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Treatment of Epileptic Encephalopathies: Current State of the Art

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Abstract

Childhood epileptic encephalopathies are age-dependent disorders of the brain whose hallmarks include loss of neurologic function over time, abnormal electroencephalographic findings, and seizures. Ictal and interictal electrographic activity are conjointly thought to be at the root of the often devastating neuropsychological deterioration, which is specific to the maturing brain. The goals of treatment are not only to control seizures, but also to prevent or reverse neurologic loss of function. In general, time is of the essence in diagnosis, and experienced specialists should promptly design a treatment plan. Hormonal and immune therapies are at the forefront of treatment in many cases, with traditional antiepileptic drugs and surgery (when an identifiable lesion is present) playing a limited role. However, gold standard evidence for treatment of epileptic encephalopathies remains limited. Ongoing clinical and basic research may lead to better understanding of these catastrophic conditions and to better and more effective therapies.

Keywords

abnormal interictal EEG; cognitive outcome; hormonal therapy; immune therapy; intractable seizures

Epileptic encephalopathies are age-dependent disorders of the brain in which ictal and interictal epileptogenic activity is the apparent cause of progressive cognitive and neuro-psychological regression or impairment, which may be rapid in onset or may take place over a longer course of time. In this review, we summarize the current state-of-the-art treatment

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approaches for these disorders. This is an expanded version of information presented at the Neurobiology of Disease in Children Symposium at the Child Neurology Society Meeting in October 2015.

The focus of this paper will be on infantile spasms or West syndrome, Lennox-Gastaut syndrome, electrical status epilepticus in sleep, Landau-Kleffner syndrome, and autoimmune encephalitis. Other conditions, such as Dravet syndrome and the early infantile and early myoclonic encephalopathies, will be mentioned peripherally; however, they will not be discussed extensively. First, a separate extensive literature focusing directly on these entities exists, and second, the examples chosen are meant to highlight different aspects of these disorders that are applicable to others as well as possibly amenable to treatment. There is minimal or only anecdotal data on the treatment of the early infantile encephalopathies, whose outcomes remain dismal. While we do have treatment for the seizures in Dravet syndrome, at this time there are few data on treatment that may reverse the cognitive decline, which is really the focus of this review.

In addition to the classic epileptic encephalopathies, we also discuss autoimmune syndromes. The autoimmune syndromes may indeed be fundamentally different in etiology from the other epileptic encephalopathies described, but they share features that are worth highlighting, including progressive neurologic and cognitive decline and response to immune therapy. Further, with the increase in diagnosis of “antibody negative autoimmune encephalitis,” it has become clear that use of both hormonal and immunomodulating therapies may be undertaken without having an identifiable serologic targeted antibody[1] or a distinctive syndromic presentation. The nature of “autoimmune” versus “immunotherapy-responsive” is, therefore, not clear-cut, and there may be a greater overlap than previously realized between classic epileptic encephalopathies and the more recently described autoimmune syndromes. A partial listing of the epileptic encephalopathies can be found in Table 1, with some of the main identified autoimmune encephalopathies listed in Table 2.

The shared clinical feature of the epileptic encephalopathies is that they are associated with loss of neurologic function over time. This loss can be rapid, as in the case of infantile spasms or Landau-Kleffner syndrome, or very gradual over years, as is the case with Lennox-Gastaut syndrome. The neurologic change is clearly separate from the seizures themselves. Although Lennox-Gastaut syndrome is generally associated with intractable seizures, syndromes such as electrical status epilepticus in sleep and Landau-Kleffner syndrome do not even always have associated clinical seizures and, when present, they are usually not difficult to control. In infantile spasms, the seizures themselves are brief, self-limited, and not very dramatic, but the loss of neurologic function can be profound, leading to Dr Shields’s famous dictum, “little seizures, big consequences.”[2] Conceptually, the term epileptic encephalopathy embodies the notion that “the epileptic activity itself may contribute to severe cognitive and behavioral impairments.”[3] This is, therefore, one of the few settings where treating electroencephalographic (EEG) abnormalities even when seizures are fully controlled or absent may be important, as we assume that the electrical epileptic activity itself is contributing to progressive disturbance of cerebral functions (especially in infantile spasms and electrical status epilepticus in sleep). Thus, the goal of treatment is not simply to control seizures but also to eliminate the underlying EEG

abnormality, with the hope of preventing loss of neurologic function. Ideally, one also hopes to restore lost function, though that is always more difficult.

Given these goals of treatment, there are major differences between the treatment of epileptic encephalopathies and other epilepsies. Perhaps most significantly, for most epilepsies, our treatments are considered “antiseizure” in the sense that they suppress clinical seizures but are not disease-modifying. For epileptic encephalopathies, the true goal is to modify the disease. Thus, when we give high-dose adrenocorticotropic hormone (ACTH) for 2 weeks to children with infantile spasms, especially to those with infantile spasms of unknown etiology, the expectation is that we abolish both the clinical seizures and the hypsarrhythmia, and that this effect will continue when medication is withdrawn. This would not be the case when prescribing carbamazepine for localization-related epilepsy.

The second major difference is the need for early treatment. Because in most epilepsies, the treatments are not disease-modifying and the disorder is not progressive, the data are pretty clear that delay in treatment does not alter long-term prognosis.[4–9] These data are what allow us to not immediately treat children with, for example, a single first unprovoked seizure.[7,10] Where the clinical picture and the electrographic evidence speak to the presence of a childhood epilepsy syndrome, early treatment may indeed be recommended. It is also increasingly clear that even in the cases of “benign” childhood epilepsy syndromes such as childhood absence epilepsy and benign epilepsy with centrotemporal spikes (BECTS), neuro-psychological deficits and academic difficulties are frequently present. However, it is not clear that treatment, however beneficial from the perspective of reducing the number of seizures or reduction of parental anxieties, changes these sequelae. These neurologic comorbidities are, further, usually present at baseline and do not worsen over time.[11]

This is decidedly not the case for epileptic encephalopathies. Here, the best evidence is from studies of infantile spasms, where there are compelling data that early treatment is associated with both better seizure control and cognitive outcomes.[12–14] Although infantile spasms has the most data, other epileptic encephalopathies fall into the same category. For example, it is believed that treating electrical status epilepticus in sleep and other syndromes prior to major loss of function will result in better outcomes.[15–17] Again, considering the goals of treatment for epileptic encephalopathies, it should come as no surprise that our conventional antiepileptic drugs are of limited benefit when used as sole therapy. They are actually reasonably effective in controlling clinical seizures in many of the described syndromes, and some medications, such as valproate, may even help normalize the EEG. But because seizure control here is secondary to the dual goals of treating the underlying EEG and preventing/reversing loss of neurologic function, other drugs are the mainstays of therapy. These include hormonal therapy (steroids and ACTH) and immune modulators (steroids, intravenous immunoglobulin, rituximab). Vigabatrin occupies a unique role in treatment of infantile spasms associated with tuberous sclerosis complex. We present an overview of the current state of the art in the treatment of selected epileptic encephalopathies.

Specific Syndromes

Infantile Spasms or West Syndrome

Infantile spasms, particularly when of unknown etiology, is perhaps the paradigmatic model of the epileptic encephalopathies. In this devastating disorder, a previously normal child develops epileptic spasms that may, especially if untreated before the onset of developmental regression, result in permanent cognitive impairment.

The syndrome was first identified in 1841 by William James West, in a case report in the *Lancet* describing the course of the disease in his own son and thus carrying his name. Since that time, West syndrome has come to be defined by a triad of clinical and electrographic findings, including spasms (flexor, extensor, or mixed), a pattern of hypsarrhythmia on EEG, and psychomotor delay/arrest.[18] In current usage, the term *infantile spasms* has come to signify not only the actual spasms but also the syndrome itself; it has also become accepted that diagnosis can be made on the basis of the presence of any 2 of these 3 findings.[19] Current terminology also separates common etiologies into *genetic* (identifiable genetic condition with seizures as the primary finding), *structural/metabolic* (eg, hypoxic-ischemic encephalopathy, brain malformations, tuberous sclerosis complex), and *unknown*; a significant percentage of cases remain in this latter category despite best efforts at diagnosis.[2]

Although the seizures themselves in infantile spasms are individually brief and may be quite subtle clinically, the developmental regression is devastating. It is believed that this regression is mediated via the chaotic EEG described as hypsarrhythmia. The need to abolish both seizures and the hypsarrhythmia in order to improve the cognitive outcome leads to the definition of a responder in infantile spasms that is different from that for most epilepsies. A “responder” in infantile spasms is specifically defined as (1) complete cessation of spasms, as confirmed by video EEG, and (2) abolition of hypsarrhythmia on prolonged EEG.[18,20] It is clear that a mere reduction in seizures, even when significant, is not enough. Unless the spasms are eradicated and the hypsarrhythmia is abolished, there is progression and cognitive decline.[18,20,21]

There are no randomized trials of delayed versus early treatment; treatment is started as soon as the disorder is diagnosed. Nevertheless, there is a substantial body of retrospective literature that indicates early treatment is associated with better outcomes, both seizurewise and cognitively. The significance of the outcome of treatment, therefore, may be profound. Although we think of infantile spasms as a catastrophic disorder with poor outcome, the data suggest that for cases of unknown etiology where the patient had normal development prior to the onset of spasms, and both the spasms and the hypsarrhythmia are quickly abolished prior to any regression, normal development may continue.[12–14,18,21,22] Even in genetic or structural/metabolic cases where prior development is clearly not normal, optimal development can still be preserved with quick and appropriate treatment.[17,19–22]

Two modalities have clear evidence of efficacy in treating infantile spasms: ACTH and vigabatrin; both also have potentially severe side effects. The use of ACTH carries the risk of infection, hypertension, gastric or intracerebral bleeding, cardiomyopathy, renal tubular

necrosis, and electrolyte disturbances; early studies showed a mortality rate of up to 4.9%.[23] Vigabatrin's major side effect is permanent bilateral concentric visual field constriction, with risk increasing with higher doses and cumulative exposure; careful ophthalmologic surveillance is therefore recommended with use of this medication, although the rigor of the screening protocol has recently been relaxed by the US Food and Drug Administration (FDA).[24] It is not clear, moreover, how often this results in a clinical deficit,[25] especially in children. Other side effects commonly reported are generally mild and include irritability, insomnia, agitation, and weight gain.

There are a variety of processes by which ACTH may work, including both direct action on the adrenals and via central mechanisms. For the peripheral mechanisms, low dose is sufficient, but for the central ones a high dose is needed to cross the blood-brain barrier.[26] Both low- and high-dose protocols have been used with varying efficacy for cessation of spasms, abolishing hypsarrhythmia, and normalizing cognitive outcome, and there is no consensus on the precise optimal treatment parameters (see Table 3). The ACTH regimen with the best evidence overall is the twice-a-day high-dose regimen, which is the one referenced by the FDA when the drug was approved for the treatment of infantile spasms after years of being used off label as the first-line treatment.[18,27]

Despite its precise mechanism of action being unknown, ACTH is thought to be not only a treatment but also a disease-modifying agent.[28] For cases of infantile spasms of unknown etiology, ACTH also has the best supporting data for long-term favorable developmental outcomes.[12,14,18,21] Vigabatrin, comparatively, has shown an overall responder rate of 42% at 24 weeks in a placebo-controlled trial[29] using dosages ranging from 50 to 150 mg/kg/d. Vigabatrin is especially effective in cases of infantile spasms associated with tuberous sclerosis complex.[18,20] In cases of infantile spasms of unknown etiology, it appears less effective than ACTH or high-dose oral steroids.[18,21] More significantly, although long-term control of clinical spasms was similar across treatment groups, developmental outcomes were improved in children with infantile spasms receiving hormonal treatment (synthetic ACTH or prednisone) compared with those receiving vigabatrin.[30] (It should be noted that children with infantile spasms due to tuberous sclerosis complex were excluded from that trial and treated preferentially with vigabatrin.)

There are also limited data comparing ACTH to oral steroid treatment. In one randomized clinical trial, high-dose ACTH (150 U/m^2/d) was shown to be more effective than prednisone (2 mg/kg/d) (responder rate at 2 weeks, 87% vs 29%); this study's findings have not been consistently replicated and the dosage of prednisone may have been suboptimal.[27] Data better support the efficacy of hormonal therapy with high-dose oral corticosteroids. Regrettably, the randomized controlled trials using the United Kingdom Infantile Spasms Study (UKISS) regimen (prednisolone 40–60 mg daily) have not used EEG confirmation of response, so it is difficult to judge the effect on abolishing hypsarrhythmia as distinct from clinical seizures. The one such study using a dosage of 8 mg/kg/d that did use video EEG confirmation[31] showed a higher response rate than those reported in studies using the 2 mg/kg/d dosing, but this was not a randomized trial. Some nonresponders to initial therapy with oral steroids did then subsequently respond to ACTH; it is not clear whether this indicates a difference in peripheral versus central mechanisms of action. Treatment with

either oral steroids or with ACTH also resulted in better developmental outcomes than treatment with vigabatrin in the UKISS study.[30] There is no consensus on whether oral steroids should be considered first-line therapy at this time.[18,21] Overall, however, a recent prospective observational nonrandomized pragmatic study evaluating early and sustained responses to treatment confirmed that regardless of etiology, 46% of children treated with standard therapy (ie, ACTH, oral corticosteroids, and vigabatrin) responded, compared with only 9% of those receiving any of the alternatives.[32]

Recent data published by the International Collaborative Infantile Spasms Study (ICISS) in November 2016 addresses the question of whether hormonal therapy (either ACTH or prednisone) combined with vigabatrin was more effective at stopping infantile spasms than hormonal therapy alone. The early results indicate that the combined therapy resulted in quicker cessation of clinical spasms (133 of 186 patients or 72% of the combined group vs 108 of 191 patients on hormonal monotherapy, or 57%). Electroclinical response (defined as cessation of spasms and resolution of EEG features supporting the diagnosis of infantile spasms) was also achieved in a greater percentage of patients on combination therapy (66% vs 55%). Complication rates were similar in both treatment groups. These results are intriguing. However, the key question of whether there will be a long-term difference in developmental outcome has yet to be determined; these data are being collected and will be presented at the 18-month follow-up of this ongoing and important study.[33]

Among other medication choices, vitamin B_6 (pyridoxine) has been used, primarily in Japan, where the responder rate is between 13% and 30%.[34] However, no evidence exists that this is greater than the natural spontaneous remission rate.[20] Valproic acid has been used with success in some cases, with up to 40% demonstrating good control of spasms, but again, long-term developmental outcome data are lacking.[35] Additionally, many clinicians are hesitant to use valproic acid in this age group because of increased risk of hepatotoxicity.[36] Other conventional antiepileptic drugs, including zonisamide, topiramate, and levetiracetam, have been used but have insufficient evidence to support their efficacy.[20]

Surgical treatment should be always considered in cases with focal features and can be very effective, achieving class I outcome in 79% of cases if MRI or PET scan shows a resectable lesion with concordance to EEG abnormalities.[37] Even when there is no clear dysplasia or lesion, a “zone of cortical abnormality” may be inferred from a concordance of evidence.[38] Unfortunately, only a minority of cases are due to identifiable focal lesions amenable to surgical intervention.

The ketogenic diet, previously used as an alternative therapy in cases of intractable infantile spasms, has more recently been investigated as a possible first-line treatment. In one retrospective study, the ketogenic diet was shown to have some efficacy at suppressing seizures at 1 month, but the response rate was low compared with ACTH (62% vs 90%). Further, in the subset that had EEGs at 3 to 4 weeks of therapy on the diet, only 1 of 11 (9%) had full resolution of the hypsarrhythmia, and thus the vast majority did not meet the definition of a responder at that time.[39] For these reasons, the ketogenic diet is not considered a first-line therapy.[18,21] A summary of the major studies regarding treatment options in infantile spasms is presented in Table 3.

Better understanding of the underlying mechanisms of the generation of infantile spasms in specific conditions may lead to more effective and etiology-specific treatments. Infantile spasms in children with Trisomy 21 is exquisitely sensitive to ACTH, and other therapies are not usually considered; however, in other conditions, alternate treatments are emerging. In patients with GLUT1 deficiency causing infantile spasms, the ketogenic diet is emerging as first-line treatment.[40] As previously mentioned, vigabatrin is now considered first-line treatment for infantile spasms in patients with tuberous sclerosis complex[21,30,41]; it has even been suggested that an abnormal EEG is of itself an indication for treatment with vigabatrin in this context, without the presence of clinical seizures.[42] Moreover, tuberous sclerosis complex reveals a novel target for not only the resolution of infantile spasms but also, potentially, the prevention of epileptogenesis; drugs targeting the mTOR (mammalian target of rapamycin) pathway are currently under extensive investigation. Apart from its role in tuberous sclerosis complex, mTOR has been proposed as part of the pathophysiology of epilepsy in a variety of cortical malformations. Identification of a common target may lead to novel antiepileptogenic treatments as well as disease-modifying therapies in these neurologic conditions.[43]

Although the precise mechanisms of infantile spasms are not yet completely understood, a consensus for the overall diagnosis and management of infantile spasms has been established, including the need for an extensive clinical and neurologic evaluation to determine etiology if possible, use of ACTH and vigabatrin as proven first-line therapies, the need for timely reassessment of treatment efficacy, and above all, the “all or none” definition of response as an outcome measure (complete cessation of spasms and resolution of hypsarrhythmia).[18] Infantile spasms remains the prime example for an epileptic encephalopathy in early life.

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a childhood epilepsy of later onset than infantile spasms, generally appearing at 2 to 6 years of age. It is characterized by a slow (<2.5 Hz) spike-wave pattern on EEG, cognitive impairment, and multiple seizure types (tonic, atonic, myoclonic, and atypical absence) beginning in childhood.[44] The known etiologies of Lennox-Gastaut syndrome are virtually identical to those of infantile spasms— in fact, 17% to 30% of patients actually have a history of infantile spasms, and this subset of patients has a worse prognosis for both developmental and seizure outcomes.[44,45] In Lennox-Gastaut patients without this history, the progressive pathway to cognitive decline is more prolonged and treatment choices and options are less clear.

It is tempting to speculate with that if a “responder” in Lennox-Gastaut syndrome were to be defined similarly to a responder in infantile spasms, with complete abolition of seizures and of the encephalopathic EEG pattern, that this response would be associated with improved developmental outcomes. Unfortunately, at this time we do not have any treatment for Lennox-Gastaut syndrome that has been reliably shown to completely abolish seizures and to normalize the EEG. Treatment at this time, therefore, focuses on the single goal of seizure control.

This is not a simple task. Not only are the seizures in Lennox-Gastaut syndrome frequent, but their nature also often leads to repeated physical injury due to falls. Seizures are in fact often so numerous that simply substantially reducing seizure frequency often results in the patient being more alert and functional. This is not true disease modification, but rather an avoidance of comorbidities that worsen outcome. Unfortunately, in Lennox-Gastaut syndrome the seizures are also frequently refractory to conventional antiepileptics. Valproate is typically the first drug of choice in appropriate patients. Rufinamide and clobazam are also specifically useful in this population. In addition, lamotrigine, topiramate, zonisamide, and even felbamate are also commonly used.[46] Polypharmacy is often required because of both the intractability of the seizures and multiple seizure types, and good overall seizure control is difficult to achieve without unacceptable levels of side effects. Response of one seizure type without improvement in others is common. However, even with improved seizure control, cognitive outcomes remain poor, with most patients meeting criteria for moderate to severe cognitive impairment by adulthood.[47]

Also in contrast to the example of infantile spasms, hormonal therapy is not effective in the long term either for seizure control or in normalizing the EEG, and such treatment is not currently recommended.[48,49] The ketogenic diet has been reported as effective for seizure control in some retrospective studies, but did not show clear efficacy in a prospective randomized controlled trial tracking electrographic events; in addition, the diet is often of practical difficulty in children who are cognitively impaired but not neurologically devastated and dependent on enteral feeds.[50]

Immunotherapy with intravenous immunoglobulins has been attempted without success.[51] The use of cannabidiol, which has been of historic medicinal interest since antiquity, has recently come to the forefront of multiple investigations. Early data suggest there may be a role for cannabidiol in both seizure control and improvement of quality of life in Lennox-Gastaut syndrome[52]; however, seizure freedom remains an elusive goal and there are no data on developmental outcomes, which remain a major concern. As the results of the pivotal randomized clinical trials of cannabidiol, although announced to be positive, have not yet been published in a peer-reviewed setting, it is at this point in time considered a promising and intriguing but not yet proven therapy for Lennox-Gastaut syndrome.

Surgical options are largely palliative. As is the case with infantile spasms, when a focal lesion is present, resective surgery is a good option. However, this is not common and the vast majority of Lennox-Gastaut cases are not amenable to surgical resection. Other options include corpus callosotomy, historically the recommended surgical treatment for tonic and atonic seizures resulting in falls. This treatment has been shown to be effective for these targeted seizure types,[53] with up to 80% reduction in the majority of patients. The procedure is less effective for other seizure types.[54,55] Vagus nerve stimulator, another palliative modality, may also reduce the frequency of atonic seizures and improve quality of life. Vagal nerve stimulation has the additional advantage of an extremely low side effect profile, with very few patients experiencing negative effects of treatment.[56,57]

In short, currently there is no good treatment for Lennox-Gastaut syndrome to prevent cognitive decline or give full seizure freedom, except rare lesional cases for surgery. The use

of multiple modalities is the rule and outcomes remain grim. Unsurprisingly, given the devastating neuropsychiatric outcome of this disorder, there is widespread interest in the development of both more effective and potentially disease-modifying treatments.

Electrical Status Epilepticus in Sleep/Continuous Spike-Wave in Slow-Wave Sleep

Electrical status epilepticus in sleep was first described in 1971 in a case series of 6 children who were found to have continuous spike-wave discharges in non–rapid eye movement sleep, with resolution upon awakening.[58] These discharges were described as characteristic of petit mal status epilepticus, but were without clinical correlate or disturbance of normal sleep patterns. However, all of the children in the study had epilepsy and either developmental delays or regression.

Since the initial identification of these cases, it has come to be recognized that multiple clinical presentations and several distinct epileptic syndromes are associated with this dramatic EEG pattern. The term *continuous spike-wave in slow wave sleep* is sometimes used to differentiate one such syndrome from the EEG pattern itself; however, the terms are generally interchangeable.[3] For the purposes of this review, the term *electrical status epilepticus in sleep* will be used to refer both to the pattern and to the syndrome.

The hallmarks of electrical status epilepticus in sleep are sleep-induced epileptic discharges and acquired impairment of cognition or behavior.[58] The discharges are classically defined as diffuse, continuous 1- to 3-Hz epileptiform activity occupying at least 85% of the slow sleep tracing, although most current investigators use the less stringent criteria of “significant activation of epileptiform discharges by sleep” in the context of a recognizable clinical syndrome.[59–61] In one retrospective study, significant sleep activation was defined as a spike-wave index of 25% or higher of the total sleep record; however, a spike-wave index of >50% was more likely to be associated with global developmental disturbances.[62]

The clinical features of the syndrome vary and no single manifestation is required for diagnosis. Age at onset ranges from 1 to 14 years, with a peak between the ages of 4 and 8,[63] and one-third of patients have a previous neurologic abnormality.[64] Seizures are the most frequent presenting symptom and are seen in 80% of patients, the onset of which is often followed by a developmental delay, arrest, or regression. This regression is frequently severe and global, encompassing loss of language, diminished temporospatial skills, memory deficits, and motor deficits; the language deficit is primarily an expressive aphasia in which comprehension is generally spared (in contrast to Landau-Kleffner syndrome, below).[59,65] Seizure types and semiologies vary widely; most frequently seen are nocturnal partial motor seizures or generalized convulsive events, but atonic, absence, and myoclonic seizures may also be present. Notably, tonic seizures are absent.[64,65] Seizures are a prominent feature and can, on occasion, be refractory to conventional antiepileptic drugs.[64] Lastly, the seizures and the EEG pattern typically remit in adolescence; however, the neurologic deficits can persist.

The model of treatment of electrical status epilepticus in sleep mirrors that of infantile spasms in that control of the seizures, although desirable, is not sufficient. Unless the underlying continuous electrographic abnormalities are also resolved, neuropsychological

deficits will persist; the theory that the work of the brain to “spin” neural networks that are then undone by “spikes” overnight has led some to describe electrical status epilepticus in sleep as the “Penelope Syndrome.”[60,66] Moreover, some investigators identify an association between duration of the EEG abnormalities and poorer cognitive outcome,[16,64] which would suggest that earlier treatment is essential; others have not found this linkage.[17] It is not yet clear, therefore, whether treatment can prevent permanent cognitive impairment. The seizures themselves can certainly respond to conventional antiepileptic drugs, particularly valproic acid or a combination of valproic acid and ethosuximide,[67] although some drugs (including carbamazepine, phenytoin, and phenobarbital) are usually avoided, as they have been known to worsen both the epileptiform discharges and the neuropsychological symptoms.[68] Other studies have used high-dose benzodiazepines.[69] The full resolution of the electrical status epilepticus in sleep and the associated neuro-psychological changes, however, often requires treatment with high-dose oral steroids (or, less frequently, ACTH),[65,70,71] which is also the reviewers’ experience.

A comparison between modalities was performed in a recently published meta-analysis, which reported that treatment with oral steroids was associated with some improvement in designated parameters (cognition or EEG) in 81%, with benzodiazepine in 68%, and with traditional antiepileptic drugs in 49%. This pooled analysis is the best evidence to date for the efficacy of steroids compared with conventional antiepileptic drugs. In cases with clear evidence of focality or lateralization, surgical treatment yielded improvement in cognition or EEG in 90%.[63] Here too these cases are a minority, although the presence of a focal lesion should always be considered and investigated. As this analysis was based on combining different cohorts, rather than on randomized clinical trials, the data were quite suggestive but insufficient to make definite treatment recommendations.

With regard to long-term outcome, irrespective of treatment, prognosis is guarded. Normal language and cognition is seen in only 10% to 44% of patients.[17,60] The clearest predictors of poor outcome were earlier age of onset and length of duration of abnormal EEG findings, leading to the conclusion that early treatment with therapies that abolish the EEG abnormalities is likely essential for improvement.[16,64] A randomized controlled European multicenter study (RESCUE ESES, Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep) was initiated in 2014 to provide more definitive answers with regard to treatment choices. This multicenter European study will directly compare steroid treatment (either intravenous methylprednisolone or oral prednisone) to oral clobazam in a randomized controlled trial. This is the first major study in which cognition is the primary outcome measure, with changes in EEG and seizures as well as safety and tolerability as secondary findings; outcomes are to be measured at 6 and 18 months. As a randomized clinical trial, it will provide more definitive answers as to whether treatment with steroids results in better cognitive outcomes in electrical status epilepticus in sleep, as well as on seizure control and improvement in the EEG, and is likely to change clinical practice once completed.

Landau-Kleffner Syndrome

The Landau-Kleffner syndrome, also known as acquired epileptic aphasia or the acquired aphasia-epilepsy syndrome, was first described in a landmark paper by Landau and Kleffner in 1957.[72] The onset is usually seen between the ages of 2 and 8 in a previously normal child. This disorder is thought to be closely related to electrical status epilepticus in sleep but is characterized by a more focal regression limited to an acquired aphasia, although other clinical symptoms may be present (irritability, hyperkinesis, attention-deficit disorder, and autistic behaviors). This aphasia takes the form of an auditory agnosia; in contrast to the language deficit in electrical status epilepticus in sleep, where there is a primarily expressive aphasia with intact comprehension, children with Landau-Kleffner syndrome may appear to be unconscious of spoken words, or effectively deaf.

EEG findings are variable, especially during wakefulness. Focal, multifocal, or generalized spike and wave discharges may be present, often with posterotemporal predominance,[59,60,65,73] but the waking EEG can also be normal. Sleep, and especially sleep onset, tends to activate epileptiform potentials, which can become continuous or nearly continuous in sleep, suggesting an overlap between Landau-Kleffner syndrome and electrical status epilepticus in sleep. However, the EEG does not necessarily meet the criteria of electrical status epilepticus in sleep throughout the course of the disease.[65] It is theorized that many or even most children with Landau-Kleffner syndrome do pass through a period of electrical status epilepticus in sleep on EEG at some point during their course,[59,65,74] although this remains speculative. Another difference is that epileptiform discharges can continue or even increase during REM sleep, whereas in electrical status epilepticus in sleep, they either remit or resemble the waking record.[58,65,75]

In Landau-Kleffner syndrome, seizures are present in 70% to 80% of cases, but are usually infrequent, with 1 in 3 patients suffering only a single clinical seizure or a solitary episode of status epilepticus.[59,65] Common seizure types include nocturnal partial motor seizures similar to those seen in benign partial epilepsy of childhood with rolandic spikes; generalized tonic-clonic seizures and atypical absences are also seen, and less frequently, myoclonic-astatic or tonic events.[74,75] The seizures in Landau-Kleffner syndrome are not only infrequent but also are usually easily controlled by traditional antiepileptic drugs; they also decrease in frequency with age and remit by adolescence.[75] For these reasons, until recently, Landau-Kleffner syndrome was considered to be a benign self-limited epilepsy syndrome.

However, there is discordance between the severity of the epilepsy and of the language loss, which is generally out of proportion to both the frequency of seizures and the abnormalities on EEG, and which persists even after the seizures and EEG abnormalities have remitted.[73,76] It is this potentially profound deficit that must be treated, and the best evidence is for early treatment with corticosteroids. Prolonged treatment may be required, with relapses seen if medication is withdrawn.[15,68,75,77] In addition, if the aphasia has persisted for more than a year, it may show no improvement with steroids despite the normalization of the EEG.[15] Traditional antiepileptic drugs, including valproic acid, ethosuximide, levetiracetam, and benzodiazepines, have partial and sometimes transient

effects on the clinical and electrographic picture.[68] Case studies of response to vigabatrin have also been reported.[69,78,79]

Evidence for surgical management of Landau-Kleffner syndrome, typically using multiple subpial transections in the Wernicke area, remains limited to small case series.[80–83] This procedure, which is intended to disrupt the horizontal interaction of cortical neurons while preserving vertical connections, was developed to treat medically intractable focal epilepsy (of any etiology) originating from eloquent cortex previously considered unresectable. The prevention of the propagation of epileptiform discharges is thought to be achieved by preventing synchronization of firing of adjacent cortical neurons, while preserving normal physiologic function in their vertical columnar structure. It is fairly easy to conceptualize how this could limit seizures as well as epileptiform discharges. However, in the case of Landau-Kleffner syndrome, there is increasing evidence that there is also improvement in language function over the course of months or even years following the surgery. This may suggest that like our primary example of infantile spasms, clinical improvement is tied to elimination of the epileptiform discharges.[81–84]

The rarity of the syndrome makes randomized controlled trials of Landau-Kleffner syndrome difficult, even in a multi-center setting. However, the similarities to electrical status epilepticus in sleep mean that the RESCUE ESES trial will likely inform the treatment of Landau-Kleffner syndrome by analogy; in particular, whether treatment with steroids results in better developmental outcomes than treatment with more conventional antiepileptic drugs.

Another tantalizing potential treatment modality is the use of intravenous immunoglobulins, which has been reported in case studies to have successfully treated both the electrographic abnormalities and the language regression of Landau-Kleffner syndrome.[80,85–87] Interestingly, Landau-Kleffner syndrome has been associated with infections or postinfectious processes in a number of reports[88]; further, in one study, autoantibodies to brain epithelial IgG and IgM were seen in children with Landau-Kleffner as well as other neurologic disorders at a higher rate than in neurotypical children.[89] There is mounting evidence for a role of autoimmunity in a variety of neurologic disorders and increasing interest in the expansion of the use of immunomodulating agents in their treatment. The rarity of the disorder makes cohort studies difficult in Landau-Kleffner patients. However, studies in other disorders may again be informative by analogy.

Autoimmune Encephalitis

Acute encephalitis is an abrupt presentation of an inflammatory disorder of the brain commonly causing altered mental status, focal neurologic deficits, and seizures; it constitutes a medical emergency. Regardless of cause, prompt recognition and proper treatment of any encephalitis is essential to reduce morbidity and mortality. Although patients with acute encephalitis frequently undergo extensive testing, the underlying cause remains unknown in roughly 60% of cases.[90,91] Autoimmune processes are increasingly recognized as a frequent and potentially reversible cause of encephalitis.[91–93] The authors recognize that autoimmune encephalitis is not yet clearly interconnected with the foregoing designated epileptic encephalopathies. However, we feel that the topic warrants inclusion in

the discussion of the epileptic encephalopathies not only because of similarities in presentation but also because of the utility of similar treatment options and the possibility that a spectrum of disease exists, perhaps with as-yet-unidentified causative agents.

In children, identified autoantibodies causing encephalitis are typically part of a group targeting neuronal cell surface epitopes, collectively called “neuronal surface antibodies.” The most common among these is anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis,[94] which is more common than any single viral etiology of acute encephalitis.[91] Multiple other autoantibodies have been identified that present with characteristic syndromes, including LGI1, CASPR2, GAD65, and the voltage-gated potassium channels (see Table 2).

Even in the absence of an identifiable serologic or cerebrospinal fluid agent, some patients presenting with fulminant and apparently noninfectious encephalitis demonstrate good recovery after treatment with steroids or immunomodulators, leading to the concept of an *antibody-negative autoimmune encephalitis*.[95] It is likely that this diagnosis will become less common as more antibodies are identified; even without antibody positivity, nonspecific markers such as cerebrospinal fluid lymphocytosis or oligoclonal bands may be found. It is imperative to consider the possibility of an autoimmune process during the workup, as serum levels of antibody must be compared with those in the cerebrospinal fluid to avoid false-positive serology.[96]

There are similarities between some of the previously described epileptic encephalopathies and the autoimmune encephalitides, including the tendency for seizures to be present. By definition, too, any encephalitis involves altered cognitive function, and it is similarly necessary to treat both the seizures and the underlying pathology to achieve reversal of this decline. Anti-NMDAR encephalitis, for instance, often presents with seizures and an abnormal EEG in which conventional antiepileptic drugs treatment may control the seizures but do not reverse cognitive decline unless the underlying autoimmune process is also treated.[97]

However, there are clearly differences as well. Unlike the previously discussed classic epileptic encephalopathies, motor findings are prominent in many of the autoimmune syndromes, ranging from ataxia to dyskinesias and dystonias and even catatonia.[98] Psychiatric symptoms, especially psychosis, are also more common with autoimmune encephalitides. Dysautonomias, while also present in some epilepsy syndromes, are more marked and frequent in autoimmune disorders. In addition, in treating autoimmune encephalitis, treatment is clearly intended to be immunomodulatory. This is not clearly the case with the epileptic encephalopathies, where although steroids and hormonal treatments may be used, it is not clear that their efficacy is directly immunologic. Some entities, such as Rasmussen encephalitis and Hashimoto encephalitis, may represent one end of a spectrum of disorders that are suspected but not proven to be autoimmune-mediated.

First-line treatment generally consists of corticosteroids, intravenous immunoglobulin, and plasmapheresis. Cyclophosphamide and rituximab are considered second-line if there is no improvement.[99,100] Part of the challenge of treatment is that response may take weeks to

months, raising the question of when to move on to second-line therapies; further, antibody testing may not be completed in the early stages of treatment. In antibody-negative or unproven encephalopathies that have not responded to more conventional therapy, it may be wise to have the courage of our convictions and move rapidly to second-line therapies, given the commonality across the board that delay in therapy leads to worse outcomes.

Currently there are no evidence-based consensus guidelines on treatment; incidence of these cases is low and initial clinical symptoms can be nonspecific, making design of randomized controlled trials challenging. Furthermore, it may well be the case that each entity may require a somewhat different approach. For example, anti-NMDAR encephalitis is often associated with an ovarian lesion and treatment requires removal of that lesion, which may be challenging in young women. One would not typically search for an ovarian lesion to remove in the other forms of encephalitis. Etiology and pathogenesis is poorly understood in all but a few of these disorders, further complicating diagnosis and management. Vigilance on the part of the diagnosing physician and early and aggressive treatment, with rapid advance to second-line therapies when there is no clear early response, are necessary for optimal outcomes.

Summary

Although epileptic encephalopathies are a small proportion of all childhood epilepsies, given the potentially devastating developmental outcomes, they account for a disproportionate effect on cognition, quality of life, and economic burden on families. Current understanding of these syndromes limits clinicians striving to achieve the ultimate primary goal of treatment, which is to improve overall neurologic outcomes. In most cases, conventional antiepileptic drugs are not effective in achieving this outcome, which has led to a shift in treatment focus to steroids and other immunomodulatory therapies. Given the success of using these modalities even in conditions where there is no clear immunologic component, as we better understand the etiology and genetics of these conditions, it may become clear that there is a larger autoimmune component to many of these disorders than previously realized. Genetic discoveries may also eventually guide novel and directed therapies in some cases. Clinicians are in need of effective and evidence-based guidelines to better shape treatment of the epileptic encephalopathies. Given the relative rarity of the conditions, this will likely require multicenter and/or multinational studies.

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Table 1

Epileptic Encephalopathies.

	Age of onset	Etiology	Seizure types	EEG features	Loss of function
EIEE/EME	Neonatal periods (before 3 mo)	Brain malformations, metabolic disorders, genetic mutations	Tonic spasms (EIEE), myoclonic (EME), and other types	Burst suppression pattern	Severe developmental impairment, evolution to other types of epileptic encephalopathies (infantile spasms, Lennox-Gastaut syndrome)
Infantile spasms	Infancy (3–7 mo)	Unknown (30%), known (70%; genetic, structural, metabolic disorders)	Epileptic spasms	Hypsarrhythmia (interictal) and electrodecremental response (ictal)	Developmental regression, evolution to Lennox-Gastaut syndrome
Dravet syndrome	During first year of life	Genetic mutations (*SCN1A*)	Febrile seizures during initial phase, generalized tonic-clonic, focal, and other types later on	Initially normal. Evolution to generalized spike-and-wave and focal epileptiform discharges later on	Developmental regression
Lennox-Gastaut syndrome	Childhood (1–7 y)	Similar to infantile spasms	Tonic, atonic, myoclonic, atypical absences, and others	Generalized slow spike-and-wave (interictal)	Developmental regression, slowly progressive
ESES	Childhood (peak 4–8 y)	Unknown, genetic mutations (*GRIN2A*)	Focal clonic, absences, generalized tonic-clonic	Continuous spike-and-wave during slow-wave sleep	Regression in cognition and behavior; domain may reflect location of epileptiform discharges
LKS	Childhood (around 5–7 y)	Unknown, genetic mutations (*GRIN2A*)	Similar to ESES, but can have no seizures	Some have continuous spike-and-wave during slow-wave sleep	Acquired aphasia (auditory agnosia)
Autoimmune epilepsy	Infancy to adulthood	Autoantibodies (anti-NMDAR antibodies, anti-neuronal proteins antibodies) may be detected	Generalized tonic-clonic, focal, status epilepticus	Generalized or focal epileptiform discharges	Regression in cognition and behavior (can be reversible with immune therapy)

Abbreviations: EIEE, early infantile encephalopathy (also known as Ohtahara syndrome); EME, early myoclonic encephalopathy; ESES, electrical status epilepticus in sleep; LKS, Landau-Kleffner syndrome; NMDAR, *N*-methyl-D-aspartate receptor.

Table 2

Autoimmune Encephalitis in Children.

	Clinical presentation	Underlying etiology	EEG findings	Treatment
Autoimmune epilepsy	Frequent or intractable seizures associated with cognitive impairment and learning disability	Unknown etiology, but antibodies against neuronal proteins (VGKC, LGI1, CASPR2, GAD65, NMDAR) can be detected.	Generalized and/or focal epileptiform discharges	Response to steroids, IVIG, plasmapheresis, cyclophosphamide
Anti-NMDAR encephalitis	Psychiatric symptoms (behavioral changes, hallucinations) and neurologic symptoms (seizures, movement disorders)	Anti-NMDAR antibodies in CSF affect nervous system. Teratoma may present in female.	Generalized background slowing, extreme delta brush	Response to steroids, IVIG, plasmapheresis, rituximab, cyclophosphamide
Limbic encephalitis	Seizures, alteration in behavior and memory	Commonly seen with paraneoplastic antibodies against neuronal proteins (Hu, Ma2, GAD65) or VGKC.	Epileptiform discharges and/or slowing in the temporal areas, generalized background slowing	Response to steroids, IVIG, plasmapheresis
Acute disseminated encephalomyelitis (ADEM)	Fever, fatigue, headache, nausea/emesis, and coma (in severe cases). Seizures not common.	Parainfectious (association with viral infection or immunization)	Generalized background slowing	Response to steroids, IVIG, plasmapheresis
Rasmussen encephalitis	Progressive refractory partial seizures, cognitive deterioration, focal neurologic deficit	Unknown (T cell-mediated?)	Focal epileptiform discharges and/or slowing	Response to steroids and IVIG at early stage of the disease, hemispherectomy being the only definitive treatment

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; NMDAR, *N*-methyl-D-aspartate receptor.

Table 3

Treatment Options in Infantile Spasms.

Treatment	Dosage	Class	n	Study	Etiology	Efficacy in cessation of clinical spasms	Efficacy in cessation of clinical spasms and abolishing hypsarrythmia	Efficacy in normalizing cognitive outcome
ACTH (high-dose)	150 U/m^2/d × 2 wk, then taper	I/II	15	Baram, 1996	Combined	–	87% (at 2 wk)	–
	150 U/m^2/d × 3 wk, then taper	I/II	26	Hrachovy, 1994	Combined	–	50% (during 3 mo)	–
	Tetracosactide 1 mg (equivalent to ACTH 100 U/d) q48h × 2 wk, then taper	III	37	Kivity, 2004	Cryptogenic	–	100% (treatment within 1 mo), 87% (treatment after 1 mo), assessed over 1–4 wk	100% (treatment within 1 mo), 47% (treatment after 1 mo), assessed over 6–21 y
	110 U/m^2/d × 3 wk, then taper	III	128	Lombrosso, 1983	Combined	48% (after 10 mo)	43% (after 10 mo)	50% (ACTH 8 wk), 59% (ACTH 8 wk + 14 wk of oral steroids) after 6 y (in cryptogenic cases, n = 73)
	Tetracosactide 0.75 mg (equivalent to ACTH 75 U/d) q48h × 2 wk, then taper	I/III	25	Lux, 2004	Combined	76% (at 2 wk)	–	–
ACTH (low-dose)	20–30 U/d, then taper	I/II	24	Hrachovy, 1994	Combined	–	58% (during 6 wk)	–
Oral steroids	Prednisone 2 mg/kg/d × 2 wk, then taper	I/II	14	Baram, 1996	Combined	–	29% (at 2 wk)	–
	Prednisolone 40–60 mg/d × 2 wk, then taper	I/III	30	Lux, 2004	Combined	70% (at 2 wk)	–	–
	Prednisolone 8 mg/kg/d (max 60 mg/d) × 2 wk	III	27	Hussain, 2014	Combined	–	63% (at 2 wk)	–
	Prednisolone 2 mg/kg/d × 8 wk, then taper	III	77	Lombrosso, 1983	Combined	38% (after 10 mo)	35% (after 10 mo)	12% after 6 y (in cryptogenic cases, n = 17)
Hormonal therapy	Prednisolone 40–60 mg/d, or tetracosactide 0.75 mg q48h × 2 wk, then taper	I/III	55	Lux, 2005	Combined	75% (at 12–14 mo)	–	In cryptogenic group, VABS 88.2 (better than vigabatrin group of 78.9) at 12–14 mo
Vigabatrin	Initial dose 50 mg/kg/d, maximum 150 mg/kg/d	I	20	Appleton, 1999	Combined	35% (VGB) vs 10% (placebo) at 5 d, 42% after 24 wk with open-label phase	25% (VGB) vs 5% (placebo) at 5 d	–
	Initial dose 50 mg/kg/d, maximum 150 mg/kg/d	I/III	52	Lux, 2004	Combined	52% (at 2 wk)	–	–
	Initial dose 50 mg/kg/d, maximum 150 mg/kg/d	I/III	52	Lux, 2005	Combined	76% (at 12–14 mo)	–	In cryptogenic group, VABS 78.9 (worse than hormonal therapy group of 88.2) at 12–14 mo

Treatment	Dosage	Class	n	Study	Etiology	Efficacy in cessation of clinical spasms	Efficacy in cessation of clinical spasms and abolishing hypsarrythmia	Efficacy in normalizing cognitive outcome
	Initial dose 50 mg/kg/d, maximum 150 mg/kg/d	IV	180	Djuric, 2014	Combined	–	56% (at 2 wk)	44% (mean follow-up, 11 y after treatment)
Valproate	Initial dose 15–20 mg/kg/d, maximum 60 mg/kg/d	IV	19	Bachman, 1982	Combined	42% (during 2 y)	–	–
Topiramate	Initial dose 25 mg/d, maximum 24 mg/kg/d	IV	11	Glauser, 1998	Combined	–	45% (during 90 d)	–
Zonisamide	Initial dose 3–5 mg/kg/d, maximum 10 mg/kg/d	IV	11	Suzuki, 1997	Combined	–	36% (at 3 wk)	–
	4–13 mg/kg/d	IV	54	Suzuki, 2002	Combined	–	20% (at 3 wk)	5/7 (71%) responders had normal DQ (mean follow-up, 53 mo after treatment)
Levetiracetam	Initial dose 20 mg/kg/d, maximum 80 mg/kg/d	IV	7	Mikati, 2008	Combined	–	14%	–
Pyridoxine	Pyridoxal phosphate 30–400 mg/d	IV	118	Ohtsuka, 1987	Combined	13%	13%	43% in responder
Ketogenic diet	–	III	13	Kossoff, 2008	Combined	62% (at 1 mo)	9% (at 1 mo)	–
Surgery	–	IV	65	Chugani, 2015	Lesional cases	71% class I (mean follow-up period at 45 mo)	–	–
	–	IV	47	Shields, 2002	Lesional cases	60% class I (at 24–60 mo)	–	–

Abbreviations: ACTH, adrenocorticotropic hormone; DQ, Developmental quotient; VABS, Vineland Adaptive Behavior Scales; VGB, vigabatrin.