

Treatment of Lennox-Gastaut syndrome: overview and recent findings

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Abstract: Lennox-Gastaut syndrome (LGS) is a rare, age-related syndrome, characterized by multiple seizure types, a specific electro-encephalographic pattern, and mental regression. However, published data on the etiology, evolution, and therapeutic approach of LGS are contradictory, partly because the precise definition of LGS used in the literature varies. In the most recent classification, LGS belongs to the epileptic encephalopathies and is highly refractory to all antiepileptic drugs. Numerous treatments, medical and non-medical, have been proposed and results mostly from open studies or case series have been published. Sometimes, patients with LGS are included in a more global group of patients with refractory epilepsy. Only 6 randomized double-blind controlled trials of medical treatments, which included patients with LGS, have been published. Overall, treatment is rarely effective and the final prognosis remains poor in spite of new therapeutic strategies. Co-morbidities need specific treatment. This paper summarizes the definition, diagnosis and therapeutic approach to LGS, including not only recognized antiepileptic drugs, but also “off label” medications, immune therapy, diet, surgery and some perspectives for the future.

Keywords: Lennox-Gastaut syndrome, treatment, VNS, surgery, epileptic encephalopathies, LGS, refractory

Introduction

The term Lennox-Gastaut syndrome (LGS) appeared in the literature for the first time in 1969 (Niedermeyer 1969), but this syndrome was actually first described by Lennox and Davis in 1950 and by Gastaut et al in 1966. The International League Against Epilepsy (ILAE) Commission (Classification Epilepsia 1989) classified LGS among the cryptogenic or symptomatic generalized epilepsies, but, more recently, the ILAE Task Force classified it among the age-related epileptic encephalopathies (Engel 2001). LGS comprises atypical absences with slow spike-and-wave (SW) complexes, tonic seizures that are mostly sleep-related, and cognitive deterioration (ILAE). However, LGS has also been defined as diffuse SW pattern on electroencephalogram (EEG), mental retardation, and multiple types of seizures without reference to age or to nocturnal tonic seizures (French et al 2004). This broader definition, mostly used in the US, may include for example, Dravet syndrome, Doose syndrome, or focal cryptogenic epilepsies, especially of frontal lobe origin. According to Genton et al (2000), EEG criteria should include not only bilateral slow SW but also 10–20 Hz epileptic fast rhythms, predominantly in sleep. Furthermore, this syndrome belongs to the age-related epileptic encephalopathies and starts during childhood. When using these full criteria, LGS appears to be rare.

Largely as a result of the different definitions, the literature presents, or seems to present, contradictory data about the frequency of seizure types, epidemiology, treatment options, prognosis, and long term evolution of LGS. Furthermore, results of clinical studies are difficult to compare in terms of efficacy and most of them, especially randomized studies, do not cover more than a few weeks (Hancock and Cross 2003).

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Treatment is rarely effective and the final prognosis remains poor in spite of new therapeutic strategies, with persistent seizures, mental retardation/deterioration, and behavioral problems.

Epidemiology-etiology

LGS is rare, with an annual incidence of 0.2–2.8/10,000 births in European countries (Heiskala 1997) but the prevalence of LGS is higher (5% of all epilepsies and about 10% of childhood epilepsy) because of its refractory characteristics (Trevathan et al 1997).

LGS can appear *de novo* in cryptogenic cases (about 30%) or be the result of brain injury of various etiologies (pre- or peri-natal insult, infection, various malformations including dysplasia, and brain tumor) in symptomatic cases. In these latter cases, LGS is often (18%–50%, mean 30%) preceded by West syndrome or focal seizures (Glauser 2004).

LGS starts between 2 and 8 years (peak 3–5 years), slightly later in cryptogenic cases than in symptomatic ones, and is more common in boys than in girls. The age-related link suggests an influence of brain maturation on symptoms and disease evolution. Indeed, the usual age of onset corresponds with maturation of the frontal lobes and most of the clinical and EEG signs have a frontal lobe semiology.

Recently, a defect in the mitochondrial chain has been suggested as the cause of LGS (Lee et al 2008) and this metabolic pathway should be carefully explored in the so-called cryptogenic cases.

Diagnosis

LGS is characterized by an electroclinical triad: Multiple seizure types, specific EEG pattern and mental slowing and/or regression. However, etiological diagnosis and identification of co-morbidities are important for correct global management.

Clinical features

The first clinical sign, at least in cryptogenic cases, is often the occurrence of abrupt falls. These are followed by intractable generalized seizures, including myoclonic, tonic, atonic, and atypical absences and by mental slowing then regression. Some patients may have tonic and/or non-convulsive status epilepticus (SE). These episodes of SE may aggravate or precipitate cognitive decline.

The most disabling seizures are falls, sometimes called “epileptic drop attacks” and may be secondary to atonic or tonic seizures and, more rarely, to myoclonic or

myoclonic-atonic seizures, these being more typical of Doose syndrome. The causes of these epileptic drop attacks are difficult to differentiate clinically and they can result in recurrent injuries and additional handicap. The frequency of drop attacks has been used as the primary outcome in most randomized studies in LGS. Tonic seizures may appear with variable severity from subtle symptoms to generalized stiffness and falls and may be triggered or worsened by benzodiazepines (BZDs) (Tassinari et al 1972; Dimario and Clancy 1988).

Atypical absences are characterized by an alteration in, rather than a loss of, consciousness. They may be accompanied by other subclinical signs, such as discreet loss of tonus, subtle myoclonus, head nodding.

Myoclonic seizures in LGS are considered rare by some authors but as an important and difficult to treat part of the syndrome by others. However, if this type of seizure is predominant, an alternative diagnosis should be suspected. These seizures may be aggravated by some antiepileptic drugs (AEDs) (Feucht and Brantner-Inthaler 1994).

Fewer than 50% of patients have focal seizures and, globally, tonic-clonic seizures are rare (Dulac 2001), although, again, other authors consider them as frequent and resistant to medical treatment.

Patients with LGS will have at least one episode of status epilepticus in their history, mainly atypical absence status or tonic status with subtle signs. Some AEDs can precipitate status, especially benzodiazepines (BZDs) (Tassinari et al 1972).

Non-convulsive status epilepticus (NCSE) occurs in more than 50% of patients. Typically, NCSE appears as subcontinuous atypical absences repeatedly interrupted by brief tonic seizures or as subtle tonic status with progressive reduction of motor manifestations and prolonged obtundation with mild myoclonias.

Progressively, after seizure onset, slowing or arrest of cognitive development occurs with behavioral problems in about 50% of cases, including hyperactivity, aggressiveness, autistic traits. These features are more marked in early onset or symptomatic LGS.

Neurological examination is non specific, from normal to lateralized, depending on the underlying etiology.

Later in the disease, it can be difficult to differentiate problems related to LGS, from those occurring as a result of AEDs, or because of numerous falls or frequent SE.

Teenagers with a history of LGS may continue to have atypical absences, generalized tonic-clonic seizures and atonic

seizures, but while some authors report that tonic seizures become rare to absent, for others, tonic seizures remain the major problem (Roger et al 1989, Dulac and Engel ILAE link).

Electroencephalogram (EEG) and magnetoencephalogram (MEG) features

Slow (≤ 2.5 Hz) SW, first described by Gibbs et al (1939), is the most prominent feature in interictal awake EEG. The average age of onset of slow SW is 8.2 years, with a mean duration of 8.6 years. However, EEG criteria should also include 10–20 Hz epileptic recruiting or fast rhythm, appearing principally in sleep (Genton et al 2000).

Generalized polySW and lower voltage of short duration fast activities are usual during slow sleep. Photic stimulation has no impact on the EEG while hyperpnea may exacerbate slow SW. Focal paroxysmal discharges or slowing may be recorded in symptomatic LGS, related to the underlying pathology.

The ictal EEG pattern depends on the seizure type. Atypical absences are recorded during slow SW but they are sometimes difficult to distinguish from the background from a clinical and EEG point of view. Myoclonic seizures are associated with bilateral and symmetrical SW and polySW whereas fast activities are typical of tonic seizures.

With age and disease evolution, EEG changes and multifocal spikes may be seen as well as diffuse or localized slowing. Diffuse slow SW tend to be “frontalized”.

MEG records the magnetic signal generated by the intraneuronal current. This signal is not attenuated or distorted as is the electric signal. MEG, with up to more than 100 channels, is more powerful in dipole localization and in evaluating transcallosal spread in generalized epileptiform discharges due to secondary bisynchrony. In most cases, MEG information is combined with MRI images and can provide anatomic localization of interictal epileptiform activities (Technology Evaluation Center 2003).

Anecdotal case reports (Sakurai et al 2006) offer some support for the use of MEG in “atypical” LGS, particularly if surgical treatment is being considered.

Imaging (positron emission tomography (PET) scan, magnetic resonance imaging (MRI) features

The MRI is by definition, normal in cryptogenic cases, ie, in about 30% of cases. However, high MRI resolution may show small amounts of cortical dysplasia in a previously normal MRI. Occasionally, a brain tumor (Quarato et al 2002) or broad dysplasia (You and Lee 2007b) can be found with

MRI and consequently surgery may be offered as a curative treatment. Usually, symptomatic cases have a worse prognosis than cryptogenic LGS. Goldsmith et al (2000) did not find (in a retrospective study of 107 confirmed cases of LGS from 245 presumed cases) any prognostic value of MRI on seizure outcome; 74 of the 107 patients were followed-up for ≥ 3 years. However, these investigators divided their LGS patients into three groups: cryptogenic, symptomatic and indeterminate. According to the ILAE, only cryptogenic and symptomatic cases are recognized. Based on the descriptions given by Goldsmith et al the indeterminate cases belong to the cryptogenic group and this multiple subdivision gives less weight to the statistics.

PET scan may show focal hypometabolism even in cryptogenic cases (Gur RC et al 1982; Ferrie et al 1996). Therefore, this imaging technique is recommended for presurgical evaluation, even if the MRI is normal or the EEG shows multifocal abnormalities.

Differential diagnosis

Clinically, the differential diagnosis of drop attacks is the major concern. The slow SW pattern represents another challenge for diagnosis on awake EEG.

Some epileptic syndromes or clinical situations must be excluded:

- Atypical cases of continuous SW during slow sleep with akinetic absence status and/or negative myoclonia
- Doose syndrome
- Dravet syndrome
- Toxic encephalopathy
- Metabolic diseases, such as Glut-1 deficiency syndrome (De Vivo et al 1991; Wang et al 2005) and pyruvate dehydrogenase deficiency (Wexler et al 1997),
- Focal or multifocal epilepsy with secondary bisynchrony on EEG
- Late onset epileptic spasms

It is, therefore, mandatory to record a sleep EEG and, if necessary, video-EEG monitoring or polygraph recording, before making a diagnosis of LGS.

It is not rare (up to 40% of secondary generalized epilepsies in childhood) (Camfield and Camfield 2007) for children with mental handicap, slow SW and several seizure types to remain with an undetermined diagnosis despite full investigation.

Evolution and prognosis

Overall prognosis remains poor in spite of new therapeutic strategies. About 90% of patients become mentally

handicapped with a progressive deterioration in IQ, and more than 80% continue to experience seizures throughout life; tonic seizures tend to be prominent over time for some authors, while for others tonic-clonic or atonic seizures, or atypical absences persist. Psychiatric and behavioral problems with autistic features are common and sometimes require intensive treatment. Mechanisms of deterioration have been proposed (Blume 2004) but remain hypothetical.

The mortality rate is high, but varies in the literature from about 3%–7%, mostly related to accidents (Glauser 2004), to 25% due to underlying neurological conditions (Camfield and Camfield 2007).

Recently, Yamatogi and Ohtahara (2006) reported on the long-term evolution of severe epileptic encephalopathies, and suggested a new syndrome, the “severe epilepsy with multiple independent spike foci” as the final evolution of LGS.

Data on evolution and prognosis are, however, often contradictory, mainly due to different definitions of LGS not only over time but also in different countries.

Treatment

Chronic medical treatment remains disappointing and only six randomized double-blind controlled trials (The group of Cinromide 1989; Inanaga et al 1989; Felbamate study group 1993; Sachdeo et al 1999; Motte et al 1997; Glauser et al 2000) have been published; of these, 4 gave significant results (Table 1). Other randomized controlled studies have been published in patients with refractory epilepsy, some

of them suffering from LGS, but individual results cannot be extrapolated from the global data (Battaglia et al 1991; van Rijckevorsel et al 1994). Treatment of the multiple seizure types often requires broad spectrum AEDs and/or polypharmacy. AEDs that are effective for one seizure type may worsen another or provoke SE. Furthermore, there is no specific experimental model for syndromes such as LGS, and rodent models cannot mimic the complexity of LGS for effective drug development (Jensen 2006).

Co-morbidities often necessitate specific treatments, eg, psychotropic drugs, which may secondarily aggravate seizures. In addition, seizures are often very frequent and difficult to count because most are subtle. The seizures may also be difficult to classify (tonic versus atonic or tonic-clonic) and slow disease fluctuations over several weeks or months may occur independently of drug treatment. For these reasons, there may be considerable inter-observer differences in reporting of the numbers and types of seizures in individual patients, which may influence study results and analysis over the relatively short-term evaluation of clinical studies (average of 3 months).

Occasionally surgery, eg, corpus callosotomy, vagus nerve stimulation (VNS) (Patwardhan et al 2000) or resection of an underlying focalized lesion, may be beneficial, and non-AED medical treatments, eg, ketogenic diet or research treatments such as deep brain stimulation (DBS) (Velasco et al 1991) or intravenous immunoglobulin (IVIG) (van Engelen et al 1994b; Duse et al 1996; van Rijckevorsel 1999), may offer some improvement in selected cases.

Table 1 Comparison of double-blind, randomized, placebo-controlled studies in LGS

Authors	Patients	Study design	Results
FBM study group 1993 Jensen 1994; Delanty and French 1998	73* participants (37 FBM) final results for 50 (28 FBM) age: 4–36 years 45 mg/kg/day or 3600 mg/day	Placebo controlled multicenter randomized duration: 70 days	19% total seizure reduction (37 FBM) 34% atonic seizure reduction (37 FBM) 44% atonic seizure reduction in the 28 FBM patients
Motte et al 1997; Delanty and French 1998	179* (79 LTG) results for 169 (78 LTG) age: 3–25 years	Multicenter randomized double-blind placebo controlled duration: 16 weeks	34% median major type seizure reduction 32% median total seizure reduction 37.3% of $\geq 50\%$ RR for drop attacks
Sachdeo et al 1999	112 participants results for 97* (48 TPM) seizure onset age 1–30 years	multicenter, randomized double-blind, placebo-controlled duration: 11 weeks	33% have a $\geq 50\%$ seizure reduction 14.8% median seizure reduction 20.6% total seizure reduction
Glauser et al 2005	138* patients (74 RUF) Age : 4–37 years	Multicenter, double-blind, placebo controlled	42.5% median seizure reduction and for RR for tonic-atonic seizures 53.4% with improvement in seizure reduction

* = broad definition.

Abbreviations: FBM, felbamate; LGS, lennox-gastaut syndrome; LTG, lamotrigine; RUF, rufinamide; TPM, topiramate.

Chronic medical treatment

“Old” antiepileptic drugs

Benzodiazepines (BZDs)

BZDs, since their development in the 1970s, remain among the most powerful available AEDs, particularly in SE. They can be divided into two groups: 1,4-BZDs (clonazepam, clorazepate, diazepam, nitrazepam, lorazepam) and 1,5-BZDs (clobazam). The BZDs act on the BZD receptor, as agonists, to potentiate gamma-aminobutyric acid (GABA) neurotransmission, on voltage sensitive calcium channels and on Na⁺ channels. They reportedly increase the frequency of chloride channel opening and act by suppressing the spread of seizure activity but not by abolishing the abnormal discharge of the epileptic focus. BZDs reduce the inhibitory output of the reticular neurons and, therefore, prevent absence seizure activity. BZDs have been used as acute parenteral or rectal agent (diazepam, lorazepam, midazolam) or for chronic oral use (clobazam, clonazepam, clorazepate, nitrazepam) (Vassella et al 1973; Muller and Lenard 1988; Trimble 2002). BZDs remain, in most guidelines, the treatment of choice for acute or subacute seizures, but should be avoided, particularly the 1,4-BZDs, for prolonged therapy because of tolerance, somnolence, risk of withdrawal seizures, increased bronchial or oral secretions, etc. However, in practice, they are still widely prescribed with the specific risk in LGS of precipitating tonic SE (Dimario and Clancy 1988).

Clobazam (CLB)

CLB, the only 1,5-BZD, works, in animal models, by intensifying GABA-mediated inhibitory effects and by increasing the activity of glutamate transporters. CLB is metabolized by CYP3A4 and 2C19 to the active metabolite-N-Desmethyloclobazam (NCLB). This BZD presents several advantages over the 1,4-BZDs, especially for add-on therapy, including a: rapid onset of action, broad spectrum of activity, long half-life, and few important drug interactions. Vajda et al (1985) studied the effects of CLB in patients with refractory epilepsy, some of them suffering from LGS; however, it is not possible to analyze the effects on patients with LGS independently of the global results. CLB may have fast and impressive results (Farrell 1986; Munn and Farrell 1993) and is better tolerated than other BZDs. According to the literature, long-term efficacy can be maintained in 40 to ≥60% of patients with refractory epilepsy (Ng and Collins 2007). Schmidt and Bourgeois (2000) recommend the temporary add-on use of CLB while modifying or reducing doses of concomitant AEDs. In a Phase 2 trial, CLB significantly reduced drop seizures compared to baseline. A phase 3 trial is ongoing

in patients with LGS (on May 1, 2008: <http://clinicaltrials.gov/ct2/results?term=clobazam>; clinicaltrials.gov identifier: NCT00518713). In 2008, CLB has been designated as an orphan drug by the FDA for patients with LGS.

Clonazepam (CZP)

This AED was considered as one of the drugs of choice for the management of myoclonic epilepsies, including LGS (Pinder et al 1976). Unfortunately, tolerance develops in approximately 30% of patients, even after adjustment of dosage. Withdrawal seizures are frequent and sometimes severe in case of irregular intake or (non) accidental withdrawal. Furthermore, CZP may precipitate the occurrence of tonic-clonic seizures and tonic (Tassinari et al 1972, Dimario and Clancy 1988) or absence SE. The most frequent side effects are drowsiness in about 50% of patients and ataxia in approximately 30%. Seizures related to drowsiness may, therefore, be increased. Furthermore, significant interactions exist with other AEDs and other common medications, including cimetidine, disulfiram, oral contraceptives, digoxin, and rifampicin. CZP should, therefore, not be prescribed for chronic use, or only as a last option. Nevertheless, this AED is still often used as a first or second option, partly because of its low cost.

Clorazepate (CLZ)

This BZD is prescribed in refractory epilepsies (Trimble 2002) and some excellent results have been published (Naidu et al 1986), but there are no specific data for LGS and no controlled data. This BZD is mostly prescribed as a second line AED in focal seizures.

Diazepam (DZP), lorazepam (LZP), midazolam (MDL)

These BZDs are mainly used for acute, prolonged or cluster seizures and SE. They can be administered intrarectally, by intravenous infusion or, for midazolam, by intramuscular, intranasal or intrabuccal routes (Scott et al 1999).

Nitrazepam (NZP)

This BZD tends to be used in pediatric epilepsy, specifically in infantile spasms and LGS. However, only uncontrolled data are available (Chamberlain 1996; Farrell 2002; Hosain et al 2003) and excessive sedation has been described in numerous children.

Carbamazepine (CBZ), oxcarbazepine (OXC)

These AEDs act mainly by inhibiting the voltage-activated Na⁺ channels. OXC differs from CBZ by also inhibiting

voltage-gated Ca^{++} channels. CBZ and OXC can control tonic-clonic and focal seizures and reduce tonic seizures, but aggravation of atypical absences and/or myoclonic seizures is common (Delanty and French 1998; Perucca et al 1998; Schmidt and Bourgeois 2000; Dulac 2001).

There are no specific studies with OXC in LGS.

Cinromide

In preclinical studies, cinromide seems to offer a broad spectrum of action with inhibitory effects like those of phenytoin (PHT) and CBZ but also effects similar to valproate (VPA) and ethosuximide (ESM).

In the 1980s, open-label studies (Lockman et al 1980) reported the efficacy of cinromide in the treatment of LGS. The first multi-center double-blind placebo-controlled clinical trial of treatment for LGS was designed (The group of Cinromide 1989) and 73 patients, 2–18 years old (data available only for 56 participants, 26 on study drug) were enrolled. However, the study was terminated prematurely when it was clear that cinromide was not superior to placebo and further development of this drug was stopped.

Succinimides

Succinimides reduce the low threshold T-type Ca^{++} currents in thalamic neurons but also decrease the persistent Na^{+} and Ca^{++} -activated K^{+} currents in thalamic and layer V cortical pyramidal neurons. More recently, succinimides, particularly ESM have been shown to reduce the elevated glutamate levels present in the primary motor cortex in animals with absence seizures.

- Methsuximide has been used as adjunctive treatment of atypical absences, tonic and myoclonic seizures associated with LGS (Browne 1995). However, only anecdotal results are available.
- Trimethadione has considerable efficacy against absence seizures. Lennox (1945) emphasized that trimethadione was also effective against the atypical absences and myoclonic and atonic seizures of LGS. This drug is no longer used because of its toxicity.
- ESM is considered as a fourth-line and adjunctive therapy in by Schmidt and Bourgeois (2000) for its effects on controlling atypical absences and improving myoclonic and atonic seizures.

Phenobarbitone (PB), primidone (PRM)

Barbiturates such as PB act as positive allosteric modulators of GABA_A receptors, but in a different way than BZDs. In addition, they also act on other ion channel systems, including Ca^{++} and Na^{+} channels.

In a double-blind crossover trial (Vassella et al 1978), VPA was compared with PB in 17 epileptic children with LGS. VPA appeared to be somewhat more effective than PB but the difference was not statistically significant. PB may worsen behavioral problems (Delanty and French 1998) in children and has cognitive and sedative side effects. These AEDs should be avoided even though they can control tonic-clonic seizures (Vassella et al 1973; Muller and Lenard 1988).

Phenytoin (PHT)

PHT, like CBZ, inhibits the voltage-activated Na^{+} channels but also the flux of Ca^{++} ions across synaptic and other membranes. PHT can control tonic-clonic seizures and reduce tonic seizures in LGS, but aggravation of atypical absences and myoclonic seizures is common (Schmidt and Bourgeois 2000; Dulac 2001; Sazgar and Bourgeois 2005) and chronic use should, therefore, be avoided. Acute use may be necessary to manage convulsive SE.

Valproate (VPA)

VPA acts by several mechanisms: It potentiates GABA-ergic inhibitory effects; interacts with the metabolism of gamma-hydroxybutyrate, a metabolite of GABA; suppresses N-methyl-D-aspartate (NMDA)-evoked depolarization; and inhibits Na^{+} channels. At higher concentrations, VPA may affect calcium and potassium channels (Johannessen and Johannessen 2003). Other potential mechanisms have also been described recently (Xu et al 2007).

This broad spectrum AED is considered by most practitioners and authors to be the drug of choice in this multiseizure type syndrome (Wheless et al 2005). However, VPA alone is rarely sufficient and children with polypharmacy are at greater risk of serious hepatic toxicity or pancreatitis. Only one double-blind study (Vassella et al 1978) has been conducted with 17 patients, crossed-over with PB. The results were not statistically significant although there was a trend in favor of VPA. Other studies (Jeavons et al 1977) involved patients with a mixture of epileptic syndromes, including LGS, and it is sometimes difficult to extract results specific to LGS. Moreover, these studies were observational or retrospective.

Vigabatrin (VGB)

VGB's main actions are on the GABA-ergic synapse as an irreversible inhibitor of the GABA-degrading enzyme, GABA transaminase. This single mode of action can explain the frequent worsening of seizures in LGS. Published results are variable (Luna et al 1989, Livingston et al 1989), but VGB may aggravate myoclonic seizures (Dulac et al 1991)

while 85% of children experiencing a $\geq 50\%$ reduction in total seizure frequency at least in the short term (Feucht and Brantner-Inthaler 1994). Other authors (Schmidt and Bourgeois 2000) consider VGB as a fourth-line treatment. At the present time, in most countries, the use of this drug is restricted to West syndrome because of the occurrence of visual field defects.

Newer antiepileptic drugs

Felbamate (FBM)

FBM, a carbamate-type anticonvulsant, showed a broad spectrum and several modes of action (White et al 2007) in preclinical trials (ability to limit the spread of seizure activity and to raise seizure threshold, to modulate the glycine NMDA receptor and to be a weak inhibitor at the BZD GABA_A receptor). This AED was the first to be approved for adjunctive therapy in LGS after a double-blind, randomized, placebo-controlled study showed a significant effect on "major" seizures (FBM study group 1993). Open studies (Dodson et al 1993; Jensen 1994; Gay et al 1995; Avanzini et al 1996; Eriksson et al 1998) and another double-blind study (Siegel et al 1999) confirmed these initial results.

Unfortunately, FBM is intensively metabolized and severe life-threatening adverse events (aplastic anemia and hepatic failure) appeared a few months after approval, limiting FBM use since 1994 to cases refractory to other AEDs. A review of the past 10 years of clinical experience (more than 35,000 new cases) has demonstrated that the risk/benefit of FBM therapy supports its use as an important add-on option for patients with highly refractory epilepsies (Pellock et al 2006). However, in some countries, its use has been restricted to refractory LGS despite efficacy in focal epilepsy.

Lamotrigine (LTG)

LTG, with its Na⁺ channel blocking actions, was initially introduced for add-on therapy of focal seizures in adults, but it was rapidly demonstrated that it was a broad spectrum AED. Additional mechanisms of action have been demonstrated, including stabilizing neural membranes and inhibiting the release of excitatory (glutamate and aspartate) neural transmitters (White et al 2007). Current data demonstrate efficacy against focal seizures, tonic-clonic seizures, tonic seizures, absence seizures, and atonic seizures. More recently (Cianchetti et al 2002; Conry 2004), LTG was shown to be effective in West syndrome. From the early 1990s, apparent efficacy in open-label studies (Timings et al 1992; Schlumberger et al 1994; Donaldson et al 1997; Farrell et al 1997) in LGS led to double-blind, randomized clinical

trials (Motte et al 1997; Eriksson et al 1998), confirming a statistically significant improvement, at least in major seizures. Worsening or no improvement of myoclonic jerks has been reported in LGS (Donaldson et al 1997; Dulac and Kaminska 1997) and related syndromes.

Most children with LGS already receive one or more AED, and the addition of LTG can be difficult if they are already being treated with an enzyme-inducing AED, VPA or both. Co-medication may have a dramatic effect on the half-life of LTG (and consequently on efficacy and acute adverse events), and on safety issues, particularly the risk of rash, which is as high as 5% to 10% in younger patients. Titration of LTG thus requires careful attention, especially in children.

Topiramate (TPM)

Like LTG, TPM has several modes of action (modulation of voltage-dependent Na⁺ channels, potentiation of GABA-induced chloride fluxes, and decreased glutamatergic excitability [blockade of kainate glutamate receptors]). TPM was initially approved for use in focal seizures in adults, and later also for children and in generalized tonic-clonic seizures. However, TPM also showed efficacy in drop attacks associated with LGS in open (Uvebrandt and Bauzière 1994; Sachdeo et al 1996; Glauser et al 1997; Ritter et al 1998) and in double-blind studies of patients with refractory epilepsies, including LGS (Glauser et al 1998). In 1999, a double-blind randomized study (Sachdeo et al 1999) confirmed the efficacy of TPM in reducing the frequency of atonic seizures associated with LGS. Additional studies and small series have confirmed the long-term efficacy of TPM (Tartara et al 1996; Guerreiro et al 1999; Glauser et al 2000; Coppola et al 2002; Mikaeloff et al 2003; Al Ajlouni et al 2005) with improvement in quality of life (QOL) associated with better seizure control (Alva-Moncayo and Ruiz-Ruiz 2003). The overall safety profile makes this drug option appealing when compared to the possible life-threatening adverse events of FBM and LTG. Rapid titration is possible in emergencies, but aggravates central nervous system (CNS) adverse events, including somnolence, mental slowing, fatigue, and ataxia. A slow dose-titration schedule is, therefore, usually necessary to avoid particularly cognitive and language problems worsening with a rapid dose escalation. Weight decrease could be an issue in some children, but can be welcome in others. Unexpected adverse events have been published, such as acute glaucoma (Banta et al 2001) or oligohydrosis (Arcas et al 2001). However, to date, TPM has not been associated with any life-threatening adverse events.

Rufinamide (RUF)

RUF is a novel compound with anticonvulsant activity, a triazole derivative structurally unrelated to currently marketed AEDs, and of largely unknown mechanisms of action (Arroyo 2007; Kluger and Bauer 2007). RUF probably acts by an inhibition/modulation of Na⁺-dependent action potentials in neurons and by inhibitory effect at the GluR5 subtypes at high concentrations (Perucca et al 2008). The protective index of RUF, in animals, is much higher than that of most common AEDs. RUF has a broad spectrum of anti-epileptic actions including focal and generalized seizures. RUF is extensively metabolized by non-CYP450 systems. The most commonly reported adverse effects are CNS related (headache, somnolence, fatigue and tremor). Randomized, placebo-controlled trials in the 1990s showed efficacy against focal seizures. The development of RUF for neuropathic pain and epilepsy was stopped by Novartis in 2001. This drug was further investigated in LGS in a single (Hakimian et al 2007) and a double-blind (Glauser et al 2005), randomized, placebo-controlled study which showed a statistically significant efficacy in reducing seizures associated with LGS: there was a 42.5% median seizure reduction and 42.5% of responders ($\geq 50\%$ seizure reduction) for tonic-atonic seizures, while 53.4% of patients had some reduction in seizure frequency.

Antiepileptic and other drugs used “off label” in LGS

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is known to have efficacy against multiple types of seizures and is usually well-tolerated (Lombroso et al 1956; Holowich and Thurston 1958; Lombroso and Forsythe 1960). Acetazolamide could, therefore, be useful as add-on therapy in LGS. However, newer and more powerful AEDs, such as TPM, also inhibit carbonic anhydrase, making acetazolamide less interesting.

Allopurinol (ALL)

Some reports in the “older” literature suggested an antiepileptic effect of the xanthine oxidase inhibitor, ALL, when added to traditional drugs (Marrosu et al 1990). Six patients with LGS, from 41 epileptic non-hyperuricemic subjects, aged 2–54 years, already medicated with 2 or 3 AEDs were treated with ALL in doses ranging from 150 to 300 mg daily (DeMarco and Zagnoni 1986). A progressive decrease in the weekly seizure frequency was observed in two-thirds of the cases in this open-label study. Further efficacy has never been proven.

Bromide

Bromide, introduced in 1857, was, in fact, the first effective antiepileptic agent, long before the discovery of PB in 1912. The mechanisms of action are largely unknown but bromide could act via GABA-activated chloride channels, leading to stabilization and decreased sensitivity to epileptic foci. The major problem with bromide is in obtaining a positive balance between seizure suppression and the occurrence of adverse events. After the introduction of newer AEDs, bromide was largely forgotten. In the 1990s, it was tested again in several severe seizure disorders, including LGS (Woody 1990). Results were encouraging, but studies were only short term and without a control group. This drug is still used in catastrophic epilepsies, such as malignant migrating partial seizures in infancy or Dravet syndrome (Tanabe et al 2008), with inconsistent results.

Flunarizine (FLN)

FLN, a calcium channel blocker, was shown to have electrophysiological effects *in vitro* in the late 1980s, suggesting anticonvulsant efficacy. In the early 1990s, FLN was tried in a few difficult-to-treat epilepsy patients with some success. One placebo-controlled, cross-over study (Battaglia et al 1991) looked at the effect of FLN in 20 patients with refractory epilepsy, 6–18 years old, 10 of whom had LSG. Thirteen patients completed the study with a 30%–60% reduction in seizure frequency. This drug is no longer used in epilepsy.

Gabapentin (GBP) and pregabalin (PRG)

GBP synthesized as a GABA-ergic drug does not interact with the GABA receptors but is a ligand of the $\alpha 2\delta$ voltage-activated Ca⁺⁺ channels resulting in inhibition of glutamate release at excitatory synapses. PRG is an analog of GBP with the same binding affinity. The clinical profile of GBP in epilepsy patients is restricted to the treatment of focal seizures, with or without secondary generalization. It has been tried in other syndromes and Vossler (1996) reported a worsening of seizures when using GBP in LGS. There is no study of PRG in LGS but this AED may provoke myoclonus (Modur and Milteer 2008).

Levetiracetam (LEV)

SV2A, a synaptic vesicle protein, has recently been identified as the likely target of LEV, making this a new and unique mechanism of action among the AEDs (Kaminski et al 2008). LEV was added-on in 6 patients with LGS in a retrospective survey (De Los Reyes et al 2004). Myoclonic seizures were the best controlled while tonic seizures remained unchanged. Irritability was the most common adverse event.

Ten other patients, aged 28–48, with generalized epilepsy, including four with LGS were given LEV as compassionate use in a pilot prospective study. There was a mild or no effect on seizure reduction (Weber and Beran 2004). Labate et al (2006) studied the effect of LEV in 35 patients with refractory epilepsy, including two with LGS: seizure frequency improved in one and worsened in the other.

Pyridoxine (vitamin B6)

Since the initial description of this disorder in 1954, pyridoxine-dependent seizure has been recognized as a rare cause of refractory autosomal-recessive seizures in neonates. Diagnosis may be more difficult in later onset cases when other seizure types have been described, including brief focal, atonic and myoclonic seizures or infantile spasms. Pyridoxine and pyridoxal phosphate have then been tested in the treatment of West syndrome and other conditions. Furthermore, Lee et al (2008) reported cases of LGS (25%) in patients with atypical mitochondrialopathies and pyridoxine belongs to the so-called “mitochondrial cocktail supplement” (vitamins B, C, E, coenzyme Q10 and L-carnitine). Pyridoxine, alone or as part of this cocktail, could be tried in refractory patients with cryptogenic LGS. In their assessment of LGS therapies published in 2000, Schmidt and Bourgeois (2000) already considered the use of pyridoxine as a fourth-line treatment.

Sulthiame (STM)

STM, already used as early as the 1960s (Garland and Sumner 1964), is a carbonic anhydrase inhibitor responsible, at least partly, for beneficial effects on epileptiform activity secondary to intraneuronal acidosis. It has been used in West syndrome with some success. Reports on its use in myoclonic epilepsies and as a sole AED are few and inconclusive, but in LGS, STM appears to be an efficacious adjunct to currently-used agents (Lerman and Nussbaum 1975), at least in older studies. More recent use of STM is reserved to continuous SW during sleep syndromes and some idiopathic focal epilepsies. Indeed, one possible mechanism implicated in the development of cognitive deficits is a pathologic enhancement of physiological apoptotic neuronal death in the developing brain. Animal studies show that STM may significantly enhance neuronal death in the developing rat brain (Manthey et al 2005). STM has the potential to precipitate acute psychotic episodes, especially in predisposed patients (Liske and Forster 1963). Therefore, continuous follow-up and careful use of this drug

remain mandatory, especially in the pediatric population, although it is largely considered as safe.

Thyrotropin-releasing hormone (TRH)

TRH may act as an antiepileptic through a kynurenine mechanism, given that kynurenic acid acts as an antagonist on the NMDA receptor complex; however, the exact mechanism of action remains uncertain. TRH has been successfully used for treating neurologic disorders, including epilepsy with some success.

To confirm this antiepileptic effect, 190 participants were included in an open-label, dose-finding, randomized study; 98 of the patients, ≥ 2 years old, had a diagnosis of LGS. Forty-eight of the patients received a low dose of 0.4 mg/kg/day of TRH DN-1417 and were compared to 50 patients treated with the high dose of 1.6 mg/kg/day for 8 weeks. There was no significant treatment effect for high dose TRH and no reported discontinuations due to adverse events (Inanaga et al 1989).

Tiagabine (TGB)

TGB is a selective competitive inhibitor of GAT1 that prevents GABA uptake. By slowing the reuptake of GABA, TGB prolongs inhibitory postsynaptic potentials. In preclinical studies, TGB increases the amount of time with SW discharges in absence models but shows some antiepileptic and neuroprotective effects in status models. It has been shown to be effective in focal seizures but non-convulsive SE and its very narrow spectrum limits clinical use, especially in LGS.

Zonisamide (ZNS)

ZNS is a broad-spectrum AED with a mechanism of action apparently based on its ability to block voltage-gated Na^+ and T-type calcium channels. It shows a modest inhibitory effect on carbonic anhydrase probably unrelated to its antiepileptic action. It has been licensed as adjunctive treatment for focal seizures in adults.

Anecdotal improvement has been reported when ZNS is used as add-on therapy in pediatric epilepsy (Santos and Brotherton 2005) and in refractory LGS (Peters and Sorkin 1993; Glauser and Pellock 2002; You et al 2008a). Yagi (2004) analyzed the efficacy of ZNS in 132 patients with LGS from pooled data grouping 1008 patients from controlled and uncontrolled Phase II and III studies and 726 from postmarketing studies: 32% of the patients had a $\geq 50\%$ seizure reduction. The most frequent adverse events were drowsiness, ataxia, loss of appetite or gastrointestinal symptoms and slowing of mental activity.

Antiepileptic drugs in development

Carisbamate (RWJ-333369)

Carisbamate is an investigational drug (Kulig and Malawska 2007) with broad anticonvulsant activity in preclinical studies, elevating seizure threshold and preventing seizure spread. In animal models, it is effective in focal and generalized seizures, and may prevent the development of spontaneous recurrent epileptiform discharges and damage related to SE. The safety profile seems encouraging as do results from initial studies in epileptic patients. In view of these properties, this AED could become a drug of choice for LGS.

Fluoro-felbamate

Fluorofelbamate, a dicarbamate, is a drug candidate in development, designed to retain the broad spectrum activity of FBM, but with a modified metabolism that avoids the production of the reactive metabolite, aldehyde, believed to be the cause of the idiosyncratic life-threatening toxicity (Roecklein et al 2007; Bialer et al 2007). Results in vitro are promising and research is ongoing. If the better safety profile of this AED is confirmed, it could become a useful treatment in LGS.

Ganaxolone (GNX)

GNX belongs to a novel class of neurosteroids called epalons, which specifically modulate the GABA_A receptor in the CNS, acting through binding sites which are distinct from the BZD binding site. Chemically related to progesterone but devoid of any hormonal activity, the epalons have potent antiepileptic activities in animals. (Monghan et al 1997).

In view of its potential efficacy and after preliminary encouraging results in patients (Laxer et al 2000; Pieribone et al 2007), clinical trials are planned in several epilepsy syndromes, including LGS (Perucca et al 2007).

Derivatives of LEV: brivaracetam and seletacetam

Brivaracetam (BRI) possesses a binding affinity for the synaptic vesicle protein 2A (SV2A) that is ten-fold more powerful than LEV and also shows an ability to inhibit Na⁺ channels. Acute toxicity is low and the safety profile in humans is favorable. BRI is primarily metabolized via hydrolysis of the acetamide group and by CYP2C8. Clearance of BRI is reduced in patients with hepatic insufficiency and there is a potential for some drug-drug interactions (Bialer et al 2007, von Rosenstiel 2007). However, this drug could be promising in LGS because of its potential broad spectrum of action, in spite of probable drug-drug interactions.

Seletacetam (SEL) is another new pyrrolidone derivative structurally related to LEV (Bennet et al 2007; Bialer et al 2007), discovered because of its high binding affinity to the synaptic vesicle 2A (SV2A) protein. Pharmacokinetic studies in animals suggest a linear pharmacokinetics with no or mild metabolic interactions and a low plasma protein binding (<10%). This suggests a low potential for drug-drug interactions. SEL shows very potent seizure suppression in different models of acquired or genetic epilepsy, suggesting a broad spectrum of activity and may be useful in LGS.

Remacemide (RMC)

RMC is a low-affinity NMDA receptor blocker as well as Na⁺ channel blocker. The drug exerts anticonvulsant activity in various animal seizure models and in clinical studies (Malek et al 2003). In addition, the drug seems to provide some neuroprotection. In view of its potential broad spectrum of action, RMC could be useful in LGS.

Stiripentol (STP)

STP was first identified in 1978 with clinical trials starting in the 1980s in all forms of epileptic syndromes, including LGS in which it was used in combination with CBZ (Tran et al 1996). The LGS study BC-274, a single blind triphasic study showed a decrease in fits in 72% of the 24 participants aged 1–22 years. (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/diacomit/H-664-en6.pdf>).

STP was recently shown to increase GABA-ergic transmission (Quilichini et al 2006) in vitro in an experimental immature rat model and to act as a direct allosteric modulator of the GABA receptor. Clinical studies were based on the fact that STP also acts as a powerful inhibitor of CYP3A4, CYP1A2, and CYP2C19, but gave disappointing results in adult patients. STP has been shown to be effective in atypical absences (Farwell et al 1993) and in myoclonic epilepsies, if combined with VPA and CLB (Chiron 2007). At the present time, STP is mainly used in Dravet and related syndromes added to CLB and VPA. However, the interactions of STP with a large number of drugs or toxic endogenous products need to be carefully considered from a long term safety perspective.

Other AEDs in development

Among the other numerous AEDs in the pipeline, VPA-like agents, such as diisopropyl acetamide (PID) and valroceamide are the most promising drugs in LGS because they have a similar broad spectrum of activity to VPA but fewer adverse events in terms of somnolence, weight problems and teratogenicity (Rogawski 2006).

Immune treatments

Since the success of steroids in epileptic encephalopathy (Klein and Livingston 1950) and West syndrome (Sorel and Dusaucy-Bauloye 1958), these drugs have been systematically tried in refractory epilepsies, including LGS. Nevertheless, there have been few reports of steroid use in childhood epilepsy after the first year of life. Some benefits have been previously reported with ACTH (Yamatogi et al 1979) and corticosteroids (Roger et al 1989) in patients with LGS.

Prednisone was added to regular antiepileptic medications for the treatment of 28 children (aged 18 months to 10 years) with intractable epilepsy, including 10 with LGS. Seven of these patients became seizure free (Sinclair 2003). Other small series have been published in patients with intractable epilepsy, with different protocols, products and epilepsy syndromes, with various but often favorable results (Verhelst et al 2005). Side effects and lack of objective long-term effects have limited the use of steroids. Furthermore, new AEDs have become available since these older publications. However, Schmidt and Bourgeois (2000) consider the use of corticotrophin or corticosteroids as a fourth-line treatment in acute or subacute deterioration of LGS (You et al 2008b).

Intravenous immunoglobulins (IVIG)

The immune system has been sometimes called the “circulating brain” because of the numerous, reciprocal and continuous interactions between the immune and neurological systems (Billiau et al 2005). Consequently, the concept that the immune system may play an active role in epileptogenesis is more than 25 years old (Aarli and Fontana 1980) and has been developed in experimental animal models of epilepsy. Pechadre et al in 1977 noted that epileptic children treated with intramuscular immunoglobulins for recurrent infections had fewer seizures. Since this observation, Ariizumi et al (1983) reported a dramatic improvement in infants with West syndrome treated with IVIG while numerous studies have reported on the existence of a variety of immunological alterations, such as hypoIgA, in epileptic patients as well as the association of some well-known immune-mediated disease states, eg, lupus erythematosus disease, with epilepsy (Duse et al 1996; van Rijckevorsel 1999; Aarli 2000). The link seems substantial in some epileptic syndromes, eg, Rasmussen disease, with the presence of autoantibodies and a favorable evolution after immunomodulatory treatments. However, the mechanisms of action of IVIG remain hypothetical (such as antiviral effect, substitutive therapy in case of concomitant immune deficiency, idiotype-anti-idiotype interaction,

neuromodulant effect). The available data come mostly from open studies (van Rijckevorsel et al 1986; van Engelen et al 1994a; Billiau et al 2007), case reports (Fois et al 1990; Echenne et al 1991; Sterio et al 1992; Gross-Tsur et al 1993; Espinosa et al 2002), one single-blind (Ilum et al 1990) and one double-blind (van Rijckevorsel et al 1994). Doses, duration, and schedule of infusion, were different and results from the more than 370 treated children cannot be combined for a global analysis (van Engelen et al 1994b; Duse et al 1996; van Rijckevorsel 1999). However, the global review of published cases suggests that IVIG might be effective in some patients with refractory epilepsy, including LGS (Orange et al 2006; Feasby et al 2007).

Ketogenic and modified Atkins diet

Descriptions of the beneficial effects of fasting were already mentioned by Hippocrates and in the New Testament. Later, the concept of ‘diet’ evolved and it was clear that a high-fat diet can mimic ketosis secondary to fasting. The ketogenic diet was therefore “born” and first developed in the 1920s (Swink et al 1997), when only a few AEDs were available. With the development of different AEDs this therapeutic option was used less frequently. This treatment may have serious long-term adverse effects and is difficult to manage for prolonged periods (Hemingway et al 2001).

More recently, there has been new interest in this diet for use after failure of drug therapy, above all in children with refractory seizures (Kinsman et al 1992; Freeman et al 1998; Freeman and Vining 1999; Lefevre and Aronson 2000; Henderson et al 2006). Alternative ketogenic diets compared to the first description have been proposed in order to improve long-term compliance and to decrease adverse events, notably on growth (for a review see Hartman and Vining 2007).

The first published results may be difficult to interpret because the description of clinical signs is limited and some patients with specific genetic disorders may be included, eg, GLUT-1 deficiency syndrome characterized by intractable epilepsy (atonic seizure, myoclonus, absences), slow SW on EEG, mental retardation (Leary et al 2003) and highly responsive to ketogenic diet (Wexlet et al 1997; Wang et al 2005). Nevertheless, Levy and Copper (2003) consider the diet as a possible option in the therapy of LGS.

Treatment of status epilepticus (SE)

Treatment of SE in LGS is the same as for other epileptic syndromes, at least for convulsive SE. However, BZDs

should be used with caution because of the risk of worsening the status or precipitating tonic SE. EEG monitoring is recommended, especially if the patient does not recover consciousness. Non-convulsive SE may require special management, such as corticoids or a ketogenic diet (Dan and Boyd 2005).

Surgical treatment

Generalized symptomatic epilepsies with bilateral EEG abnormalities may be secondary to a focal lesion and be improved by surgery (Wyllie et al 2007). Because of refractoriness to medical treatment and severity of seizures, various surgical procedures, even in cryptogenic cases, have been developed to treat epileptic drop attacks, the most devastating seizures, including callosotomy, (multi)lobar disconnection, multiple subpial transections (Patil et al 2004) or protocols of vagus nerve or deep brain stimulation.

Furthermore, early surgery may improve the global prognosis of these children (Liu et al 2007).

Callosotomy

First described in 1940 by Van Wagenen and Herren, and previously recommended for epileptic drop attacks (tonic, atonic seizures) (Purves et al 1988; Nordgren et al 1991) callosotomy shows a lower efficacy for tonic-clonic seizures and is still considered as a palliative treatment. Early cases encountered severe complications, including hemispheric edema, mesial hemisphere infarcts, even death. Progress in new microsurgical techniques dramatically improved the safety of callosotomy. Complete callosotomy is recommended for children with severe mental handicap (Rathore et al 2007) while a two-third or three-fourth anterior disconnection is preferred in later onset LGS or in cryptogenic cases with moderate mental handicap. Nevertheless, acute disconnection syndrome (reduction in verbal output, urinary incontinence, apathy, hemineglect) or callosal split syndrome (intermanual conflict) may occur, temporarily for a few weeks or for more prolonged periods. Worsening of focal seizures may occur postoperatively.

Determinants of seizure outcome vary from one study to another. A better outcome has been related to the absence of focal abnormalities (Cukiert et al 2006), and a worse outcome to drop attacks associated with focal cerebral abnormality, to a greater mean duration of drop attacks, and to the presence of SW on EEG (Reutens et al 1993). Atypical absences have been noted to be dramatically improved in some reports (Machara et al 1996) but poorly influenced in other reports.

The degree of significant improvement reported after callosotomy is highly variable, depending on the time of publication, the extent of disconnection, the selection of patients, the seizure type analyzed and so on. About two-thirds of patients have been significantly improved after callosotomy (Purves et al 1988; Rougier et al 1997; Kwam et al 2006; Cukiert et al 2006), but this improvement can be lost over time.

Taken together, typical results consist of a (significant) seizure reduction in 40% to 80% of patients, but specific effects on patients with LGS are rarely detailed. More recently, new surgical techniques, such as gamma knife (Pendl et al 1999; Eder et al 2006; Feichtinger et al 2006), have been developed for callosotomy (see below).

Vagus nerve stimulation (VNS)

VNS therapy was studied and approved in 1997 as add-on therapy in patients aged 12 years or older with refractory focal seizures. However, VNS should only be considered for patients who have been rejected for surgery or after surgery failure. There is however one exception to this general rule: VNS is now recommended before callosotomy. This recommendation is essentially based on subjective data but above all because VNS is fully reversible with fewer surgical risks compared to callosotomy.

Nonetheless, failure in one option can be improved by the second option, whatever the order. Both techniques are considered as palliative treatments and seem to have equal efficacy (Karceski 2001; You et al 2007b) even if results are difficult to analyze because of the multitude of different parameters.

Only a few adverse events related to surgery or to the device and stimulation have been reported, including infection, transient pain, voice alteration, and increased coughing as for other implanted patients. However, special care should be taken with patients who have swallowing difficulties, as stimulation may cause dysphagia and/or excessive salivation.

In LGS, VNS shows a 24%–42% global seizure reduction (Horning et al 1997; Lundgren et al 1998; Ben-Menachem et al 1999; Parker et al 1999; Hosain et al 2000; Frost et al 2001; Aldenkamp et al 2002; Rychlicki et al 2006) with rare patients becoming seizure free (Parker et al 1999; Majoie et al 2001; Alexopoulos et al 2006). Some studies analyzed results from refractory childhood epilepsy including LGS, and it is not always possible to isolate data specific for LGS (Lundgren et al 1998; Parker et al 1999; Rychlicki et al 2006). Results seem better in the group with less mental

handicap at baseline, which could suggest that mental retardation may be a negative prognostic factor for VNS success. Improvement of alertness, even after long term follow-up, (Aldenkamp et al 2002) and QOL have also been described (Frost et al 2001).

Cortectomy/lobar disconnection

Some case reports have been published with selective cortectomy and sometimes spectacular results have been reported after surgery (You et al 2007a). Some LGS cases may be seizure free or free from disabling seizures after resective surgery (Quarato et al 2002), sometimes completed by subpial transections in the eloquent cortex. However, each case needs a personalized presurgical evaluation, sometimes including invasive video-EEG to find the “driver” hemisphere and/or lobe (van Rijckevorsel et al 2006; Vaz et al 2008). From the published cases, the parietal (Angelini et al 1979; Quarato et al 2002) or frontal lobes (You et al 2007a; van Rijckevorsel et al 2006; Vaz et al 2008) are mainly involved in LGS.

Gamma-knife

Radiosurgery has been used for callosotomy (Pendl et al 1999; Eder et al 2006; Feichtinger et al 2006). Short-term follow-up reports the same amount of seizure reduction as classical callosotomy with a seizure reduction of 60%, especially of drop attacks. Gamma-knife callosotomy seems safer for the early short term, but longer follow-up periods are needed to exclude the risk of secondary brain tumor or radionecrosis.

Multiple subpial transection (MST)

Multiple subpial transection (MST) is a new approach for epilepsy surgery, first described by Morrell et al in 1989. MST can be an alternative to resection/disconnection when the epileptogenic zone transcends critical areas in the brain, and removal of the cortex may result in serious deficits. MST is performed alone in functional areas or in combination with resection, cortectomy, lobe disconnection, etc. This technique is used in Landau-Kleffner and related syndromes and in focal epilepsies. However, anecdotal case reports in LGS suggest that these patients can improve dramatically after such surgery (Spencer et al 2002; Zhao et al 2003; van Rijckevorsel et al 2006; Vaz et al 2008).

Deep brain stimulation (DBS)

In the last 15 years, several clinical investigators (Velasco et al 1991) have considered stimulation therapy – broadly

known as DBS – for targeting different subcortical structures such as the anterior thalamic nucleus, subthalamic nucleus, or amygdalohippocampus in patients with refractory epilepsy and rejected for epilepsy surgery. LGS patients, most of the time with a very broad definition of LGS, were included in some of these studies (Velasco et al 1993; Velasco et al 2006) However, definitive conclusions regarding the optimal therapeutic target remain to be clarified.

The future

Neuroprotection

Although neuroprotection is successful only against some aspects of a complex cascade of multiple events during the repetition of seizures and the development of epilepsy, it might be a promising option in the treatment of refractory cases. Based on animal studies, some of the newer AEDs show possible neuroprotective activity in epilepsy (Stépieň et al 2005). However, to prevent epileptogenesis, interventions need to be directed against the processes implicated in the brain changes that underlie hyperexcitability (Dichter et al 2002) and not only in the prevention of neuronal death. Animal studies have focused on SE or post-traumatic epilepsy models. Neuroprotection may not involve standard AEDs, but free radical scavengers to protect against oxidative injury, for example, or NMDA receptor antagonists.

In this regard, some papers have demonstrated possible neuroprotective effects of melatonin in the elderly (Han et al 2000) and in epilepsy (Chung et al 2003), as well as an anticonvulsant effect (Peled et al 2001; Yildirim and Marangoz 2006). At the present time, there is no ongoing study of neuroprotection in LGS.

Gene therapy

Gene therapy is an old dream among epileptologists and neuroscientists (Freese et al 1997). Gene therapy represents, at the present time, an innovative and promising alternative for the treatment of refractory epileptic patients, especially if inaccessible to surgery. Several gene targets could be used to correct the balance between inhibitory and excitatory aspects of epilepsy with recombinant viral vectors (Freese et al 1997) or transduction of neuropeptide genes (Noe et al 2007).

Although the proof of concept may have been established, further investigations are required to demonstrate a

therapeutic role of gene therapy in epilepsy and to evaluate safety concerns and possible side-effects.

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 (Figure 1), based on the likelihood of better seizure control and QOL balanced against the likely risks for each strategy (diet, stimulation, surgery, etc).

It is reasonable to consider non-medical treatments after failure of two to three AEDs. 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.

Psychiatric problems or severe mental handicap are no longer considered as contra-indications for surgery.

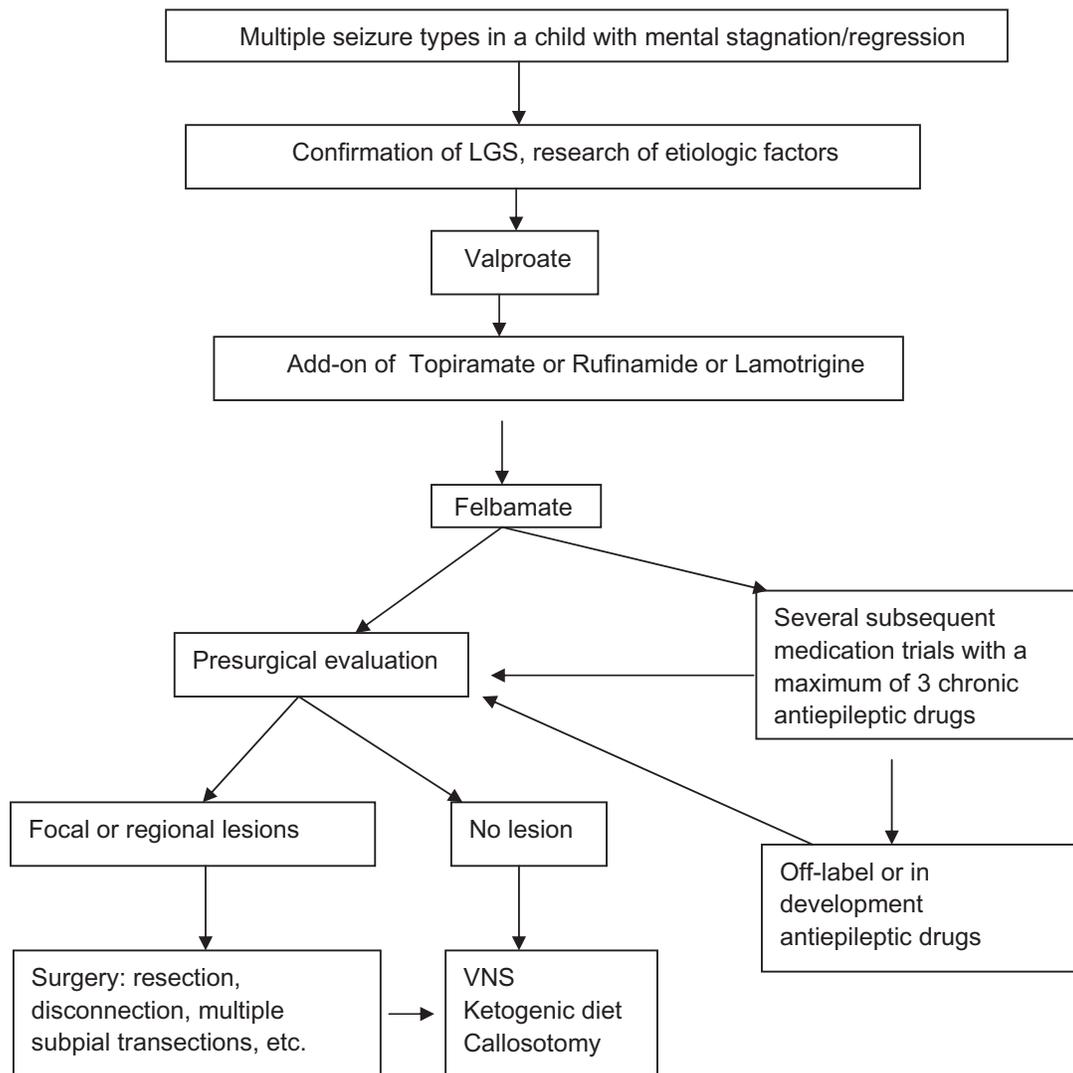


Figure 1 Treatment strategy for children with highly pharmacoresistant seizures.

The worst approach to patients with LGS is one of pessimism, considering that the prognosis is definitively 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.

Disclosures

The has no conflicts of interest to disclose.

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