability of invasive investigations and/or human tissue from the critical early stages of disease development. Over the last few years, a number of animal models of IS have emerged, leading to new insights regarding the underlying mechanisms (Galanopoulou and Moshe, 2015). Some of these models are chemically induced while other are based on genetic modifications.

2.1. Models of acquired causes of IS

Among the models representing the different causes of IS are:

2.1.1. The corticotropin-releasing hormone model

This model is derived from the finding that the stress hormones ACTH and glucocorticoids can be used to treat epileptic spasms (Brunson et al., 2001a). CRH release is increased by stress. The model has been created by the intraperitoneal or intracerebroventricular administration of CRH during the second week of life in rats, causing

severe seizures by inhibiting the hypothalamic–pituitary–adrenal axis (Baram and Schultz, 1991). The semiology of the seizures suggests a limbic origin, consistent with rhythmic, sharp activity on EEG (Baram and Schultz, 1991). This model does not show any epileptic spasms, and acute ACTH treatment does not have an impact on seizures. The CRH model mainly provides pivotal insight into the actions of ACTH and glucocorticoids, as mentioned above.

2.1.2. The NMDA model

The NMDA model is induced by intraperitoneal injections of the glutamate receptor agonist NMDA in rat pups between P10 and P15 (Mares and Velisek, 1992; Kabova et al., 1999). The acute seizures are characterized by hyperflexion and tonic spasms of the entire body with loss of the righting reflex. The spasms occur in clusters and the animals return to their normal behavior after a while (Kabova et al., 1999). The ictal EEG shows slow waves with superimposed fast activity, but the correlation between behavior and EEG is not well described (Kabova et al., 1999). These electroclinical characteristics mimic the human condition of IS, even though the interictal EEG does not represent true hypsarrhythmia. Cognitive deficits in the form of spatial learning and memory impairments are evident later in adulthood (Stafstrom and Sasaki-Adams, 2003).

More recently, it has been shown that the spasms start earlier and occur in greater numbers when the rats are prenatally exposed to betamethasone or restraint stress (Velisek et al., 2007; Chachua et al., 2011; Yum et al., 2012). This pretreatment was chosen to mimic prenatal stress by altering the hypothalamic–pituitary–adrenal axis. Similar to the human condition, chronic pretreatment with ACTH or chronic pretreatment with methylprednisolone at the time of the spasms significantly reduces the number of spasms and increases the latency of spasm onset. Moreover, pretreatment with vigabatrin, but not rapamycin, suppresses the spasms (Chachua et al., 2011). More recently, ganaxolone has also shown an ability to delay the onset of spasms (Yum et al., 2014). The betamethasone/NMDA model satisfies some of the criteria for IS seizure semiology: age specificity, EEG changes, pharmacological profile, and cognitive deficits. Given the lack of structural brain damage or lesions, some investigators have proposed this model as a model of cryptogenic IS (Velisek et al., 2007). In addition, the NMDA model shares interesting pharmacological response properties with the suppression of epileptic spasms using ACTH, methylprednisolone or vigabatrin (Chachua et al., 2011).

2.1.3. The tetrodotoxin model

The intrahippocampal infusion of tetrodotoxin (TTX) induces recurrent brief spasm-like seizures in P10 to P12 rat pups (Galvan et al., 2000; Galvan et al., 2003) consisting of short discharges of fast activity as recorded by EEG. TTX chronically suppresses neural activity during specific developmental windows, resulting in hyperexcitability. When TTX is injected for 28 days, beginning on P10, it initially leads to a depression of neuronal activity, followed by EEG abnormalities some time later. Around P21, one third of TTX-treated rats develop flexor or extensor spasms that occur in isolation or in clusters. The ictal EEG is characterized by a generalized slow wave followed by voltage attenuation and then low-voltage fast activity, similar to the ictal IS pattern observed in humans. Recently, it has been shown that high-frequency EEG activity may occur throughout ictal events (Frost et al., 2011). Interestingly, the interictal EEG pattern consists of high-voltage activity with slow waves and multi-spikes. This interictal EEG is comparable to hypsarrhythmia. These electroclinical features persist after the end of the TTX infusion, when the spasms give way to prolonged seizures. The TTX model provides convincing evidence for hypsarrhythmia and electrodecremental activity (Lee et al., 2008). While in this model, spasms occur very late during brain maturation, it emphasizes that blocking the neuronal activity of a normal brain may result in epileptic spasms. Moreover, TTX could also be an interesting tool for understanding the mechanisms by which spasms evolve into other seizure types.

The behavioral consequences and efficacy of antiepileptic drugs need to be further studied in this model.

2.1.4. The multiple-hit model of IS

The multiple-hit model uses severe damage to cortical and sub-cortical structures. Doxorubicin is injected into the cerebral ventricles, and lipopolysaccharide is administered intracerebrally in P3 rats. Doxorubicin, an anthracycline chemotherapeutic agent, is used to induce neuronal damage, whereas lipopolysaccharide, a component of bacterial walls that acts as an agonist of the toll-like receptor 4, is used to induce inflammation. These initial brain injuries are followed by an intraperitoneal injection of chlorophenylalanine at P5 in order to inhibit tryptophan hydroxylase and block the synthesis of brain serotonin. Serotonin is known to reduce brain excitability. In this model, rats begin to exhibit recurrent seizures from P4 to P13. These seizures are initially characterized by clusters of spasms associated with electroencephalographic decrement. Other types of seizures start at P9 (behavioral arrest, wild running, myoclonic, myoclonic-drop attacks, or seizures resembling stage 4–5 limbic seizures), and adult rats also exhibit seizures (Scantlebury et al., 2010; Raffo et al., 2011; Akman et al., 2014). The multiple-hit model is considered a model of symptomatic IS, representing the most common etiology of IS in humans (Watanabe, 1998). ACTH does not suppress spasms, whereas vigabatrin has a transient effect on spasms. This model may be helpful in evaluating treatments for refractory IS (Scantlebury et al., 2010). More recently, new treatments have been evaluated, including rapamycin, which has been shown to suppress spasms in a dose-dependent way and to improve visuo-spatial learning (Raffo et al., 2011), carisbamate, CPP-155 (a vigabatrin analog), which also shows acute effects on spasms, while no effect has been reported with NAX 5055 (a galanin analog) (Ono et al., 2011; Briggs et al., 2014; Gyax et al., 2014).

2.2. Models of genetic causes of IS

2.2.1. The Down syndrome model – Ts65Dn mice

A mouse model of Down syndrome (Ts65Dn) has been developed (Galdzicki and Siarey, 2003), but these mice exhibit spontaneous spike-wave discharges in EEG recordings without any seizures at baseline (Cortez et al., 2009). The administration of baclofen or γ -butyrolactone (the prodrug of the GABA-B agonist γ -hydroxybutyrate) to Ts65Dn mice (1 week to 2 months old) results in clusters of extensor spasms associated with polyspike-wave bursts and electrodecrement, whereas γ -butyrolactone injected into wild-type mice causes spike-wave discharges and absence seizures (Snead et al., 1999). Antiepileptic drugs used to treat IS (ACTH and vigabatrin) improve this epileptic phenomenon, suggesting that this model of spasms is pharmacologically reliable (Cortez et al., 2007; Cortez et al., 2009). An assessment of long-term consequences in this model would be interesting. These mice can be considered a model of a genetic cause of IS, since IS occur in $\leq 10\%$ of children with Down syndrome (Stafstrom and Konkol, 1994). The major limitations are an absence of spontaneous or chronic epileptic spasms, and the fact that induced spasms are observed in 2-month-old mice. The need for an injection of a GABA-B receptor agonist in order to develop spasms suggests that GABA-B receptors are involved in the pathogenesis of IS, at least those associated with Down syndrome. The mechanism by which GABA-B receptor alteration causes spasms needs to be further studied.

2.2.2. The *Aristaless*-related homeobox mutation model – ARX spasms model

Mutations in the *ARX* gene (OMIM *300,382) are associated with a variety of neurological syndromes including IS (Hirose and Mitsudome, 2003). *Arx* KO mice exhibit deficient proliferation of several cell types, including GABAergic interneurons (Kitamura et al., 2002). Mice with a conditional deletion of *ARX* in inhibitory interneurons of the cortex have been created. *Arx* knock-in in these mice reproduces

the 23 alanine codons in human *ISSX-ARX*(GCG)₁₀ + 7. These pups display twice as many spontaneous spasm-like movements as do wild-type littermates. *Arx*(GCG)₁₀ + 7 mice display EEG abnormalities including sharp waves, spikes, slow-wave transients followed by attenuation of background activity and increase in high-frequency rhythmic background activity. These EEG findings are not observed in older mutants. These mice also display abnormally low anxiety and cognitive impairment. Between the ages of 3.5 and 10 weeks, *Arx*(GCG)₁₀ + 7 mutants develop spontaneous seizures characterized by versive or clonic movements lasting more than 10 s, associated with a generalized attenuation of the EEG background with low-voltage fast activity and followed by generalized high-frequency and high-amplitude spikes and polyspikes in different brain areas. The *ARX* spasm model seems to share critical phenotypic features with human IS, so that the persistence of seizures should allow the modeling of the transition from spasms to other types of seizures (Price et al., 2009). More recently, early postnatal administration of estradiol prevents spasms in infancy and seizures in adult mutants. This effect of estradiol seems related to the ability of early estradiol administration to decrease mRNA levels of three downstream targets of *Arx* (*Shox2*, *Ebf3*, and *Lgi1*) and to restore depleted interneuron populations without increasing GABAergic synaptic density (Olivetti et al., 2014).

The various models of IS should be regarded as an opportunity to reflect the variability of IS in terms of phenotype, etiology and response to treatment. A large number of IS models would permit multiple approaches to further elucidate the underlying mechanisms of this condition. One of the next steps in the understanding of IS is to further study the pathophysiology of hypsarrhythmia. In fact, while the TTX model could show electrophysiological evidence for multifocal origins and the role of high-frequency oscillations, the mechanisms leading to the development of hypsarrhythmia and the question of whether this EEG pattern contributes to cognitive consequences and/or epileptogenesis have not yet been studied. In most models, long-term studies will allow us to better understand the role of IS on epileptogenesis and cognitive outcome.

3. Dravet syndrome

Dravet syndrome (DS) is a refractory epilepsy syndrome characterized by early-onset, febrile or afebrile, generalized or unilateral, clonic or tonic-clonic seizures. Usually, the first seizures are long-lasting episodes of status epilepticus (SE) occurring during the first year of life in an otherwise normal infant. Later, myoclonus, atypical absences and partial seizures are observed. Mutations in the voltage-gated sodium channel gene *SCN1A* are the main genetic cause of DS (60–80% of the patients) (Depienne et al., 2009). Developmental delays are constant, resulting from stagnation rather than cognitive regression. This usually begins to be evident after 2 years of age. Behavioral disturbances are also very common and seem to be correlated with the degree of cognitive impairment (Bruncklaus et al., 2011; Guzzetta, 2011). Until recently, it has been suggested that its epileptic characteristics (age at onset, type and duration of seizure) play an important role in determining the heterogeneity of outcomes in these patients.

At adulthood, all patients show intellectual disability, but even though severe intellectual disability is prevalent, heterogeneous outcomes have also been described. The electroclinical phenotype seems to be predictive of the level of cognitive impairment, with milder intellectual disability observed in patients with atypical DS (Takayama et al., 2013). Two other studies have analyzed the developmental profile across childhood in greater detail. The first study showed that cognitive impairment occurred early, and no patient with DS had a normal intelligence quotient (IQ) after the age of 6 years. They exhibited a profile of poor communication and poor capacity for autonomy, whereas their socialization skills seemed better preserved. Interestingly, there was no correlation between IQ (between 6 and 10 years of age) and epileptic characteristics (age at seizure onset, number of prolonged seizures) during early development,

i.e. the first 2 years of life (Villeneuve et al., 2014). These data are consistent with a second report of 81 neuropsychological evaluations performed in 67 patients with DS (Nabbout et al., 2013). In this study, cognitive involvement was also an early process with an IQ above 70 observed until 3 years of age followed by a marked decrease (mean IQ: 48) after this age. Notably, none of the patients experienced psychomotor or cognitive regression. Once again, the cognitive impairment of patients with DS appeared unrelated to major epileptic factors (age, type or duration of first seizure, age, number and fever-related episodes of SE, photosensitivity at EEG recording, or treatment parameters). Both studies indicate that cognitive impairment in DS is likely not a direct consequence of epilepsy, and that the presence of a mutation in *SCN1A* is actually a more reliable predictor of cognitive outcome (Nabbout et al., 2013).

The use of a 'Dravet' mouse model generated by KO of the *Scn1a* gene (*Scn1a*^{+/-}) has contributed to a better understanding of the neurobiology of this syndrome. The genetic modification is responsible for the altered function of Na_v1.1 sodium channels in neurons clustered throughout the brain (Ogiwara et al., 2007). An impairment of GABAergic firing has been observed in hippocampal interneurons, resulting in seizure susceptibility in cerebellar Purkinje cells, explaining motor symptoms such as ataxia (Yu et al., 2006; Ogiwara et al., 2007). In the mouse model, the consequences of an *SCN1A* abnormality differ according to the genetic background. In a heterozygous *Scn1a* KO (*Scn1a*^{+/-}) mouse model of DS, the animals exhibit strain-dependent seizure severity and survival: *Scn1a*^{+/-} in the mouse strain 129S6/SvEvTac (129.*Scn1a*^{+/-}) have no overt phenotype and show normal survival compared with *Scn1a*^{+/-} mice bred from a C57Bl/6J background (F1.*Scn1a*^{+/-}), which display severe epilepsy and premature mortality. These findings also correlated with cellular recordings (sodium current density in pyramidal neurons and GABAergic interneurons and spontaneous action potential firing in pyramidal neurons) (Mistry et al., 2014). Contrasting findings in GABAergic interneurons from the two different genetic backgrounds probably explain the different phenotypes (Mistry et al., 2014).

More recently, behavioral problems have also been reported in the Dravet models, including learning impairment, hyperactivity, stereotyped behaviors and deficits in social interactions (Han et al., 2012; Ito et al., 2013). These behavioral disorders seem to be related to a reduced expression of GABAergic interneurons especially in the prefrontal cortex, which shows particularly low expression of the Na_v1.1 channel. Interestingly, low-dose clonazepam, a positive allosteric modulator of GABA-A receptors, completely rescues the abnormal social behaviors and deficits in fear memory (Han et al., 2012), suggesting that the behavioral/cognitive abnormalities are due to the impairment of GABAergic neurotransmission. Other experimental studies have demonstrated that genetic modifications of *SCN1A* can result in cognitive impairment without seizures. Using an siRNA approach to selectively knockdown the Na_v1.1 in the medial septum and diagonal band of Broca in mice led to a dysregulation of hippocampal oscillations in association with a spatial memory deficit, although the mice did not exhibit spontaneous seizures (Bender et al., 2013). This study also suggests that the *SCN1A* mutation directly contributes to cognitive impairment independently of seizure induction. Both neuropsychological studies and these experimental studies suggest that genetic factors play an important role in the cognitive outcome of DS, and that this syndrome should be regarded as a genetic encephalopathy with epilepsy rather than an EE (Auvin, 2014).

4. Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a childhood EE. The main clinical hallmarks of the syndrome were identified and accurately described early on (Lennox and Davis, 1950; Gastaut et al., 1966). The diagnosis is not always easy since the electroclinical characteristics appear progressively. Moreover, the term LGS has often been loosely used to define all kinds of severe childhood epilepsy syndromes (Arzimanoglou et al., 2009). This is an important clinical issue since their treatment and



Fig. 4. EEG in a 10-year-old girl with Lennox-Gastaut syndrome showing slow spike-wave pattern. Note the bifrontal 0.2–0.5 Hz discharges. On the ECG line, there is contamination from the EEG signal.

outcomes may not be the same. This is also an issue for studies focusing on understanding the underlying mechanisms of LGS.

LGS, when fully developed, is defined by the association of many types of seizures including tonic seizures, cognitive impairment, and an interictal EEG pattern of diffuse, slow spike-wave complexes. The main seizure types are tonic seizures, atonic seizures and atypical absences. Tonic seizures remain the main feature, and will persist over time, even into adulthood (Ferlazzo et al., 2010). The classic interictal EEG feature is the slow spike-wave pattern (Fig. 4), consisting of slow spikes or slow spikes-and-waves organized in prolonged discharges at 1–2 Hz. Bilateral fast rhythm patterns (10 Hz or more) or “polyspikes” are typically recorded during slow sleep and, when EMG electrodes are used, it is not unusual to observe a concomitant tonic contraction.

Children with LGS usually experience cognitive regression around the time of diagnosis and established LGS is almost always associated with moderate to severe cognitive impairment. Cognitive impairment seems linked to the age of onset and persistence of seizures (Arzimanoglou et al., 2009). Moreover, a follow-up study of 72 patients for a mean duration of 17 years has suggested progressive cognitive impairment, with a 15 point decrease in IQ from diagnosis to the end of the follow-up period (Oguni et al., 1996).

No single underlying mechanism has been demonstrated to lead to the development of LGS. Several etiologies, as well as various preceding clinical courses (e.g. LGS following West syndrome, LGS following a brain injury, LGS occurring in the course of epilepsy with focal seizures) can be observed (Arzimanoglou et al., 2009). However, some common mechanisms in the developing brain presumably cause these various conditions and result in this age-dependent epileptic phenotype. It is remarkable that the major features of LGS, such as tonic seizures and

interictal discharges, are similar regardless of the presence, location or pathology of a causative lesion. The EEG features suggest widespread cortical involvement during ictal and interictal abnormalities. Electrophysiological and imaging studies have provided information on the various brain areas involved in LGS. However, the underlying mechanisms leading to the interplay of several cortical and subcortical structures remain unclear. The absence of an animal model mimicking some of the major features of LGS is also a limitation (Auvin et al., 2012b).

Initially, two main theories on the brain structure involved in LGS (cortical versus subcortical) were the subject of much debate. Later, it was suggested that the electroclinical phenotype originated from the abnormal interaction of cortical and subcortical circuits rather than in a specific region alone (Niedermeyer, 1996; Blume, 2001). Cortical structural abnormalities have been described among the etiologies of LGS. Moreover, the surgical removal of cortical lesions can abolish seizures and improve interictal discharges (Arzimanoglou et al., 2009). A global decrease in cortical excitability has also been reported using transcranial magnetic stimulation in LGS patients compared to healthy controls or other refractory epilepsies (Badawy et al., 2012).

Subcortical structures are also involved in LGS. Based on electrophysiology, neuroimaging studies and EEG-fMRI, Archer et al. have suggested that the thalamus acts as a synchronizer and an amplifier rather than as an initiator of the seizure (Archer et al., 2014). The pons also seems to be involved, particularly in the occurrence of tonic seizures, although it does not act as the initiator of epileptic activity (Siniatchkin et al., 2011; Intusoma et al., 2013).

In the various ictal and interictal features of LGS, the brain structures involved can differ from one type of abnormality to another. In the case

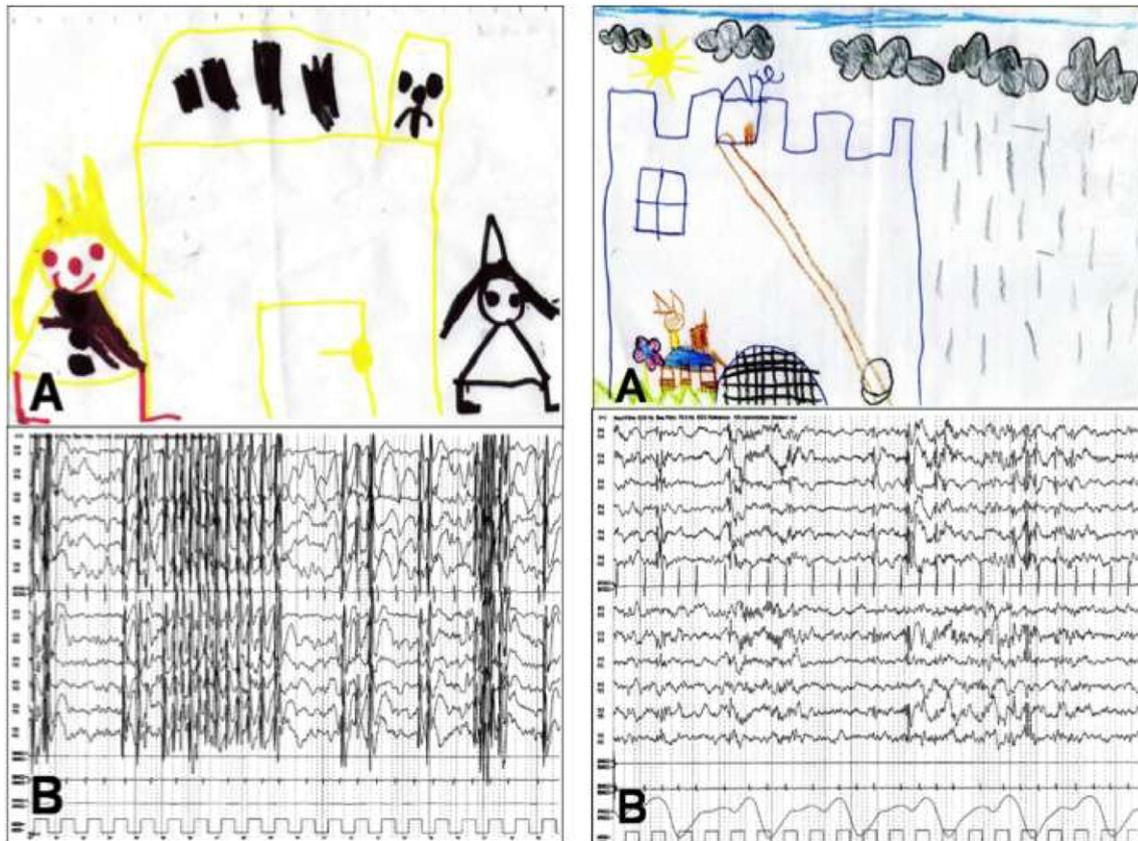


Fig. 5. Drawings and sleep EEG recording of a 6-year-old girl with epileptic encephalopathy with continuous spikes and waves in sleep at diagnosis and after successful treatment. A Left: Drawing at the time of diagnosis, one month after the start of the cognitive regression. A Right: Drawing one month after the start of clobazam. B Left: Sleep EEG recording showing almost continuous generalized spike-and-wave discharges in a 6-year-old girl previously diagnosed with rolandic epilepsy, who recently experienced cognitive regression and a few myoclonic seizures. B right: One month after treatment initiation, the sleep EEG recording shows the disappearance of the continuous spike-and-wave discharges. The regression has progressively disappeared under treatment.

of paroxysmal fast activity, an EEG–fMRI study has shown diffuse network activation including simultaneous activation of association cortices with an activation of subcortical structures (brainstem, thalamus, and basal ganglia), while a different pattern is observed during slow spike-and-wave activity consisting of an activated primary cortical area and subcortical activations and deactivations (Pillay et al., 2013).

Functional neuroimaging studies have recently contributed to the understanding of this epileptic phenotype, showing the activation of a complex pathological system. Prospective functional neuroimaging studies in patients shifting from West syndrome to LGS, or in children with epilepsy with focal seizures due to structural abnormalities who develop LGS, would probably help to determine the structure initiating this complex interplay between various brain structures. The development of animal models is needed to understand how various etiologies affect the neurobiology of the developing brain to result in this complex epileptic phenotype.

5. EE with continuous spike-and-wave during sleep/Landau-Kleffner syndrome

EE with continuous spike-and-wave during sleep (EE-CSWS) and Landau-Kleffner syndrome (LKS) are two distinctive EEs with different clinical phenotypes. These rare epilepsy syndromes typically start with seizures around 2–4 years of age in a child with normal or moderately abnormal baseline development. Seizures are not frequent. Around age 5–6 years, severe and global neuropsychological regression occurs and seizures including head drop become usually more frequent. Both syndromes are characterized by the regression of all or a part of cognitive abilities in a child with spike-wave discharges during sleep. Landau-Kleffner syndrome is mainly characterized by a gradual inability to understand and use spoken language due to verbal agnosia while the seizures usually respond well to treatment. The sleep EEG recording shows continuous spikes and waves (Fig. 5).

These syndromes should be considered prototypes for the EEs. Two to 4 years after the occurrence of the regression, seizures tend to remit and neuropsychological deficits tend to stabilize or even improve, although severe residual impairments remain, particularly when treatment is not able to modify the CSWS EEG pattern (Sanchez Fernandez et al., 2012).

The cognitive regression has a wide range of severity, resulting in an evident decrease of IQ in the majority of patients. In the particular case of LKS, the regression consists of verbal agnosia, which later results in global language deterioration (Sanchez Fernandez et al., 2012).

The sleep EEG pattern was first described in 1971 (Patry et al., 1971). The EEG pattern is sometimes called electrical status epilepticus in sleep (ESES) in the literature as opposed to CSWS, used to refer to the epilepsy syndrome. The ESES pattern consists of generalized bilateral and symmetric 1.5–3 Hz spike-waves. An initial definition stated that 85% of non-REM sleep should be occupied by spike-wave discharges (1989, Tassinari et al., 2000). It is currently unclear if the percentage of SW discharges occupying non-REM sleep represents a threshold level for the observation/initiation of behavioral/cognitive involvement in these syndromes.

The literature does not use common terminology to distinguish the EEG pattern from the epilepsy syndrome (Sanchez Fernandez et al., 2013). Most often, the authors use “ESES” when referring to the EEG pattern, “CSWS” when referring to the EE with global regression and “Landau-Kleffner syndrome” when discussing EE with predominant language regression. In EE-CSWS, the main feature is the cognitive regression observed while continuous spikes-and-waves during sleep can be recorded. The recording of a similar pattern in a patient without any cognitive regression should not lead to a diagnosis of EE-CSWS. The interchangeable use of “ESES”, “CSWS”, and “Landau-Kleffner syndrome” leads to difficulties in understanding the underlying concepts (Sanchez Fernandez et al., 2013).

The role of prolonged epileptiform activity in neuropsychological deficits remains unclear. It was initially hypothesized that a “functional ablation” of eloquent cortical areas was induced by the “persistent convulsive discharge”, resulting in neuropsychological impairment. Epileptiform activity during sleep may also interfere with learning and mechanisms of memory consolidation (Diekelmann and Born, 2010; Boelsterli et al., 2011). Consequently, near-continuous epileptiform discharges have been considered to underlie the severe neuropsychological regression in EE-CSWS (Aldenkamp and Arends, 2004; Holmes and Lenck-Santim, 2006). While some authors have reported a good correlation between the cortical location of interictal discharges and the disrupted function, others have not found any correlation (De Tiege et al., 2004; Sanchez Fernandez et al., 2012). Moreover, the temporal

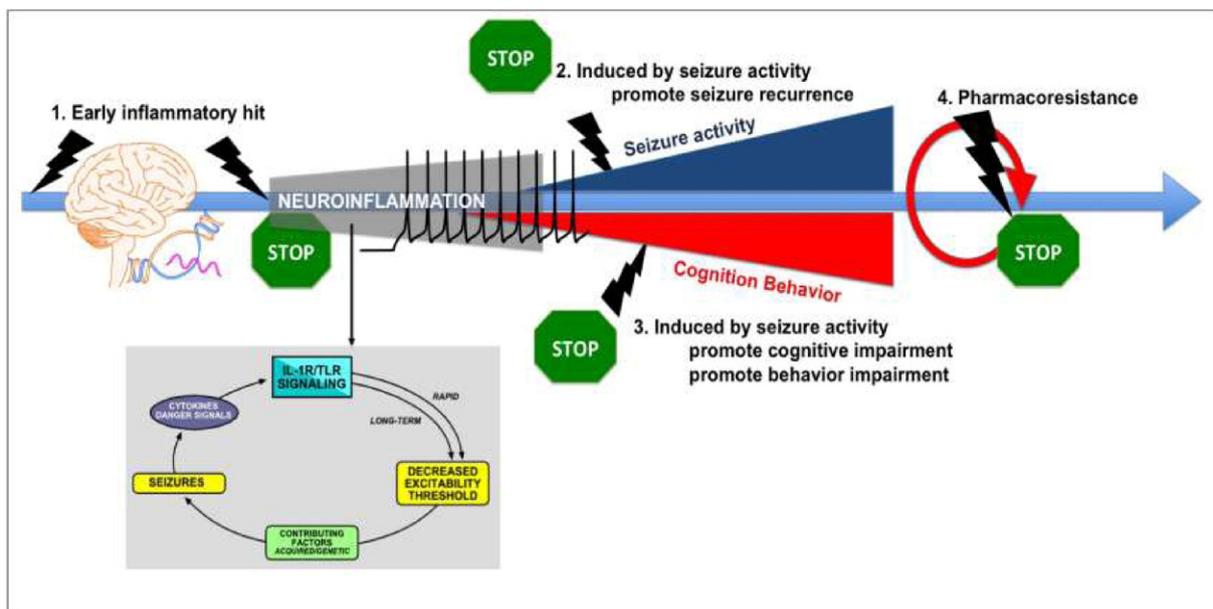


Fig. 6. Schematic representation of the hypothetical chain of pathological events occurring in epileptic encephalopathies, and the role of neuroinflammation. A triggering event (e.g. fever, infection or other unknown causes) might act as a second hit in patients with acquired or genetic EEs. This neuroinflammation might promote the start of seizures as well as cognitive/behavioral involvement. Experimental data indicate that seizures in turn induce neuroinflammation and that the establishment of an inflammatory substrate in the brain lowers seizure threshold in animal models by inducing rapid changes in neuronal excitability, thereby promoting seizure recurrence.

association between the occurrence of CSWS on EEG and neurological regression is not always strict (Rapin, 1988; Hirsch et al., 1990).

In addition to a deficit in learning and memory consolidation mechanisms during sleep, there are probably several other components involved in the neuropsychological regression, including the cause of EE-CSWS, the effect of seizures on brain activity, and a deficit in information processing during the epileptiform activity. Polytherapy and high doses of antiepileptic drugs may also contribute to cognitive dysfunction and worsen the neuropsychological deficit (Loring and Meador, 2004).

Connectivity studies by functional imaging have provided some insights into the mechanisms of EE-CSWS. FDG-PET has shown areas with increased glucose metabolism corresponding to epileptic foci and other hypometabolic cortical areas (De Tiege et al., 2004; De Tiege et al., 2008). It has thus been suggested that the epileptic foci affect other cortical areas by surrounding inhibition when the hypometabolic area is located at the border of the hypermetabolic area, or by remote inhibition when the hypometabolic area is distant from it. In some patients, the epileptic foci are not intense enough to be imaged by PET (De Tiege et al., 2004; De Tiege et al., 2008). At remission, a regression of both focal hypermetabolism and hypometabolism is observed, and functional connectivity between regions showing increased and decreased glucose metabolism during the active phase of CSWS returns to normal, suggesting that in addition to the epileptic focus, the inhibited area plays a role in cognitive regression (De Tiege et al., 2008). Data from EEG-fMRI studies also support this hypothesis, showing an increase in perfusion in the epileptic focus and a decrease in perfusion in distinctive connected cortical areas (De Tiege et al., 2009; Siniatchkin et al., 2010).

Animal models mimicking EE-CSWS are currently unavailable. However, experimental studies have explored how interictal epileptiform activity may impact cognition. Interictal spikes cause transitory cognitive impairment in adult rodents (Kleen et al., 2010). Interictal spikes during early brain development may have long-term adverse effects on developing neural circuits. In particular, interictal spikes can have two types of effects of cognitive functions: a transitory interruption inducing direct behavioral effects, and the alteration of brain plasticity and memory processes (Holmes, 2014). Transitory interictal spikes during development induced by prefrontal intracortical injections of bicuculline in P21 rats lead to a deficit in attention and sociability (Hernan et al., 2014). Interictal spikes can be induced without seizure using low-dose fluorothyl in rats pups (Khan et al., 2010). When rats are tested as adults, there is an impairment in spatial memory as well as in LTP. Moreover, the animals show decreased neurogenesis and hippocampal cell counts (Khan et al., 2010).

A better understanding of the mechanisms of EE-CSWS might have a global impact on the understanding of cognitive involvement in all types of EEs. There are typically few seizures in EE-CSWS, while cognitive regression is the principal issue, explaining why this syndrome could be a prototype for cognitive involvement in the EEs. Identifying the neurobiological mechanisms of EE-CSWS is a real challenge and mainly needs the development of new animal models.

6. Role of inflammation in the neurobiology of EE

Emerging evidence highlights a putative pathogenic role of neuroinflammation, both in sustaining the recurrence of seizures and in mediating the development of long-term morbidity (Nabbout et al., 2011; Vezzani et al., 2013) (Fig. 6). Neuroinflammation is defined as an “innate immunological response of the nervous system, involving its own immune cells (microglia, astrocytes), releasing cytokines and chemokines, thus activating down-stream inflammatory effector molecules, and related molecular processes” (Graeber et al., 2011).

Neuroinflammation was first detected in seizure-prone areas of animal models of acute seizures (Minami et al., 1990; Minami et al., 1991; Vezzani et al., 1999; De Simoni et al., 2000). The occurrence of this

phenomenon was then validated in chronically epileptic animals (Aronica et al., 2012; Vezzani et al., 2013) and in various drug-resistant forms of surgical structural/lesional human epilepsy (Vezzani et al., 2011a; Aronica and Crino, 2014).

Pharmacological studies, mainly performed in adult rodents, and the investigation of seizure susceptibility in adult transgenic mice with altered inflammatory pathways, have shown that neuroinflammation is not a by-stander phenomenon associated with seizures, but contributes to their precipitation and recurrence (Vezzani et al., 2011b; Vezzani et al., 2013).

The available experimental data support two main scenarios that will be discussed in the following paragraphs: 1. seizures induce neuroinflammation, which in turn fosters further seizures; 2. pre-existing neuroinflammation decreases the seizure threshold, worsens the consequences of seizures and promotes co-morbidities.

6.1. Seizures trigger neuroinflammation

In immature as in adult animals, recurrent seizures, independently of their specific trigger, cause neuroinflammation in brain regions involved in the onset and generalization of the epileptic activity. Notably, seizure-induced neuroinflammation in the rat forebrain is developmentally regulated, and the age-dependent onset of neuroinflammation depends on the seizure-triggering event (Rizzi et al., 2003; Dube et al., 2005; Marcon et al., 2009; Dube et al., 2010).

6.1.1. Chemoconvulsants

When SE is induced by the systemic injection of kainate or pilocarpine in naïve P11–P21 rats, thus provoking neuronal network hyperexcitability in the forebrain, neuroinflammation develops within 4 h in activated glial cells of the hippocampus. In contrast, in P9 rats, cell activation is only minor or absent, accompanied by a late (24 h post-SE), very limited, and transient increase in pro-inflammatory cytokines (Rizzi et al., 2003; Jarvela et al., 2008; Marcon et al., 2009; Jarvela et al., 2011; Omran et al., 2012). In adult rats, the neuroinflammatory response induced in glia by SE evoked by chemoconvulsants is faster than in early development since it occurs within minutes of SE induction, and in general lasts longer (up to several days) after the initial precipitating event (De Simoni et al., 2000; Ravizza et al., 2008; Marcon et al., 2009; Jarvela et al., 2011; NOE et al., 2013). Neuroinflammation recurs when animals exposed to SE develop spontaneous seizures (De Simoni et al., 2000; Ravizza et al., 2008; NOE et al., 2013).

The mechanisms underlying the age-dependence of seizure-induced inflammation are unknown. Notably, the lack of a neuroinflammatory response to seizures in P9 animals cannot be attributed to the inability of the immature brain to develop such a response, or to the lack of involvement of the hippocampus in seizure activity. The occurrence of neuronal cell loss in models of SE, as well as the subsequent development of epilepsy, closely match the onset and extent of neuroinflammation in the hippocampus: e.g. P9 rats develop neither cell loss nor epilepsy while both phenomena can occur in P15 rats. Moreover, both cell loss and the incidence of epilepsy are greater at P21, an age associated with longer-lasting and more pronounced neuroinflammation than earlier ages (Albala et al., 1984; Stafstrom et al., 1992; Haas et al., 2001; Rizzi et al., 2003). In a different study, P21 pre-adolescent rats exposed to systemic pilocarpine developed a neuroinflammatory response to SE in the hippocampus, in concomitance with blood-brain barrier (BBB) alteration and angiogenesis. These phenomena occurred in about 60% of animals exposed to SE of similar severity and duration, again matching the incidence of epilepsy in this model. Interestingly, only P21 rats developing epilepsy showed a chronic up-regulation of IL-1 β in activated glia in the hippocampus (Marcon et al., 2009). It is currently unknown if this type of age-dependence exists in humans, although it might be one of the mechanisms activated in some forms of EE. Moreover, it would be interesting to explore if the control of seizure activity by antiepileptic drugs decreases neuroinflammation.

6.1.2. Two-hit seizure model

Early-life seizures in rodents may increase susceptibility to later seizures in adulthood and promote neurological deficits after a second hit. Neuroinflammation appears to be significantly involved in this *sensitization-type* or *priming* phenomenon. For example, the activation of microglia and its production of pro-inflammatory cytokines in the forebrain of P45 adult rats exposed to kainate-induced seizures are greater if the animals are pre-exposed to a convulsive dose of kainate at P15. Notably, a long-lasting increase in seizure susceptibility and an aggravation of neuronal cell loss and co-morbidities have all been reported in rats exposed to a second hit, as compared to animals exposed to seizures only as adults (Somera-Molina et al., 2009). Notably, both the exacerbated neuroinflammatory response evoked by early-life seizures and the associated pathological outcomes, including decreased seizure threshold, cell loss and deficits in hippocampus-dependent spatial learning, were prevented in rats treated after the early-life first hit with minozac or minocycline, i.e. drugs that block the activation of microglia and astrocytes (Somera-Molina et al., 2009; Abraham et al., 2012).

6.2. Neuroinflammation induces long-term neurological sequelae

The exposure of P7–P14 rats to a systemic or intracerebral inflammatory challenge, mimicking bacterial or viral infection, triggers a transient surge in cytokines (e.g. IL-1 β and TNF- α in the cortex and hippocampus), resulting in a long-lasting decrease in the seizure threshold of various convulsants as well as behavioral deficits. These effects are prevented if the cerebral increase in cytokines is blocked by minocycline, or by administering the endogenous IL-1 β receptor antagonist, IL-1ra, or by inactivating TNF- α with an anti-TNF- α antibody (Galic et al., 2008a; Riazi et al., 2008; Galic et al., 2009; Galic et al., 2012). In particular, P14 rats exposed to systemic lipopolysaccharide (LPS) either alone or at the time of SE induction show a reduced seizure threshold, an increased rate of epileptogenesis, and increased disease severity in adulthood (Galic et al., 2008a; Riazi et al., 2008; Auvin et al., 2010a; Auvin et al., 2010b). Notably, LPS is a pro-inflammatory mimic of bacterial wall components that activates the Toll-like receptors (TLRs). TLR4 can also be activated by endogenous ligands, such as the protein High Mobility Group Box 1 (HMGB1), released by injured brain cells. The activation of HMGB1-TLR4, similarly to IL-1 β /IL-1R type 1, promotes seizures in animal models (Vezzani et al., 2011b). An immune challenge imposed postnatally in rodents also affects animal behavior, for example by compromising cognitive functions in adulthood (Han et al., 2011). Notably, neonatal rats infected with *Escherichia coli* exhibit cognitive deficits after a second immune challenge by LPS in adulthood (Bilbo et al., 2005a; Williamson et al., 2011), and P7–P14 offspring of dams injected during gestation with poly I:C (a TLR3 agonist that mimics viral infections), or with IL-1 β or IL-6 or their combination, display autism-like behaviors (Hagberg and Mallard, 2005; Rees et al., 2008; Pineda et al., 2013b, a) and a long-term increase in seizure susceptibility (Pineda et al., 2013a).

These data support the view that the immature brain can be permanently modified after a transient inflammatory episode. The current hypothesis is, therefore, that excessive immune activation and inflammatory signaling in specific forebrain regions during a well-defined developmental window, in response to either infection or brain injury (including prolonged seizures), can potentially interfere with normal brain development. Alternatively, *immune priming* may occur, favoring exacerbated inflammatory cytokine production in response to a second hit, thereby affecting neural processes relevant for seizures and behavior (Bilbo et al., 2005a; Bilbo et al., 2005b; Bilbo and Schwarz, 2009; Williamson et al., 2011). When these inflammatory pathways affect cognition-related processes in brain regions critical for working memory, they represent a risk factor for the development of neuropsychiatric diseases (Carpentier and Palmer, 2009; Riazi et al., 2010; Bilbo and Schwarz, 2012; Vezzani et al., 2013). These phenomena should

therefore be explored in patients with EEs in order to identify the pathophysiological processes that might be involved, in order to prevent or reverse the cognitive and behavioral impairment (Fig. 6).

6.3. Mechanisms underlying neuroinflammation-induced pathological sequelae

The link established between the overactivation of cytokine signaling and increased excitability in neuronal circuitry in seizure-prone brain areas (Vezzani et al., 2011b) explains why neuroinflammation is likely to decrease seizure threshold and enhance seizure-induced brain injury in immature rodents (Riazi et al., 2010; Galic et al., 2012). The modifications induced by inflammatory mediators, such as cytokines or chemokines (in particular IL-1 β , IL-6, HMGB1 and TNF- α produced by activated microglia, astrocytes and in some instances by neurons), in brain excitability involve both *rapid* post-translational and *long-term* transcriptional changes (Vezzani et al., 2011b). The major targets identified so far include voltage-gated and receptor-operated ion channels, genes involved in neurotransmission and synaptic plasticity, and homeostatic functions of astrocytes related to water and potassium homeostasis and extracellular glutamate re-uptake (Devinsky et al., 2013). In particular, the long-term increase in seizure susceptibility as well as the cognitive deficits induced by neuroinflammation in immature rodents are associated with modifications in hippocampal and cortical NMDA, AMPA and GABA receptor mRNA and protein levels and their subunit composition, as well as the Na—K—Cl co-transporter (Galic et al., 2008b; Harre et al., 2008), thus denoting permanent changes in neurotransmission.

Recently, epigenetic mechanisms modulating neuroinflammation have been shown to be dysregulated in epilepsy both in children and adults (Aronica et al., 2010; Iyer et al., 2012; Omran et al., 2012; Peng et al., 2013; Gorter et al., 2014).

7. Conclusion

Among the epilepsy syndromes that are considered to be EEs (Table 1), there are in our opinion not many that truly fulfill the criteria defined by Berg et al. (2010). LGS, EE-CSWS and LKS can be regarded as the best examples of this definition. In case of neonatal-onset epilepsies, the complex links between gene dysfunction and seizure activity, between gene dysfunction and cognitive involvement, and between seizures in the developing brain and cognitive outcome make it difficult to determine whether we should define these disorders as EEs or genetic encephalopathies with epilepsy. It is also still unclear whether WS and DS should be considered as EEs. In our opinion, the term “genetic or acquired encephalopathies with epilepsy”, rather than EEs, would be more appropriate to define neurological conditions with early cognitive involvement and seizures, such as DS. The use of this term would be clinically relevant to avoid excessive treatment with antiepileptic drugs that may help in controlling seizures but not improve the cognitive outcome. It should also be noted that excessive treatment (polytherapy) can even worsen the cognitive impairment (Fastenau et al., 2009; Ijff and Aldenkamp, 2013). The goal of treatment is thus to focus on the quality of life in order to optimize the interaction between the patient and his/her family (balance between seizures/sedation due to drugs).

Among the various pathophysiological mechanisms, neuroinflammation currently seems to be a putative common mechanism in different forms of EEs. The presence and role of inflammation in these various epilepsy syndromes thus needs to be further clarified. In addition, a better understanding of the mechanisms leading to cognitive impairment in the genetic EEs is needed because antiepileptic drugs, even when effective, fail to restore cognitive/behavioral function in most of these syndromes, cannot arrest the progression of cognitive deterioration, and may often have a negative impact on cognition and behavior. As an example, treatment in EIMFS should focus more on restoring the interaction between the mutated *KCNT1* C-terminal region and FMRP, since

the alteration of this specific interaction is considered to play a critical role in the severe cognitive impairment. Thus, future strategies for the management of EEs should combine antiepileptic drugs to control seizures and specifically tailored treatments targeting the underlying mechanisms, such as protein-protein interactions or neuroinflammation, to prevent/reverse the associated cognitive and behavioral impairment.

We can thus envisage a vicious pathological cycle where seizures and neuroinflammation each perpetuate the other. Neuroinflammation, in association with other mechanisms activated by seizures in epileptogenic brain areas, contributes to the progression of the disease, resulting in neurobehavioral deficits. There is experimental evidence to show that inflammatory molecules contribute to each of these outcomes (Vezzani et al., 2013). Genetic and epigenetic factors should also be considered as key determinants of the propensity of children to develop progressive pathologic sequelae when exposed to seizures and neuroinflammation.

Therapeutic interventions (indicated by the stop signal) should therefore target processes upstream of either seizures or neuroinflammation. Future treatment strategies aimed at preventing/reversing the second hit could be considered if it can be identified.

References

- Abraham, J., Fox, P.D., Condello, C., Bartolini, A., Koh, S., 2012. Minocycline attenuates microglia activation and blocks the long-term epileptogenic effects of early-life seizures. *Neurobiol. Dis.* 46, 425–430.
- Aicardi, J., Ohtahara, S. (2005) Severe neonatal epilepsies with suppression-burst. In: *Epileptic Syndromes in Infancy, Childhood and Adolescence* (Roger J., B. M., Dravet C., Genton P., Tassinari CA., Wolf P., ed), pp 39–50 Paris: John Libbey Eurotext.
- Akman, O., Moshe, S.L., Galanopoulou, A.S., 2014. Sex-specific consequences of early life seizures. *Neurobiol. Dis.* 72, 153–166.
- Albala, B.J., Moshe, S.L., Okada, R., 1984. KAINIC-acid-induced seizures — a developmental study. *Dev. Brain Res.* 13, 139–148.
- Aldenkamp, T., Arends, T., 2004. The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function. *Epilepsia* 45, 54–63.
- Amendola, E., Zhan, Y., Mattucci, C., Castroflorio, E., Calcagno, E., Fuchs, C., Lonetti, G., Silingardi, D., Vyssotski, A.L., Farley, D., Ciani, E., Pizzorusso, T., Giustetto, M., Gross, C.T., 2014. Mapping pathological phenotypes in a mouse model of CDKL5 disorder. *PLoS One* 9.
- Archer, J.S., Warren, A.E.L., Stagnitti, M.R., Masterton, R.A.J., Abbott, D.F., Jackson, G.D., 2014. Lennox-Gastaut syndrome and phenotype: secondary network epilepsies. *Epilepsia* 55, 1245–1254.
- Aronica, E., Crino, P.B., 2014. Epilepsy related to developmental tumors and malformations of cortical development. *Neurotherapeutics* 11, 251–268.
- Aronica, E., Fluiter, K., Iyer, A., Zurolo, E., Vreijling, J., van Vliet, E.A., Baayen, J.C., Gorter, J.A., 2010. Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *Eur. J. Neurosci.* 31, 1100–1107.
- Aronica, E., Ravizza, T., Zurolo, E., Vezzani, A., 2012. Astrocyte immune responses in epilepsy. *Glia* 60, 1258–1268.
- Arya, R., Shinnar, S., Glauser, T.A., 2012. Corticosteroids for the treatment of infantile spasms: a systematic review. *J. Child Neurol.* 27, 1284–1288.
- Arzimanoglou, A., French, J., Blume, W.T., Cross, J.H., Ernst, J.-P., Feucht, M., Genton, P., Guerrini, R., Kluger, G., Pellock, J.M., Perucca, E., Wheless, J.W., 2009. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol.* 8, 82–93.
- Auvin, S., 2014. Should we still consider Dravet syndrome an epileptic encephalopathy? *Epilepsy Behav.* 36, 80–81.
- Auvin, S., Hartman, A., Desnoux, B., Moreau, A., Alberti, C., Delanoe, C., Romano, A., Terrone, G., Kossoff, E.H., Del Giudice, E., Titomanlio, L., 2012a. Diagnosis Delay in West Syndrome: Misdiagnosis and Consequences *Eur J Pediatr.*
- Auvin, S., Mazarati, A., Shin, D., Sankar, R., 2010a. Inflammation enhances epileptogenesis in the developing rat brain. *Neurobiol. Dis.* 40, 303–310.
- Auvin, S., Pineda, E., Shin, D., Gressens, P., Mazarati, A., 2012b. Novel animal models of pediatric epilepsy. *Neurotherapeutics* 9, 245–261.
- Auvin, S., Shin, D., Mazarati, A., Sankar, R., 2010b. Inflammation induced by LPS enhances epileptogenesis in immature rat and may be partially reversed by IL1RA. *Epilepsia* 51, 34–38.
- Badano, J.L., Mitsuma, N., Beales, P.L., Katsanis, N., 2006. The ciliopathies: an emerging class of human genetic disorders. *Annual Review of Genomics and Human Genetics.* 7, pp. 125–148.
- Badawy, R.A.B., Macdonnell, R.A.L., Vogrin, S.J., Lai, A., Cook, M.J., 2012. Cortical excitability decreases in Lennox-Gastaut syndrome. *Epilepsia* 53, 1546–1553.
- Bahi-Buisson, N., Kaminska, A., Boddaert, N., Rio, M., Afenjar, A., Gerard, M., Giuliano, F., Motte, J., Heron, D., Morel, M.A.N., Plouin, P., Richelme, C., Portes, V.D., Dulac, O., Philippe, C., Chiron, C., Nabbout, R., Bienvenu, T., 2008a. The three stages of epilepsy in patients with CDKL5 mutations. *Epilepsia* 49, 1027–1037.
- Bahi-Buisson, N., Nectoux, J., Rosas-Vargas, H., Milh, M., Boddaert, N., Girard, B., Cances, C., Ville, D., Afenjar, A., Rio, M., Heron, D., Morel, M.A.N.G., Arzimanoglou, A., Philippe, C., Jonveaux, P., Chelly, J., Bienvenu, T., 2008b. Key clinical features to identify girls with CDKL5 mutations. *Brain* 131, 2647–2661.
- Baram, T.Z., Mitchell, W.G., Hanson, R.A., Snead, O.C., Horton, E.J., 1995. Cerebrospinal-fluid corticotropin and cortisol are reduced in infantile spasms. *Pediatr. Neurol.* 13, 108–110.
- Baram, T.Z., Mitchell, W.G., Snead, O.C., Horton, E.J., Saito, M., 1992. Brain-adrenal axis hormones are altered in the CSF of infants with massive infantile spasms. *Neurology* 42, 1171–1175.
- Baram, T.Z., Schultz, L., 1991. Corticotropin-releasing hormone is a rapid and potent convulsant in the infant rat. *Dev. Brain Res.* 61, 97–101.
- Barcia, G., Fleming, M.R., Deligniere, A., Gazula, V.-R., Brown, M.R., Langouet, M., Chen, H., Kronengold, J., Abhyankar, A., Cilio, R., Nitschke, P., Kaminska, A., Boddaert, N., Casanova, J.-L., Desguerre, I., Munnich, A., Dulac, O., Kaczmarek, L.K., Colleaux, L., Nabbout, R., 2012. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat. Genet.* 44, 1255–1259.
- Bender, A.C., Natola, H., Ndong, C., Holmes, G.L., Scott, R.C., Lenck-Santini, P.P., 2013. Focal Scn1a knockdown induces cognitive impairment without seizures. *Neurobiol. Dis.* 54, 297–307.
- Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, J.H., Boas, W.V., Engel, J., French, J., Glauser, T.A., Mathern, G.W., Moshe, S.L., Nordli, D., Plouin, P., Scheffer, I.E., 2010. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on classification and terminology, 2005–2009. *Epilepsia* 51, 676–685.
- Bilbo, S.D., Biedenkapp, J.C., Der-Avakian, A., Watkins, L.R., Rudy, J.W., Maier, S.F., 2005a. Neonatal infection-induced memory impairment after lipopolysaccharide in adulthood is prevented via caspase-1 inhibition. *J. Neurosci.* 25, 8000–8009.
- Bilbo, S.D., Levkoff, L.H., Mahoney, J.H., Watkins, L.R., Rudy, J.W., Maier, S.F., 2005b. Neonatal infection induces memory impairments following an immune challenge in adulthood. *Behav. Neurosci.* 119, 293–301.
- Bilbo, S.D., Schwarz, J.M., 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front. Behav. Neurosci.* 3, 14.
- Bilbo, S.D., Schwarz, J.M., 2012. The immune system and developmental programming of brain and behavior. *Front. Neuroendocrinol.* 33, 267–286.
- Blume, W.T., 2001. Pathogenesis of Lennox-Gastaut syndrome: considerations and hypotheses. *Epileptic Disord.* 3, 183–196.
- Boelsterli, B.K., Schmitt, B., Bast, T., Critelli, H., Heinze, J., Jenni, O.G., Huber, R., 2011. Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). *Clin. Neurophysiol.* 122, 1779–1787.
- Briggs, S.W., Mowrey, W., Hall, C.B., Galanopoulou, A.S., 2014. CPP-115, a vigabatrin analogue, decreases spasms in the multiple-hit rat model of infantile spasms. *Epilepsia* 55, 94–102.
- Bruncklaus, A., Dorris, L., Zuberi, S.M., 2011. Comorbidities and predictors of health-related quality of life in Dravet syndrome. *Epilepsia* 52, 1476–1482.
- Brunson, K.L., Eghbal-Ahmadi, M., Baram, T.Z., 2001a. How do the many etiologies of West syndrome lead to excitability and seizures? The corticotropin releasing hormone excess hypothesis. *Brain Dev.* 23, 533–538.
- Brunson, K.L., Khan, N., Eghbal-Ahmadi, M., Baram, T.Z., 2001b. Corticotropin (ACTH) acts directly on amygdala neurons to down-regulate corticotropin-releasing hormone gene expression. *Ann. Neurol.* 49, 304–312.
- Carpentier, P.A., Palmer, T.D., 2009. Immune influence on adult neural stem cell regulation and function. *Neuron* 64, 79–92.
- Chachua, T., Yum, M.-S., Veliskova, J., Velisek, L., 2011. Validation of the rat model of cryptogenic infantile spasms. *Epilepsia* 52, 1666–1677.
- Cilio, M.R., Dulac, O., Guerrini, R., Vigeveno, F. (2008) Migrating partial seizures in infancy. In: *Epilepsy: A Comprehensive Textbook*, vol. 3 (Engel, J. et al., eds), pp 2323–2328: Lippincott Williams & Wilkins.
- Colasante, G., Collombat, P., Raimondi, V., Bonanomi, D., Ferrai, C., Maira, M., Yoshikawa, K., Mansouri, A., Valtorta, F., Rubenstein, J.L., Broccoli, V., 2008. Arx is a direct target of Dlx2 and thereby contributes to the tangential migration of GABAergic interneurons. *J. Neurosci.* 28, 10674–10686.
- Colombo, E., Collombat, P., Colasante, G., Bianchi, M., Long, J., Mansouri, A., Rubenstein, J.L., Broccoli, V., 2007. Inactivation of Arx, the murine ortholog of the X-linked lissencephaly with ambiguous genitalia gene, leads to severe disorganization of the ventral telencephalon with impaired neuronal migration and differentiation. *J. Neurosci.* 27, 4786–4798.
- Coppola, G., Plouin, P., Chiron, C., Robain, O., Dulac, O., 1995. Migrating partial seizures in infancy — a malignant disorder with developmental arrest. *Epilepsia* 36, 1017–1024.
- Cortez, M.A., Sadeghnia, H., Aleem, I., Trepanier, C., Ashraff, A., Kanawaty, A., Shen, L., Snead III, O.C., 2007. II. A new animal model of infantile spasms: ACTH and antiepileptic drug profiles. *Neurology* 68, A211.
- Cortez, M.A., Shen, L., Wu, Y., Aleem, I.S., Trepanier, C.H., Sadeghnia, H.R., Ashraf, A., Kanawaty, A., Liu, C.-C., Stewart, T., Snead III, O.C., 2009. Infantile spasms and down syndrome: a new animal model. *Pediatr. Res.* 65, 499–503.
- De Simoni, M.G., Perego, C., Ravizza, T., Moneta, D., Conti, M., Marchesi, F., De Luigi, A., Garattini, S., Vezzani, A., 2000. Inflammatory cytokines and related genes are induced in the rat hippocampus by limbic status epilepticus. *Eur. J. Neurosci.* 12, 2623–2633.
- De Tieghe, X., Goldman, S., Laureys, S., Verheulpen, D., Chiron, C., Wetzburger, C., Paquier, P., Chaigne, D., Poznanski, N., Jambaque, I., Hirsch, E., Dulac, O., Van Bogaert, P., 2004. Regional cerebral glucose metabolism in epilepsies with continuous spikes and waves during sleep. *Neurology* 63, 853–857.
- De Tieghe, X., Goldman, S., Van Bogaert, P., 2009. Insights into the pathophysiology of psychomotor regression in CSWS syndromes from FDG-PET and EEG-fMRI. *Epilepsia* 50, 47–50.

- De Tiege, X., Ligtot, N., Goldman, S., Poznanski, N., de Saint, Martin, A., Van Bogaert, P., 2008. Metabolic evidence for remote inhibition in epilepsies with continuous spike-waves during sleep. *NeuroImage* 40, 802–810.
- Depienne, C., Trouillard, O., Saint-Martin, C., Gourfinkel-An, I., Bouteiller, D., Carpentier, W., Keren, B., Abert, B., Gautier, A., Baulac, S., Arzimanoglou, A., Cazeneuve, C., Nabbout, R., LeGuern, E., 2009. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. *J. Med. Genet.* 46, 183–191.
- Devinsky, O., Vezzani, A., Najjar, S., De Lanerolle, N.C., Rogawski, M.A., 2013. Glia and epilepsy: excitability and inflammation. *Trends Neurosci.* 36, 174–184.
- Diekemann, S., Born, J., 2010. Sleep the memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126.
- Dube, C., Vezzani, A., Behrens, M., Bartfai, T., Baram, T.Z., 2005. Interleukin-1 beta contributes to the generation of experimental febrile seizures. *Ann. Neurol.* 57, 152–155.
- Dube, C.M., Ravizza, T., Hamamura, M., Zha, Q., Keebaugh, A., Fok, K., Andres, A.L., Nalcioğlu, O., Obenaus, A., Vezzani, A., Baram, T.Z., 2010. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J. Neurosci.* 30, 7484–7494.
- Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Huppi, P.S., Hertz-Pannier, L., 2014. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience* 276, 48–71.
- Dulac O, Tuxhorn I (2005) Infantile spasms and West syndrome. In: *Epileptic Syndromes in Infancy, Children and Adolescents* (Roger, J. B., M. Dravet, C. Genton, P. Tassinari, CA. Wolf, P., ed), pp 53–71 Paris: John Libbey Eurotext.
- Eksioglu, Y.Z., Pong, A.W., Takeoka, M., 2011. A novel mutation in the aristaless domain of the ARX gene leads to Ohtahara syndrome, global developmental delay, and ambiguous genitalia in males and neuropsychiatric disorders in females. *Epilepsia* 52, 984–992.
- Fastenau, P.S., Johnson, C.S., Perkins, S.M., Byars, A.W., deGrauw, T.J., Austin, J.K., Dunn, D.W., 2009. Neuropsychological status at seizure onset in children risk factors for early cognitive deficits. *Neurology* 73, 526–534.
- Ferlazzo, E., Nikaronova, M., Italiano, D., Bureau, M., Dravet, C., Calarese, T., Viallat, D., Kolmel, M., Bramanti, P., De Santi, L., Genton, P., 2010. Lennox-Gastaut syndrome in adulthood: clinical and EEG features. *Epilepsy Res.* 89, 271–277.
- Fleming, M.R., Kaczmarek, L.K., 2009. Use of optical biosensors to detect modulation of slack potassium channels by G protein-coupled receptors. *Journal of Receptors and Signal Transduction* 29, 173–181.
- Friocourt, G., Kanatani, S., Tabata, H., Yozu, M., Takahashi, T., Antypa, M., Raguénès, O., Chelly, J., Férec, C., Nakajima, K., Parnavelas, J.G., 2008. Cell-autonomous roles of ARX in cell proliferation and neuronal migration during corticogenesis. *J. Neurosci.* 28, 5794–5805.
- Frost Jr., J.D., Lee, C.L., Hrachovy, R.A., Swann, J.W., 2011. High frequency EEG activity associated with ictal events in an animal model of infantile spasms. *Epilepsia* 52, 53–62.
- Fuchs, C., Trazzi, S., Torricella, R., Viggiano, R., De Franceschi, M., Amendola, E., Gross, C., Calza, L., Bartesaghi, R., Ciani, E., 2014. Loss of CDKL5 impairs survival and dendritic growth of newborn neurons by altering AKT/GSK-3 beta signaling. *Neurobiol. Dis.* 70, 53–68.
- Fullston, T., Brueton, L., Willis, T., Philip, S., MacPherson, L., Finnis, M., Geetz, J., Morton, J., 2010. Ohtahara syndrome in a family with an ARX protein truncation mutation (c.81C > G/p.Y27X). *Eur. J. Hum. Genet.* 18, 157–162.
- Galanopoulou, A.S., Moshe, S.L., 2015. Pathogenesis and new candidate treatments for infantile spasms and early life epileptic encephalopathies: a view from preclinical studies. *Neurobiol. Dis.* 79, 135–149.
- Galdzicki, Z., Siarey, R.J., 2003. Understanding mental retardation in Down's syndrome using trisomy 16 mouse models. *Genes Brain and Behavior* 2, 167–178.
- Galic, M.A., Riazi, K., Heida, J.G., Mouhate, A., Fournier, N.M., Spencer, S.J., Kalyanchuk, L.E., Teskey, G.C., Pittman, Q.J., 2008a. Postnatal inflammation increases seizure susceptibility in adult rats. *J. Neurosci.* 28, 6904–6913.
- Galic, M.A., Riazi, K., Heida, J.G., Mouhate, A., Fournier, N.M., Spencer, S.J., Kalyanchuk, L.E., Teskey, G.C., Pittman, Q.J., 2008b. Postnatal inflammation increases seizure susceptibility in adult rats. *J. Neurosci.* 28, 6904–6913.
- Galic, M.A., Riazi, K., Henderson, A.K., Tsutsui, S., Pittman, Q.J., 2009. Viral-like brain inflammation during development causes increased seizure susceptibility in adult rats. *Neurobiol. Dis.* 36, 343–351.
- Galic, M.A., Riazi, K., Pittman, Q.J., 2012. Cytokines and brain excitability. *Front. Neuroendocrinol.* 33, 116–125.
- Galvan, C.D., Hrachovy, R.A., Smith, K.L., Swann, J.W., 2000. Blockade of neuronal activity during hippocampal development produces a chronic focal epilepsy in the rat. *J. Neurosci.* 20, 2904–2916.
- Galvan, C.D., Wenzel, J.H., Dineley, K.T., Lam, T.T., Schwartzkroin, P.A., Sweatt, J.D., Swann, J.W., 2003. Postsynaptic contributions to hippocampal network hyperexcitability induced by chronic activity blockade in vivo. *Eur. J. Neurosci.* 18, 1861–1872.
- Gastaut, H., Roger, J., Soulayrol, R., Tassinari, C.A., Regis, H., Dravet, C., Bernard, R., Pinsard, N., Saint-Jean, M., 1966. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as “petit mal variant”) or Lennox syndrome. *Epilepsia* 7, 139–179.
- Giordano, L., Sartori, S., Russo, S., Accorsi, P., Galli, J., Tiberti, A., Bettella, E., Marchi, M., Vignoli, A., Darra, F., Murgia, A., Dalla Bernardina, B., 2010. Familial Ohtahara syndrome due to a novel ARX gene mutation. *Am. J. Med. Genet. A* 152A, 3133–3137.
- Gorter, J.A., Iyer, A., White, I., Colzi, A., van Vliet, E.A., Sisodiya, S., Aronica, E., 2014. Hippocampal subregion-specific microRNA expression during epileptogenesis in experimental temporal lobe epilepsy. *Neurobiol. Dis.* 62, 508–520.
- Graeber, M.B., Li, W., Rodriguez, M.L., 2011. Role of microglia in CNS inflammation. *FEBS Lett.* 585, 3798–3805.
- Gupta, R., Appleton, R., 2005. Corticosteroids in the management of the paediatric epilepsies. *Arch. Dis. Child.* 90, 379–384.
- Guzzetta, F., 2011. Cognitive and behavioral characteristics of children with Dravet syndrome: an overview. *Epilepsia* 52, 35–38.
- Gygax, M.J., Klein, B.D., White, H.S., Kim, M., Galanopoulou, A.S., 2014. Efficacy and tolerability of the galanin analog NAX 5055 in the multiple-hit rat model of symptomatic infantile spasms. *Epilepsy Res.* 108, 98–108.
- Haas, K.Z., Sperber, E.F., Opanashuk, L.A., Stanton, P.K., Moshe, S.L., 2001. Resistance of immature hippocampus to morphologic and physiologic alterations following status epilepticus or kindling. *Hippocampus* 11, 615–625.
- Hagberg, H., Mallard, C., 2005. Effect of inflammation on central nervous system development and vulnerability. *Curr. Opin. Neurol.* 18, 117–123.
- Han, S., Tai, C., Westenbroek, R.E., Yu, F.H., Cheah, C.S., Potter, G.B., Rubenstein, J.L., Scheuer, T., de la Iglesia, H.O., Catterall, W.A., 2012. Autistic-like behaviour in *Scn1a*(+/-) mice and rescue by enhanced GABA-mediated neurotransmission. *Nature* 489, 385–390.
- Han, X., Li, N., Meng, Q., Shao, F., Wang, W., 2011. Maternal immune activation impairs reversal learning and increases serum tumor necrosis factor-alpha in offspring. *Neuropsychobiology* 64, 9–14.
- Hancock, E.C., Osborne, J.P., Edwards, S.W., 2013. Treatment of infantile spasms. *The Cochrane Database of Systematic Reviews* 6, CD001770.
- Harre, E.M., Galic, M.A., Mouhate, A., Noorbakhsh, F., Pittman, Q.J., 2008. Neonatal inflammation produces selective behavioural deficits and alters N-methyl-D-aspartate receptor subunit mRNA in the adult rat brain. *Eur. J. Neurosci.* 27, 644–653.
- Hernan, A.E., Alexander, A., Jenks, K.R., Barry, J., Lenck-Santini, P.-P., Isaeva, E., Holmes, G.L., Scott, R.C., 2014. Focal epileptiform activity in the prefrontal cortex is associated with long-term attention and sociability deficits. *Neurobiol. Dis.* 63, 25–34.
- Hirose, M., Haginoya, K., Yokoyama, H., Tanaka, S., Uematsu, M., Kaneta, T., Takayanagi, M., Kon, K., Yoshihara, Y., Iinuma, K., Tsuchiya, S., 2010. Functional cortical deafferentation from the subcortical structures in a patient with early myoclonic encephalopathy: a functional neuroimaging study. *Epilepsia* 51, 699–702.
- Hirose, S., Mitsudome, A., 2003. X-linked mental retardation and epilepsy: pathogenetic significance of ARX mutations. *Brain Dev.* 25, 161–165.
- Hirsch, E., Marescaux, C., Maquet, P., Metzluft, M.N., Kiesmann, M., Salmon, E., Franck, G., Kurtz, D., 1990. Landau-Kleffner syndrome – a clinical and EEG study of 5 cases. *Epilepsia* 31, 756–767.
- Holmes, G.L., 2014. What is more harmful, seizures or epileptic EEG abnormalities? Is there any clinical data? *Epileptic Disord.* 16, S12–S22.
- Holmes, G.L., Lenck-Santini, P.-P., 2006. Role of interictal epileptiform abnormalities in cognitive impairment. *Epilepsy Behav.* 8, 504–515.
- Ijff, D.M., Aldenkamp, A.P., 2013. Cognitive side-effects of antiepileptic drugs in children. *Handb. Clin. Neurol.* 111, 707–718.
- Inoue, T., Kawawaki, H., Kuki, I., Nabatame, S., Tomonoh, Y., Sukigara, S., Horino, A., Nukui, M., Okazaki, S., Tomiwa, K., Kimura-Ohba, S., Inoue, T., Hirose, S., Shiomi, M., Itoh, M., 2013. A case of severe progressive early-onset epileptic encephalopathy: unique GABAergic interneuron distribution and imaging. *J. Neurol. Sci.* 327, 65–72.
- Intusoma, U., Abbott, D.F., Masterton, R.A.J., Stagnitti, M.R., Newton, M.R., Jackson, G.D., Freeman, J.L., Harvey, A.S., Archer, J.S., 2013. Tonic seizures of Lennox-Gastaut syndrome: periictal single-photon emission computed tomography suggests a corticopontine network. *Epilepsia* 54, 2151–2157.
- Ito, S., Ogiwara, I., Yamada, K., Miyamoto, H., Hensch, T.K., Osawa, M., Yamakawa, K., 2013. Mouse with *Na(v)1.1* haploinsufficiency, a model for Dravet syndrome, exhibits lowered sociability and learning impairment. *Neurobiol. Dis.* 49, 29–40.
- Iyer, A., Zurolo, E., Prabowo, A., Fluiter, K., Spliet, W.G.M., van Rijen, P.C., Gorter, J.A., Aronica, E., 2012. MicroRNA-146a: A Key Regulator of Astrocyte-Mediated Inflammatory Response. *PLoS One* 7.
- Japaridze, N., Muthuraman, M., Reinicke, C., Moeller, F., Anwar, A.R., Mideksa, K.G., Pressler, R., Deuschl, G., Stephani, U., Siniahtchkin, M., 2015. Neuronal networks during burst suppression as revealed by source analysis. *PLoS One* 10.
- Jarvela, J.T., Lopez-Picon, F.R., Holopainen, I.E., 2008. Age-dependent cyclooxygenase-2 induction and neuronal damage after status epilepticus in the postnatal rat hippocampus. *Epilepsia* 49, 832–841.
- Jarvela, J.T., Lopez-Picon, F.R., Pylsjuk, A., Ruohonen, S., Holopainen, I.E., 2011. Temporal profiles of age-dependent changes in cytokine mRNA expression and glial cell activation after status epilepticus in postnatal rat hippocampus. *J. Neuroinflammation* 8.
- Kabova, R., Liptakova, S., Slamberova, R., Pometlova, M., Velisek, L., 1999. Age-specific N-methyl-D-aspartate-induced seizures: perspectives for the West syndrome model. *Epilepsia* 40, 1357–1369.
- Kaczmarek, L.K., 2006. Non-conducting functions of voltage-gated ion channels. *Nat. Rev. Neurosci.* 7, 761–771.
- Kalscheuer, V.M., Tao, J., Donnelly, A., Hollway, G., Schwinger, E., Kubart, S., Menzel, C., Hoelzenbein, M., Tommerup, N., Eyre, H., Harbord, M., Haan, E., Sutherland, G.R., Ropers, H.H., Geetz, J., 2003. Disruption of the serine/threonine kinase 9 gene causes severe x-linked infantile spasms and mental retardation. *Am. J. Hum. Genet.* 72, 1401–1411.
- Kato, M., Das, S., Petras, K., Sawaishi, Y., Dobyns, W.B., 2003. Polyalanine expansion of ARX associated with cryptogenic West syndrome. *Neurology* 61, 267–268.
- Kato, M., Koyama, N., Ohta, M., Miura, K., Hayasaka, K., 2010. Frameshift mutations of the ARX gene in familial Ohtahara syndrome. *Epilepsia* 51, 1679–1684.
- Kato, M., Yamagata, T., Kubota, M., Arai, H., Yamashita, S., Nakagawa, T., Fujii, T., Sugai, K., Imai, K., Uster, T., Chitayat, D., Weiss, S., Kashii, H., Kusano, R., Matsumoto, A., Nakamura, K., Oyazato, Y., Maeno, M., Nishiyama, K., Koder, H., Nakashima, M., Tsurusaki, Y., Miyake, N., Saito, K., Hayasaka, K., Matsumoto, N., Saito, H., 2013. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. *Epilepsia* 54, 1282–1287.
- Kerrigan, J.F., Shields, W.D., Nelson, T.Y., Bluestone, D.L., Dodson, W.E., Bourgeois, B.F.D., Pellock, J.M., Morton, L.D., Monaghan, A.P., 2000. Ganaxolone for treating intractable infantile spasms: a multicenter, open-label, add-on trial. *Epilepsy Res.* 42, 133–139.

- Khan, O.I., Zhao, Q., Miller, F., Holmes, G.L., 2010. Interictal spikes in developing rats cause long-standing cognitive deficits. *Neurobiol. Dis.* 39, 362–371.
- Kim, G.E., Kronengold, J., Barcia, G., Quraishi, I.H., Martin, H.C., Blair, E., Taylor, J.C., Dulac, O., Colleaux, L., Nabbout, R., Kaczmarek, L.K., 2014. Human slack potassium channel mutations increase positive cooperativity between individual channels. *Cell Reports* 9, 1661–1672.
- Kitamura, K., Yanazawa, M., Sugiyama, N., Miura, H., Iizuka-Kogo, A., Kusaka, M., Omichi, K., Suzuki, R., Kato-Fukui, Y., Kamiirisa, K., Matsuo, M., Kamijo, S., Kasahara, M., Yoshioka, H., Ogata, T., Fukuda, T., Kondo, I., Kato, M., Dobyns, W.B., Yokoyama, M., Morohashi, K., 2002. Mutation of ARX causes abnormal development of forebrain and testes in mice and x-linked lissencephaly with abnormal genitalia in humans. *Nat. Genet.* 32, 359–369.
- Kleene, J.K., Scott, R.C., Holmes, G.L., Lenck-Santini, P.P., 2010. Hippocampal interictal spikes disrupt cognition in rats. *Ann. Neurol.* 67, 250–257.
- Klein, K.M., Yendle, S.C., Harvey, A.S., Antony, J.H., Wallace, G., Bienvenu, T., Scheffer, I.E., 2011. A distinctive seizure type in patients with CDKL5 mutations: hypermotor-tonic-spasms sequence. *Neurology* 76, 1436–1438.
- Koo, B., Hwang, P.A., Logan, W.J., 1993. Infantile spasms — outcome and prognostic factors of cryptogenic and symptomatic groups. *Neurology* 43, 2322–2327.
- Lee, C.L., Frost Jr., J.D., Swann, J.W., Hrachovy, R.A., 2008. A new animal model of infantile spasms with unprovoked persistent seizures. *Epilepsia* 49, 298–307.
- Lennox, W.G., Davis, J.P., 1950. Clinical correlates of the fast and the slow spike-wave electroencephalogram. *Pediatrics* 5, 626–644.
- Loring, D.W., Meador, K.J., 2004. Cognitive side effects of antiepileptic drugs in children. *Neurology* 62, 872–877.
- Marcon, J., Gagliardi, B., Balosso, S., Maroso, M., Noe, F., Morin, M., Lerner-Natoli, M., Vezzani, A., Ravizza, T., 2009. Age-dependent vascular changes induced by status epilepticus in rat forebrain: implications for epileptogenesis. *Neurobiol. Dis.* 34, 121–132.
- Mares, P., Velisek, L., 1992. N-methyl-D-aspartate (NMDA)-induced seizures in developing rats. *Brain Res. Dev. Brain Res.* 65, 185–189.
- Marsh, E., Fulp, C., Gomez, E., Nasrallah, I., Mincaric, J., Sudi, J., Christian, S.L., Mancini, G., Labosky, P., Dobyns, W., Brooks-Kayal, A., Golden, J.A., 2009. Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. *Brain* 132, 1563–1576.
- Mei, D., Marini, C., Novara, F., Bernardina, B.D., Granata, T., Fontana, E., Parrini, E., Ferrari, A.R., Murgia, A., Zuffardi, O., Guerrini, R., 2010. Xp22.3 genomic deletions involving the CDKL5 gene in girls with early onset epileptic encephalopathy. *Epilepsia* 51, 647–654.
- Melani, F., Mei, D., Pisano, T., Savasta, S., Franzoni, E., Ferrari, A.R., Marini, C., Guerrini, R., 2011. CDKL5 gene-related epileptic encephalopathy: electroclinical findings in the first year of life. *Dev. Med. Child Neurol.* 53, 354–360.
- Miceli, F., Soldovieri, M.V., Ambrosino, P., Barrese, V., Migliore, M., Cilio, M.R., Tagliatela, M., 2013. Genotype-phenotype correlations in neonatal epilepsies caused by mutations in the voltage sensor of K(v)7.2 potassium channel subunits. *Proc. Natl. Acad. Sci. U. S. A.* 110, 4386–4391.
- Miceli, F., Soldovieri, M.V., Ambrosino, P., De Maria, M., Migliore, M., Migliore, R., Tagliatela, M., 2015. Early-onset epileptic encephalopathy caused by gain-of-function mutations in the voltage sensor of K(v)7.2 and K(v)7.3 potassium channel subunits. *J. Neurosci.* 35, 3782–3793.
- Milh, M., Becq, H., Villeneuve, N., Ben-Ari, Y., Aniksztejn, L., 2007. Inhibition of glutamate transporters results in a “suppression-burst” pattern and partial seizures in the newborn rat. *Epilepsia* 48, 169–174.
- Milh, M., Boutry-Kryza, N., Suter-Sardo, J., Mignot, C., Auvin, S., Lacoste, C., Villeneuve, N., Roubertie, A., Heron, B., Carneiro, M., Kaminska, A., Altuzarra, C., Blanchard, G., Ville, D., Barthez, M.A., Heron, D., Gras, D., Afenjar, A., Dorison, N., Doummar, D., de Villemeur, T.B., An, I., Jacqueline, A., Charles, P., Perrier, J., Isidor, B., Vercueil, L., Chabrol, B., Badens, C., Lesca, G., Villard, L., 2013. Similar early characteristics but variable neurological outcome of patients with a de novo mutation of KCNQ2. *Orphanet Journal of Rare Diseases* 8.
- Minami, M., Kuraishi, Y., Satoh, M., 1991. Effects of kainic acid on messenger-RNA levels of IL-1 β , IL-6, TNF- α and LIF in the rat-brain. *Biochem. Biophys. Res. Commun.* 176, 593–598.
- Minami, M., Kuraishi, Y., Yamaguchi, T., Nakai, S., Hirai, Y., Satoh, M., 1990. Convulsants induce interleukin-1 β messenger-RNA in rat-brain. *Biochem. Biophys. Res. Commun.* 171, 832–837.
- Mistry, A.M., Thompson, C.H., Miller, A.R., Vanoye, C.G., George, A.L., Kearney, J.A., 2014. Strain- and age-dependent hippocampal neuron sodium currents correlate with epilepsy severity in Dravet syndrome mice. *Neurobiol. Dis.* 65, 1–11.
- Nabbout, R., Chemaly, N., Chipaux, M., Barcia, G., Bouis, C., Dubouch, C., Leunen, D., Jambaque, I., Dulac, O., Dellatolas, G., Chiron, C., 2013. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. *Orphanet Journal of Rare Diseases* 8.
- Nabbout, R., Vezzani, A., Dulac, O., Chiron, C., 2011. Acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol.* 10, 99–108.
- Niedermeyer, E., 1996. Primary (idiopathic) generalized epilepsy and underlying mechanisms. *Clin. Electroencephalogr.* 27, 1–21.
- Noe, F.M., Polascheck, N., Frigerio, F., Bankstahl, M., Ravizza, T., Marchini, S., Beltrame, L., Bandero, C.R., Loscher, W., Vezzani, A., 2013. Pharmacological blockade of IL-1 β /IL-1 receptor type 1 axis during epileptogenesis provides neuroprotection in two rat models of temporal lobe epilepsy. *Neurobiol. Dis.* 59, 183–193.
- Numis, A.L., Angriman, M., Sullivan, J.E., Lewis, A.J., Striano, P., Nabbout, R., Cilio, M.R., 2014. KCNQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response. *Neurology* 82, 368–370.
- Ogiwara, I., Miyamoto, H., Morita, N., Atapour, N., Mazaki, E., Inoue, I., Takeuchi, T., Itohara, S., Yanagawa, Y., Obata, K., Furuichi, T., Hensch, T.K., Yamakawa, K., 2007. Na(v)1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. *J. Neurosci.* 27, 5903–5914.
- Oguni, H., Hayashi, K., Osawa, M., 1996. Long-term prognosis of Lennox-Gastaut syndrome. *Epilepsia* 37, 44–47.
- Ohba, C., Kato, M., Takahashi, N., Osaka, H., Shiihara, T., Tohyama, J., Nabatame, S., Azuma, J., Fujii, Y., Hara, M., Tsurusawa, R., Inoue, T., Ogata, R., Watanabe, Y., Togashi, N., Koder, H., Nakashima, M., Tsurusaki, Y., Miyake, N., Tanaka, F., Saito, H., Matsumoto, N., 2015. De novo KCNT1 mutations in early-onset epileptic encephalopathy. *Epilepsia* 56, e121–e128.
- Olivetti, P.R., Maheshwari, A., Noebels, J.L., 2014. Neonatal estradiol stimulation prevents epilepsy in Arx model of x-linked infantile spasms syndrome. *Sci. Transl. Med.* 6.
- Omran, A., Peng, J., Zhang, C.L., Xiang, Q.L., Xue, J.F., Gan, N., Kong, H.M., Yin, F., 2012. Interleukin-1 β and microRNA-146a in an immature rat model and children with mesial temporal lobe epilepsy. *Epilepsia* 53, 1215–1224.
- Ono, T., Moshe, S.L., Galanopoulou, A.S., 2011. Carisbamate acutely suppresses spasms in a rat model of symptomatic infantile spasms. *Epilepsia* 52, 1678–1684.
- Orhan, G., Bock, M., Schepers, D., Ilna, E.L., Reichel, S.N., Loeffler, H., Jezutkovic, N., Weckhuysen, S., Mandelstam, S., Suls, A., Danker, T., Guenther, E., Scheffer, I.E., De Jonghe, P., Lerche, H., Maljevic, S., 2014. Dominant-negative effects of KCNQ2 mutations are associated with epileptic encephalopathy. *Ann. Neurol.* 75, 382–394.
- Patry, G., Lyagoubi, S., Tassinari, C.A., 1971. Subclinical “electrical status epilepticus” induced by sleep in children. A clinical and electroencephalographic study of six cases. *Archives of Neurology* 24, 242–252.
- Pavone, P., Spalice, A., Polizzi, A., Parisi, P., Ruggieri, M., 2012. Ohtahara syndrome with emphasis on recent genetic discovery. *Brain Dev.* 34, 459–468.
- Peng, J., Omran, A., Ashhab, M.U., Kong, H., Gan, N., He, F., Yin, F., 2013. Expression patterns of miR-124, miR-134, miR-132, and miR-21 in an immature rat model and children with mesial temporal lobe epilepsy. *J. Mol. Neurosci.* 50, 291–297.
- Pieribone, V.A., Tsai, J., Soufflet, C., Rey, E., Shaw, K., Giller, E., Dulac, O., 2007. Clinical evaluation of ganaxolone in pediatric and adolescent patients with refractory epilepsy. *Epilepsia* 48, 1870–1874.
- Pillay, N., Archer, J.S., Badawy, R.A.B., Flanagan, D.F., Berkovic, S.F., Jackson, G., 2013. Networks underlying paroxysmal fast activity and slow spike and wave in Lennox-Gastaut syndrome. *Neurology* 81, 665–673.
- Pineda, E., Shin, D., You, S.J., Auvin, S., Sankar, R., Mazarati, A., 2013a. Maternal immune activation promotes hippocampal kindling epileptogenesis in mice. *Ann. Neurol.* 74, 11–19.
- Pineda, E., Shin, D., You, S.J., Auvin, S., Sankar, R., Mazarati, A., 2013b. Maternal immune activation promotes hippocampal kindling epileptogenesis in mice. *Ann. Neurol.* 74, 11–19.
- Price, M.G., Yoo, J.W., Burgess, D.L., Deng, F., Hrachovy, R.A., Frost Jr., J.D., Noebels, J.L., 2009. A triplet repeat expansion genetic mouse model of infantile spasms syndrome, Arx((CGC)10 + 7), with interneuronopathy, spasms in infancy, persistent seizures, and adult cognitive and behavioral impairment. *J. Neurosci.* 29, 8752–8763.
- Raffo, E., Coppola, A., Ono, T., Briggs, S.W., Galanopoulou, A.S., 2011. A pulse rapamycin therapy for infantile spasms and associated cognitive decline. *Neurobiol. Dis.* 43, 322–329.
- Rantala, H., Putkonen, T., 1999. Occurrence, outcome, and prognostic factors of infantile spasms and Lennox-Gastaut syndrome. *Epilepsia* 40, 286–289.
- Rapin, I., 1988. Verbal auditory agnosia in children. *Dev. Med. Child Neurol.* 30, 685.
- Ravizza, T., Gagliardi, B., Noe, F., Boer, K., Aronica, E., Vezzani, A., 2008. Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. *Neurobiol. Dis.* 29, 142–160.
- Reddy, D.S., Rogawski, M.A., 2002. Stress-induced deoxycorticosterone-derived neurosteroids modulate GABA(A) receptor function and seizure susceptibility. *J. Neurosci.* 22, 3795–3805.
- Rees, S., Harding, R., Walker, D., 2008. An adverse intrauterine environment: implications for injury and altered development of the brain. *Int. J. Dev. Neurosci.* 26, 3–11.
- Riazi, K., Galic, M.A., Kuzmiski, J.B., Ho, W., Sharkey, K.A., Pittman, Q.J., 2008. Microglial activation and TNF α production mediate altered CNS excitability following peripheral inflammation. *Proc. Natl. Acad. Sci. U. S. A.* 105, 17151–17156.
- Riazi, K., Galic, M.A., Pittman, Q.J., 2010. Contributions of peripheral inflammation to seizure susceptibility: cytokines and brain excitability. *Epilepsy Res.* 89, 34–42.
- Riikonen, R., 2004. Infantile spasms: therapy and outcome. *J. Child Neurol.* 19, 401–404.
- Rizzi, M., Perego, C., Aliprandi, M., Richichi, C., Ravizza, T., Colella, D., Veliskova, J., Moshe, S.L., De Simoni, M.G., Vezzani, A., 2003. Glia activation and cytokine increase in rat hippocampus by kainic acid-induced status epilepticus during postnatal development. *Neurobiol. Dis.* 14, 494–503.
- Rogawski, M.A., Reddy, D.S., 2002. Neurosteroids and infantile spasms: the deoxycorticosterone hypothesis. *Epilepsy, Infantile Spasms, and Developmental Encephalopathy* 49, 199–219.
- Ronen, G.M., TO, Rosales, Connolly, M., Anderson, V.E., Leppert, M., 1993. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 43, 1355–1360.
- Saito, H., Kato, M., Koide, A., Goto, T., Fujita, T., Nishiyama, K., Tsurusaki, Y., Doi, H., Miyake, N., Hayasaka, K., Matsumoto, N., 2012. Whole exome sequencing identifies KCNQ2 mutations in Ohtahara syndrome. *Ann. Neurol.* 72, 298–300.
- Saito, H., Kato, M., Mizuguchi, T., Hamada, K., Osaka, H., Tohyama, J., Urano, K., Kumada, S., Nishiyama, K., Nishimura, A., Okada, I., Yoshimura, Y., S-i, Hirai, Kumada, T., Hayasaka, K., Fukuda, A., Ogata, K., Matsumoto, N., 2008. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nat. Genet.* 40, 782–788.

- Sanchez Fernandez, I., Chapman, K.E., Peters, J.M., Kothare, S.V., Nordli Jr., D.R., Jensen, F.E., Berg, A.T., Loddenkemper, T., 2013. The tower of Babel: survey on concepts and terminology in electrical status epilepticus in sleep and continuous spikes and waves during sleep in North America. *Epilepsia* 54, 741–750.
- Sanchez Fernandez, I., Loddenkemper, T., Peters, J.M., Kothare, S.V., 2012. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. *Pediatr. Neurol.* 47, 390–410.
- Scantlebury, M.H., Galanopoulou, A.S., Chudomelova, L., Raffo, E., Betancourth, D., Moshe, S.L., 2010. A model of symptomatic infantile spasms syndrome. *Neurobiol. Dis.* 37, 604–612.
- Shah, M.M., Migliore, M., Valencia, I., Cooper, E.C., Brown, D.A., 2008. Functional significance of axonal Kv7 channels in hippocampal pyramidal neurons. *Proc. Natl. Acad. Sci. U. S. A.* 105, 7869–7874.
- Shen, J., Tareste, D.C., Paumet, F., Rothman, J.E., Melia, T.J., 2007. Selective activation of cognate SNAREpins by Sec1/Munc18 proteins. *Cell* 128, 183–195.
- Singh, N.A., Charlier, C., Stauffer, D., DuPont, B.R., Leach, R.J., Melis, R., Ronen, G.M., Bjerre, I., Quattlebaum, T., Murphy, J.V., McHarg, M.L., Gagnon, D., TO, Rosales, Peiffer, A., Anderson, V.E., Leppert, M., 1998. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat. Genet.* 18, 25–29.
- Siniatchkin, M., Coropceanu, D., Moeller, F., Boor, R., Stephani, U., 2011. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome. *Epilepsia* 52, 766–774.
- Siniatchkin, M., Groening, K., Moehring, J., Moeller, F., Boor, R., Brodbeck, V., Michel, C.M., Rodionov, R., Lemieux, L., Stephani, U., 2010. Neuronal networks in children with continuous spikes and waves during slow sleep. *Brain* 133, 2798–2813.
- Snead 3rd, O.C., Depaulis, A., Vergnes, M., Marescaux, C., 1999. Absence epilepsy: advances in experimental animal models. *Adv. Neurol.* 79, 253–278.
- Soldovieri, M.V., Boutry-Kryza, N., Milh, M., Doummar, D., Heron, B., Bourel, E., Ambrosino, P., Miceli, F., De Maria, M., Dorison, N., Auvin, S., Echenne, B., Oertel, J., Riquet, A., Lambert, L., Gerard, M., Roubergue, A., Calender, A., Mignot, C., Tagliatalata, M., Lesca, G., 2014. Novel KCNQ2 and KCNQ3 mutations in a large cohort of families with benign neonatal epilepsy: first evidence for an altered channel regulation by syntaxin-1A. *Hum. Mutat.* 35, 356–367.
- Soldovieri, M.V., Cilio, M.R., Miceli, F., Bellini, G., del Giudice, E.M., Castaldo, P., Hernandez, C.C., Shapiro, M.S., Pascotto, A., Annunziato, L., Tagliatalata, M., 2007. Atypical gating of M-type potassium channels conferred by mutations in uncharged residues in the S-4 region of KCNQ2 causing benign familial neonatal convulsions. *J. Neurosci.* 27, 4919–4928.
- Somera-Molina, K.C., Nair, S., Van Eldik, L.J., Watterson, D.M., Wainwright, M.S., 2009. Enhanced microglial activation and proinflammatory cytokine upregulation are linked to increased susceptibility to seizures and neurologic injury in a 'two-hit' seizure model. *Brain Res.* 1282, 162–172.
- Stafstrom, C.E., Konkol, R.J., 1994. Infantile spasms in children with Down-syndrome. *Dev. Med. Child Neurol.* 36, 576–585.
- Stafstrom, C.E., Sasaki-Adams, D.M., 2003. NMDA-induced seizures in developing rats cause long-term learning impairment and increased seizure susceptibility. *Epilepsy Res.* 53, 129–137.
- Stafstrom, C.E., Thompson, J.L., Holmes, G.L., 1992. Kainic acid seizures in the developing brain – status epilepticus and spontaneous recurrent seizures. *Dev. Brain Res.* 65, 227–236.
- Steriade, M., Amzica, F., Contreras, D., 1994. Cortical and thalamic cellular correlates of electroencephalographic burst-suppression. *Electroencephalogr. Clin. Neurophysiol.* 90, 1–16.
- Stromme, P., Mangelsdorf, M.E., Scheffer, I.E., Geicz, J., 2002. Infantile spasms, dystonia, and other x-linked phenotypes caused by mutations in aristaless related homeobox gene, ARX. *Brain Dev.* 24, 266–268.
- Takayama, R., Fujiwara, T., Imai, K., Shigematsu, H., Takahashi, Y., Inoue, Y., Yamakawa, K., 2013. Long-term course of Dravet syndrome: a study from an epilepsy center in Japan. *Epilepsia* 54, 101.
- Tam, L.-W., Ranum, P.T., Lefebvre, P.A., 2013. CDKL5 regulates flagellar length and localizes to the base of the flagella in chlamydomonas. *Mol. Biol. Cell* 24, 588–600.
- Tassinari, C.A., Rubboli, G., Volpi, L., Meletti, S., d'Orsi, G., Franca, M., Sabetta, A.R., Riguzzi, P., Gardella, E., Zaniboni, A., Michelucci, R., 2000. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin. Neurophysiol.* 111, S94–S102.
- Velisek, L., Jehle, K., Asche, S., Veliskova, J., 2007. Model of infantile spasms induced by N-methyl-D-aspartic acid in prenatally impaired brain. *Ann. Neurol.* 61, 109–119.
- Vezzani, A., Aronica, E., Mazarati, A., Pittman, Q.J., 2013. Epilepsy and brain inflammation. *Exp. Neurol.* 244, 11–21.
- Vezzani, A., Conti, N., De Luigi, A., Ravizza, T., Moneta, D., Marchesi, F., De Simoni, M.G., 1999. Interleukin-1 beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. *J. Neurosci.* 19, 5054–5065.
- Vezzani, A., French, J., Bartfai, T., Baram, T.Z., 2011a. The role of inflammation in epilepsy. *Nat. Rev. Neurol.* 7, 31–40.
- Vezzani, A., Maroso, M., Balosso, S., Sanchez, M.-A., Bartfai, T., 2011b. IL-1 receptor/toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain Behavior and Immunity* 25, 1281–1289.
- Villeneuve, N., Laguitton, V., Viellard, M., Lepine, A., Chabrol, B., Dravet, C., Milh, M., 2014. Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome. *Epilepsy Behav.* 31, 143–148.
- Watanabe, K., 1998. West syndrome: etiological and prognostic aspects. *Brain Dev.* 20, 1–8.
- Weckhuysen, S., Ivanovic, V., Hendrickx, R., Van Coster, R., Hjalgrim, H., Moller, R.S., Gronborg, S., Schoonjans, A.-S., Ceulemans, B., Heavin, S.B., Eltze, C., Horvath, R., Casara, G., Pisano, T., Giordano, L., Rostasy, K., Haberlandt, E., Albrecht, B., Bevtov, A., Benkel, I., Syrbe, S., Sheidley, B., Guerrini, R., Poduri, A., Lemke, J.R., Mandelstam, S., Scheffer, I., Angriman, M., Striano, P., Marini, C., Suls, A., De Jonghe, P., Grp, K.S., 2013. Extending the KCNQ2 encephalopathy spectrum clinical and neuroimaging findings in 17 patients. *Neurology* 81, 1697–1703.
- Weckhuysen, S., Mandelstam, S., Suls, A., Audenaert, D., Deconinck, T., Claes, L.R.F., Deprez, L., Smets, K., Hristova, D., Jordanova, I., Jordanova, A., Ceulemans, B., Jansen, A., Hasaerts, D., Roelens, F., Lagae, L., Yendle, S., Stanley, T., Heron, S.E., Mulley, J.C., Berkovic, S.F., Scheffer, I.E., de Jonghe, P., 2012. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. *Ann. Neurol.* 71, 15–25.
- Williamson, L.L., Sholar, P.W., Mistry, R.S., Smith, S.H., Bilbo, S.D., 2011. Microglia and memory: modulation by early-life infection. *J. Neurosci.* 31, 15511–15521.
- Yu, F.H., Mantegazza, M., Westenbroek, R.E., Robbins, C.A., Kalume, F., Burton, K.A., Spain, W.J., McKnight, G.S., Scheuer, T., Catterall, W.A., 2006. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat. Neurosci.* 9, 1142–1149.
- Yue, C.Y., Yaari, Y., 2006. Axo-somatic and apical dendritic Kv7/M channels differentially regulate the intrinsic excitability of adult rat CA1 pyramidal cells. *J. Neurophysiol.* 95, 3480–3495.
- Yum, M.-S., Chachua, T., Veliskova, J., Velisek, L., 2012. Prenatal stress promotes development of spasms in infant rats. *Epilepsia* 53, e46–e49.
- Yum, M.-S., Lee, M., Ko, T.-S., Velisek, L., 2014. A potential effect of ganaxolone in an animal model of infantile spasms. *Epilepsy Res.* 108, 1492–1500.
- Zhou, P., Pang, Z.P., Yang, X., Zhang, Y., Rosenmund, C., Bacaj, T., Suedhof, T.C., 2013. Syntaxin-1N-peptide and H-abc-domain perform distinct essential functions in synaptic vesicle fusion. *EMBO J.* 32, 159–171.