Journal of Pediatric Sciences

SPECIAL ISSUE

"Treatment of Severe Epileptic Syndromes"

Editor

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'New antiepileptic drugs in the treatment of Lennox-Gastaut syndrome'

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New antiepileptic drugs in the treatment of Lennox-Gastaut syndrome

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Abstract: Lennox–Gastaut syndrome is a childhood epileptic encephalopathy characterised by polymorphic seizures and neuropsychological decline. The most characteristic seizures are tonic fits, atypical absences and atonic seizures, in that order. Treatment options for patients with LGS are limited because of the resistance of seizures to pharmacological treatment. Owing to the many seizure types, many drugs are used in combinations that are mostly guided by anecdotal evidence or personal experience. Opinions towards treatment are further complicated because an antiepileptic drug might be of some benefit for the control of one type of seizure while aggravating another type. Concomitantly, polytherapy increases the potential for adverse events. The ultimate goal of epilepsy treatment is to achieve seizure control in a safe manner. Seizure freedom appears to be unrealistic in some refractory epilepsies, especially LGS. In this Review, we discuss newer antiepileptic drugs (Felbamate, Lamotrigine, Levetiracetam, Topiramate, Rufinamide, Vigabatrin, Zonisamide) in the treatment of Lennox-Gastaut syndrome. Investigation of the effects of newer medications might help to identify treatments that, when used in the early stages of the disorder, might have long-term beneficial effects on seizures and the associated comorbidities.

Key words: antiepileptic drugs, Lennox- Gastaut syndrome, epilepsy
Received: 24/11/2009; Accepted: 25/11/2009

Lennox–Gastaut Syndrome

Lennox–Gastaut syndrome is a childhood epileptic encephalopathy characterised by the triad of:

1. Polymorphic intractable seizure that are mainly tonic, atonic and atypical absence seizures
2. Cognitive and behavioural abnormalities
3. EEG with paroxysms of fast activity and slow (less than 2.5 Hz) generalised spike-wave discharges (GSWD)

Demographic Data

Lennox–Gastaut syndrome starts between 1 and 7 years with a peak at 3–5 years. Boys (60%) are affected slightly more often than girls. The incidence of Lennox–Gastaut syndrome is low at 2.8 per 10,000 live births.

However, because of its intractable nature, the prevalence is relatively high at approximately 5–10% of children with seizures.

Clinical Manifestations

Lennox–Gastaut syndrome is characterised by polymorphic seizures and neuropsychological decline. The most characteristic seizures are tonic fits, atypical absences and atonic

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seizures, in that order. Myoclonic jerks occur in 11–28% of patients alone or in combination with other seizures. However, myoclonic jerks do not predominate in the 'pure' Lennox–Gastaut syndrome. The onset may be insidious with symptoms appearing de novo without conspicuous reason in cryptogenic cases. Previous psychomotor deficits are apparent in symptomatic cases. Cognitive and behavioural abnormalities are present prior to seizure onset in 20–60% of patients.

Half of the cases of West syndrome and other infantile epileptic encephalopathies progress to Lennox–Gastaut syndrome. Conversely, 10–30% of patients with Lennox–Gastaut syndrome develop from West syndrome or other epileptic encephalopathies, though the transition phase is difficult to evaluate. Focal and generalised seizures are also common predecessors.

Tonic Seizures

Tonic seizures are the commonest (approximately 80–100%) and probably the most characteristic seizure type in Lennox–Gastaut syndrome. These are usually symmetrical, brief (2–10 s) and of variable severity from inconspicuous to violent. Descriptively, tonic seizures are as follows.

- Axial seizures affect the facial, nuchal, trunk, paraspinal, respiratory and abdominal muscles alone or in combination. The symptoms include raising the head from a pillow, elevation of the eyebrows, opening of the eyes, upward deviation of the eyeballs, opening of the mouth and stretching of the lips to a fixed smile. An 'epileptic cry' is common at the onset of attacks.
- Axo-rhizomelic seizures, which are axial seizures, also involve the proximal (rhizomelic) muscles of the upper and less often lower limbs. Elevation and abduction or adduction of the upper limbs and shoulders occur

together with the other symptoms of axial tonic seizures.
- Global seizures, which are axo-rhizomelic seizures, also involve the distal part of the limbs. The arms are forced upwards, abducted and semi-flexed with clenched fists 'like that of a child defending himself from a facial blow'. The lower limbs are forced into triple flexion at the hip, knee and ankle or into extension. Global tonic seizures often cause forceful sudden falls and injuries.

A series of tonic seizures, reminiscent of epileptic spasms but of longer duration, may occur, particularly when Lennox–Gastaut syndrome develops from West syndrome.

Concurrent autonomic manifestations may occasionally be the prominent symptom of the attacks. Tonic seizures occur more often during slow wave sleep than states of wakefulness. Some patients may have hundreds of them during sleep. They do not occur during REM sleep. In early onset Lennox–Gastaut syndrome clusters of tonic spasms frequently occur on awakening.

Atypical Absence Seizures

Atypical absence seizures occur in approximately two-thirds of patients. There is 'clouding' rather than loss of consciousness with gradual onset and gradual termination. The patients may continue with their activity though slower and often with mistakes. Impairment of their cognition may be so mild that it can be clinically undetectable. Selective impairment of higher cortical functions with maintained responsiveness may occur.

Changes in tone and myoclonic jerks may be very pronounced. Often, there is loss of trunk or head postural tone, facial muscle or neck muscle stiffening, eyelid or peri-oral myoclonus, random jerks of the head or limbs and head nodding. Atypical absence seizures, contrary to the typical absences, occur only in the context of mainly severe symptomatic or

cryptogenic epilepsies of children with learning difficulties who also suffer from frequent seizures of other types such as atonic, tonic and myoclonic.

Atonic Seizures

Atonic seizures consist of sudden, brief (1–4 s) and severe loss of postural tone. They occur in nearly half of patients. They are frequent and involve the whole body or only the head. The trunk and head slump forwards and the knees buckle. Generalised loss of postural tone causes a lightning-like fall. Atonic seizures are the commonest cause of falls resulting in severe injuries to the nose or teeth.

The patient collapses on the floor irresistibly without impairment of consciousness and then immediately stands up again.

Longer atonic seizures lasting for 30 s up to 1–2 min are rare. The patient remains on the floor unable to stand up.

In brief and milder attacks there is only head nodding or sagging at the knees.

Atonic seizures always alternate with tonic fits and atypical absences in Lennox–Gastaut syndrome. There may be a predominant tonic component (axial spasm) in these otherwise atonic seizures. In addition, myoclonic jerks may precede or less often intersperse with the atonic manifestations.

Myoclonic Jerks

Myoclonic jerks were initially not included amongst the seizures of Lennox–Gastaut syndrome, but they may occur in 11–28% of patients. Myoclonic attacks are very brief shock-like muscle contractions that may be isolated or repeated in a saccadic manner, usually for only a few seconds. The jerks are generally bilateral and symmetrical (massive myoclonus) and preferentially involve the axial flexor muscles and the abductors of the arms. They may cause falls.

Epileptic Falls

Epileptic falls (drop attacks) may be the result of various types of seizures such as atonic, tonic, myoclonic-atonic and more rarely myoclonic seizures. Tonic seizures are the commonest cause of falls. These are often difficult to differentiate clinically without polygraphic recording. The falls result in recurrent injury.

Non-Convulsive Status Epilepticus

Non-convulsive status epilepticus featuring all types of seizures such as atypical absences, tonic and atonic fits and myoclonic jerks occur in half of patients. It is often of very long duration (days to weeks), exhibits resistance to treatment and is repetitive. Depending on the predominant seizure type, status epilepticus in Lennox–Gastaut syndrome may be one of the following.

- Absence status epilepticus, a mild but occasionally severe confusional state that can last for days or weeks.
- Tonic status epilepticus is more often seen in adolescents than in children.
- Myoclonic status epilepticus is rare, occurring when the myoclonic jerks are the dominant seizure type.
- Mixed tonic and absence status is probably the commoner type. It consists of repetitive uninterrupted or discontinuous series of brief tonic seizures alternating with atypical absences. There is usually profound impairment of consciousness or stupor, intermixed with serial tonic attacks and sometimes with myoclonic-atonic falls.

Aetiology

The aetiology is extensive and diverse. Symptomatic Lennox–Gastaut syndrome due to severe and, less often, mild brain disorders

of any type is by far the commonest, probably 70% of all cases. The pre-, peri- and postnatal causes are similar to those responsible for West syndrome, but Aicardi syndrome and lissencephaly, which are common in West syndrome, are rare causes in Lennox–Gastaut syndrome. Malformations of cortical development are increasingly identified as a common cause of the Lennox–Gastaut syndrome. Focal cortical dysplasia can produce a typical or an incomplete form of the syndrome.

One-third of Lennox–Gastaut syndrome cases occur without antecedent history or evidence of brain pathology (idiopathic or probably symptomatic cases). There is no evidence of a genetic predisposition.

Pathophysiology

Lennox-Gastaut syndrome is a non-specific age dependent diffuse epileptic encephalopathy of unknown patho-physiological mechanisms.

Pathophysiology of the Electrical Discharges in Lennox-Gastaut Syndrome:

From the neurophysiological point of view there is no convincing explanation for the electrical interictal or ictal events. They are a severely abnormal response of the maturing brain of early childhood to diffuse, or occasionally localized, brain damage. The response may be similar to that of infants developing West syndrome but at a different age of maturation. The electrographic abnormalities are thought to reflect excessive neocortical excitability and arise from neuronal and synaptic features peculiar to the immature brain. Cortical and subcortical structures are probably involved. Frontal lesions may have a higher responsibility. SBS may be the main pathophysiological mechanism in one-third of cases of typical Lennox-Gastaut syndrome. The response of atypical absence seizures to the same drugs used in typical absence seizures, may indicate similar, but not necessarily the same, pathophysiological mechanisms of an abnormal thalamocortical oscillatory burst-firing circuit.

Pathophysiology of the Development Cognitive and Behavioural Abnormalities:

Lennox-Gastaut syndrome is considered as an epileptic encephalopathy whereby abundant epileptogenic abnormalities of slow GSWD and fast rhythms/rapid spikes play a pivotal role in the development of cognitive and behavioural impairment by altering brain connectivity and neurotransmission of the maturing brain. A reason for this may be that these electrical discharges divert the brain from normal developmental processes toward seizure-preventing mechanisms. AEDs, sleep disruption, and social isolation are significant contributing factors.

Ictal EEG

Atypical absences are associated with slow (less than 2.5 Hz) GSWD. Tonic seizures have accelerating fast paroxysmal activity, which is bilateral and often predominates in the anterior regions and the vertex. This may be of two types.

1. Very rapid (20 ± 5 Hz) and initially of low amplitude, progressively increasing to 50–100 mV.
2. A more ample and less rapid rhythmic discharge at 10 Hz, identical to that of the tonic phase of the GTCS (epileptic recruiting rhythm) except that it may be of high amplitude from the onset.

Flattening of all EEG activity alone or in combination with fast paroxysms are also common. Fast ictal paroxysms may be preceded by generalised spike-slow wave discharges or EEG suppression.

Atonic attacks occur with generalised polyspikes, slow GSWD and accelerating fast paroxysms alone or in combination.

Myoclonic attacks have mainly generalised discharges of polyspikes with or without slow waves and fast rhythms.

A combination of clinical manifestations and ictal EEG patterns is common.

Massive myoclonus, atonic seizures and myoclonic-atonic seizures mainly consist of a mixture of slow spike-wave, polyspikes and decremental events. Post-ictally, there is diffuse slowing or slow GSWD instead of EEG flattening [1].

Treatment guidelines
Treatment options for patients with LGS are limited because of the resistance of seizures to pharmacological treatment. Owing to the many seizure types, many drugs are used in combinations that are mostly guided by anecdotal evidence or personal experience. Opinions towards treatment are further complicated because an antiepileptic drug might be of some benefit for the control of one type of seizure while aggravating another type. Concomitantly, polytherapy increases the potential for adverse events. Guidelines from the American Academy of Neurology have assessed the data on the efficacy and safety of seven new antiepileptic drugs for the treatment of refractory epilepsy, including LGS [2].

These cognitive and behavioural impairments are often difficult to quantify in the short and long term but need to be considered when comparing one treatment with another.

Contrary to the conventional management of epilepsy, the aim of treatment of LGS is often to suppress or reduce the frequency of the more disabling types of seizures rather than complete freedom from seizures (although this would be the ultimate aim). The more complex aspects of LGS, such as the

occurrence of the nonconvulsive status epilepticus or the effects of the epilepsy syndrome on cognition and behaviour compared with the effects of the medication are difficult to quantify over a short response time to treatment. Many of these problems are not assessed in short-term clinical trials, which typically measure efficacy over only 10–16 weeks. The age range is also broad and, owing to the progression of the syndrome and the different expectations at different ages, the aims for benefit in treatment might differ in accordance with the stage of the disease. For example, newly diagnosed children might have had a catastrophic onset of epilepsy with developmental arrest; the aims of therapy in such a case would be to reverse, at least in part, the cognitive impairment and behavioural abnormalities of the child. However, in an older child, who might have had several years of treatment, the expectations might be reduced frequency of seizures rather than specific changes in cognition. Improved control of seizures can result in greater alertness, which might translate into altered behaviour of the patient; this change could potentially be misunderstood as a behavioural side-effect of the treatment [3].

The optimum treatment for Lennox-Gastaut syndrome remains uncertain and no study to date has shown any one drug to be highly efficacious; lamotrigine, rufinamide, topiramate and felbamate may be helpful as add-on therapy [4].

Old antiepileptic drugs
Valproate is the drug of choice because of its efficacy in all types of seizures seen in Lennox–Gastaut syndrome. However, younger children, particularly on polytherapy, are at greater risk of serious hepatotoxic reactions.

Clonazepam and other diazepines such as nitrazepam are mainly effective in myoclonic jerks and tonic attacks.

Phenytoin may reduce tonic, vibratory tonic and tonic status epilepticus.

Carbamazepine may be effective in partial seizures, but may exacerbate other types of generalised fits.

Phenobarbital and primidone may control convulsive seizures, but may be prohibited in Lennox–Gastaut syndrome because of cognitive, behavioural and sedative side effects.

Ethosuximide often controls atypical absence seizures and is useful in myoclonic and atonic seizures with falls.

New antiepileptic drugs

Felbamate
Felbamate was evaluated in patients with LGS in a 10-week, placebo-controlled, double-blind trial [5]. Felbamate treatment significantly decreased the frequencies of total seizures and atonic seizures and was subsequently approved by the FDA for use in LGS. It is available in a number of European countries and was also available in the UK for a short period, until reports of fatal aplastic anemia and fatal hepatitis led to its withdrawal shortly after it was given a license [6].

In a 12-month, open-label follow-up to the randomized trial described above [5], improvements achieved during the doubleblind phase were maintained during the follow-up period [7]. Of the patients who had previously received placebo, 62% achieved a >50% reduction in seizures within 1 month of starting felbamate treatment. Overall, 50% of patients had a >50% reduction in total seizures at 12 months. In a crossover study, felbamate or placebo was given to 13 patients with LGS, stabilized on sodium valproate, for two periods of 7 weeks [8]. There appeared to be a synergistic effect between felbamate and sodium valproate, with an overall reduction in the frequency of total seizures and drop attacks. Further, felbamate treatment significantly reduced the frequencies of astatic (atonic) seizures and generalized tonic–clonic seizures plus total seizure counts [9].

Within 1 year of felbamate's approval, reports of both aplastic anemia and hepatic failure resulted in most patients being withdrawn from the drug. It is still licensed in some European countries, but is no longer licensed in many others, such as the UK. The estimated incidence of aplastic anemia is 1 in 4785 to 1 in 37 037 felbamate-treated patients [10] and hepatotoxicity occurs in approximately 1 per 26 000 to 1 per 34 000 felbamate-treated patients. It should be noted that a similar risk of hepatotoxicity is seen with sodium valproate [11].

Lamotrigine
Lamotrigine was evaluated in LGS in a 16-week, randomized, double-blind, placebo-controlled trial [12]. It reduced the frequency of major seizures, with similar reductions seen when drop attacks and tonic–clonic seizures were looked at individually. One-third of the lamotrigine-treated group had a ≥50% reduction in the frequency of major seizures. No difference between groups was seen in the frequency of atypical absence seizures. Except for cold and viral illnesses (which were more common in the treatment group), there were no significant differences between groups in adverse events. Lamotrigine is approved for the adjunctive treatment of LGS in those who are 2 years of age or older [13].

In addition to the one randomized, double-blind, placebo-controlled trial of lamotrigine in LGS described above [12], several small trials have shown the efficacy of lamotrigine as an adjunctive therapy for reducing seizure frequency in LGS, particularly against tonic, atonic and atypical absence seizures.

In an open-label, add-on study of lamotrigine in 11 patients with LGS, [14] 10 had a >50% decrease in seizure frequency. In a report involving 120 children with epilepsy [15], six of the 10 patients with LGS had a >50% decrease in seizures after receiving lamotrigine adjunctive therapy for 3 months. In a study of 50 children with intractable epilepsy who received open-label lamotrigine, three of the eight patients with LGS had a >50% decrease in seizures [16]. In another open-label trial in 93 patients with drug-resistant epilepsy [17], four of the nine patients with LGS had a >50% reduction in seizures. In a prospective, open-label study of 56 children with intractable generalized epilepsy [18], 11 of the 15 patients with LGS achieved a ≥50% decrease in seizures when lamotrigine was given as adjunctive therapy. In a retrospective, open-label, chart review in 16 patients with LGS given adjunctive lamotrigine [19], eight had a >50% reduction in seizure frequency; the frequency of tonic, atonic, tonic–clonic and atypical absence seizures, but not myoclonic seizures, was significantly decreased. Lastly, in a double-blind, placebo-controlled crossover trial in 30 children and adolescents with refractory epilepsy (20 with LGS) [20], there was a significant reduction in seizure frequency during lamotrigine add-on therapy, compared with placebo treatment. Adverse events described with lamotrigine include sleep disturbances and rash [15,16,18,19]. The latter is more likely to occur when used in combination with sodium valproate. This combination may have a therapeutic interaction [21], but slow titration of lamotrigine when being added to sodium valproate is essential to minimize the risk of rash.

Levetiracetam

The efficacy and tolerability of levetiracetam in patients with LGS has been evaluated in two studies and one case series, with mixed results. In a 12-month, open-label, observational trial, 35 children received levetiracetam as de novo monotherapy or add-on therapy; one of the two patients with LGS showed a ≥50% reduction in seizures while the other had an increase in seizures [22]. An open-label pilot study evaluated long-term levetiracetam use in 10 patients, four with LGS; two patients experienced long-term seizure reductions, one had an increase in seizure frequency, and one withdrew from treatment [23]. In a case series of six children with LGS treated with add-on levetiracetam, 100% reductions in myoclonic and tonic–clonic seizures were seen in four patients [24]. Levetiracetam is licensed in Europe for the treatment of partial seizures with or without secondary generalization in patients 4 years of age or older [13].

Topiramate

Topiramate was evaluated in an 11-week, randomized, double-blind, placebo-controlled trial [25], which showed that topiramate treatment was associated with significant benefits compared with placebo on the frequency of drop attacks and on seizure severity (based on parental global evaluation). The proportion of patients with a ≥50% reduction in major seizures (drop attacks and tonic–clonic seizures) was significantly reduced by topiramate, although there was no apparent effect on absence seizures. The most common adverse events were CNS-related but did not result in any discontinuations. Topiramate is approved for the adjunctive treatment of LGS in patients 2 years of age or older [13].

In an open-label extension of the randomized, double-blind, placebo-controlled trial described above [25], 97 patients continued taking topiramate and other concomitant AEDs [26]. After 6 months of receiving topiramate, 45–68% of patients showed a ≥50% reduction in total seizures, drop attacks, atypical absence seizures, myoclonic seizures and tonic–clonic seizures.

Other topiramate trials have typically been open-label, add-on studies in children with intractable epilepsy, including a few with LGS. Four such studies are briefly described here. In a long-term, open-label pilot study in 18 patients with LGS receiving topiramate as add-on therapy [27], six of the eight patients still receiving topiramate had a >50% reduction in seizure frequency, with the best results seen in drop attacks, atypical absence seizures and generalized tonic–clonic seizures. Similarly, in a prospective, open-label, add-on study in 45 patients with LGS [28], topiramate treatment was associated with a >50% reduction in seizures in 18 patients after an average treatment period of 15.8 months; it was most effective at reducing the incidence of drop attacks and tonic–clonic seizures. In another add-on trial [29], 47 children (25 with LGS) received topiramate and 60% of children had a >50% reduction in seizures after at least 6 months of treatment; there was no difference in efficacy between different epilepsy diagnoses. Lastly, in contrast to the results described above, a long-term, retrospective, open-label add-on study in 277 children with drug-resistant epilepsy, who received topiramate for a mean period of 27.5 months [30], showed only two of the 15 children with LGS had a >50% reduction in seizures. A complete loss of efficacy was seen in the patients with LGS by 30 months. The most commonly reported adverse events with topiramate include infection, somnolence, drowsiness, nervousness, anorexia and weight loss [26, 28-30].

Topiramate has been associated with difficulties in language processing and therefore requires a slow dose titration schedule.

Rufinamide
Rufinamide has been evaluated in LGS in a 12-week randomized, placebo-controlled trial [31]. It significantly reduced the frequencies of total seizures and drop attacks, and significantly more patients in the rufinamide group than in the placebo group achieved a ≥50% reduction in drop attack frequency. The most common adverse events were somnolence, nausea and fatigue. Rufinamide received European approval in January 2007 as an adjunctive treatment for LGS in patients 4 years of age or older.
 An open-label extension of the randomized study described above [31] included 124 patients receiving rufinamide for a median of 432 days. The initial reduction in total seizure frequency (43% at 6 months) was maintained, with further improvements seen over 3 years [32]. The most common adverse events were somnolence, pyrexia and vomiting [32]. While drug–drug interactions are minimal between rufinamide and most other antiepileptic drugs, sodium valproate may increase levels of rufinamide in children by up to 70% [33].

Vigabatrin
The antiepileptic effects of vigabatrin in children have been demonstrated in three studies, although the numbers of patients with LGS included were small. In the earliest study [34], vigabatrin was administered as add-on therapy in an open-label, uncontrolled trial of 135 children with refractory
epilepsy; half of the 26 patients with LGS showed some reduction in seizure frequency. In a 16-week single-blind trial in 61 children with refractory epilepsy who received add-on vigabatrin, two of the seven patients with LGS experienced a >50% decrease in seizure

frequency, but four experienced a >50% increase in seizure frequency. In an open-label, dose-ranging study in 20 children with LGS, vigabatrin was added to first-line valproate therapy that was not adequately controlling seizures [35]. After titrating to either 4000 mg/day, the maximum tolerated dose, or the dose that controlled seizures, patients were maintained for 12 months. During this time, eight patients became seizure-free and nine had a >50% reduction in seizure frequency. Vigabatrin can exacerbate generalized seizures. Nevertheless, it is a first-line drug for the treatment of infantile spasms and it is licensed as a monotherapy for their management in some European countries [36].

The most commonly reported adverse events with vigabatrin are weight gain and agitation [34,35]. Since it was licensed in the UK, visual field defects resulting in the development of 'tunnel vision' have been reported in adults and children receiving vigabatrin [38], resulting in its restricted use [36].

Zonisamide

Zonisamide is indicated as an adjunctive therapy for refractory partial seizures with or without secondary generalization, but is not recommended for use in patients under 18 years of age [36]. A long-term postmarketing survey involving 1631 patients in Japan indicated that 28% of those with West syndrome or LGS improved after treatment with zonisamide [39].

Conclusions

The ultimate goal of epilepsy treatment is to achieve seizure control in a safe manner. Seizure freedom appears to be unrealistic in some refractory epilepsies, especially LGS. Four AEDs (FBM, LTG, TPM and RUF) have been officially licensed for LGS after demonstrating significant efficacy in randomized, double-blind, placebo controlled studies. Older AEDs (especially VPA) are regularly used, based on more than 40 years of clinical practice. Published results, even from randomized studies, are difficult to compare. Each trial looked at different patient populations, with diverse co-medications and etiologies, and considered different outcomes for efficacy. Unfortunately, a "magic pill" does not exist, and for that reason, other treatments are regularly tried. For children with highly pharmacoresistant seizures, an individual and tailored treatment strategy is necessary, based on the likelihood of better seizure control and QOL balanced against the likely risks for each strategy. The different steps of this continuous therapeutic approach should depend on various factors, including patient characteristics, severity of seizures and mental handicap, and local availability of sophisticated techniques. The worst approach to patients with LGS is one of pessimism, considering that the prognosis is defi nitively catastrophic. On the other hand, the reverse attitude with iterative aggressive treatments should also be avoided. A better strategy is to explain regularly to the family that the aim of the treatment is to suppress the most severe seizures, to avoid additional comorbidities and to avoid heavy polytherapy. The situation has to be regularly re-evaluated. As LGS is rare, case reports of atypical or unusual treatments may help other clinicians in deciding what type of treatment to use in difficult cases. A more holistic approach to the investigation of the effects of newer medications might help to identify treatments that, when used in the early stages of the disorder, might have long-term beneficial effects on seizures and the associated comorbidities.

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