

## Lennox-Gastaut syndrome

## Management update

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## ABSTRACT

متلازمة لينوكس جاستو هي متلازمة صرعية شديدة تصيب الأطفال وتتميز بإصابة تشنجات عصبية متنوعة ومتكررة مصحوبة بتأخر ذهني متدهور وشحنات كهربائية بطيئة بتخطيط الدماغ. وتمثل التشنجات العصبية المصحوبة بفقدان الحركة والسقوط خطورة بالإصابات الجسدية وتدهور نوعية الحياة اليومية. مع العلم أن هذه التشنجات لا تستجيب بسهولة للعلاج الدوائي وحالياً تم تطوير عقار الروفيناميد لهذا الغرض. أما في حالة فشل العلاج الدوائي فيمكن استخدام بعض العلاجات البديلة مثل الجراحة أو الحمية الكيتونية. وقد قمتنا بكتابة هذه المقالة النقدية لمراجعة آخر المستجدات العلاجية في هذا المجال. ورغم أن احتمالات الشفاء باستخدام العلاجات الحالية يظل ضعيفاً إلا أن العلاجات الجديدة تمثل أملاً لعلاج بعض هؤلاء الأطفال. وماتزال هنالك حاجة للمزيد من الدراسة والبحث لمقارنة فاعلية وسليبات العلاجات المختلفة.

Lennox-Gastaut syndrome (LGS) is a severe pediatric epilepsy syndrome characterized by mixed seizures, cognitive decline, and generalized slow (<3Hz) spike wave discharges on electroencephalography. Atonic seizures result in dangerous drop attacks with risks of injury and impairment of the quality of life. The seizures are frequently resistant to multiple antiepileptic (AED) drugs. Newer AEDs, such as rufinamide, are now available. When multiple AED trials fail, non-pharmacological treatments such as the ketogenic diet, vagus nerve stimulation, and epilepsy surgery, should be considered. The aim of this review is to present an updated outline of LGS and the available treatments. Although the prognosis for complete seizure control remains poor, the addition of newer therapies provides an improved hope for some of these patients and their families. Further long term randomized controlled trials are required to compare different therapeutic interventions in terms of efficacy and tolerability.

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Lennox-Gastaut syndrome (LGS) is a severe pediatric epilepsy syndrome characterized by multiple seizure types including tonic, atonic, atypical absence, and generalized tonic-clonic seizures.<sup>1</sup> These are associated with generalized slow (<3 Hz) spike wave discharges on electroencephalography (EEG) and cognitive decline.<sup>2</sup> Lennox-Gastaut syndrome develops during the first decade of life, typically between 3-5 years of age and is more common in males.<sup>3</sup> It accounts for up to 10% of all cases of childhood epilepsy.<sup>4,5</sup> Up to 80% of patients suffer from seizures that are refractory to multiple antiepileptic drug (AED) treatment.<sup>6</sup> Many patients continue to have daily seizures resulting in significant morbidity and deterioration in the quality of their life.<sup>7</sup> The objective of this review is to present an updated outline of LGS and the different pharmacological and non-pharmacological treatments.

**Clinical features.** Some clinical features, such as cognitive decline, may not be apparent at the onset of the seizures. This makes early diagnosis difficult; however, the syndrome will evolve over a few months-years and subsequently all classical features will

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appear.<sup>8,9</sup> Tonic seizures, which are the hallmark of the syndrome, may be quite subtle and may only appear during sleep.<sup>10</sup> In addition, atonic and atypical absence seizures may appear later on or may be difficult to recognize in younger children.<sup>11,12</sup> Eventually, 80% of children will develop tonic seizures, 65% develop atonic seizures, 60% develop atypical absence seizures, and 55% develop generalized tonic-clonic seizures.<sup>13</sup> Myoclonic and partial seizures are less common. Comorbid behavioral, sleep, and learning difficulties are frequently encountered.

**Etiology and classification.** Most children with LGS (75%) have an underlying structural (symptomatic) brain abnormality.<sup>14</sup> These include developmental cortical malformations, neurocutaneous syndromes, post hypoxic-ischemic insult, post meningitis/encephalitis, or metabolic encephalopathy. Prior history of infantile spasms, frequently symptomatic, is reported in up to 60% of patients.<sup>15,16</sup> The syndrome is unknown (cryptogenic) in 25% of patients. While an idiopathic (genetic) category is not well established, positive family history of epilepsy was noted in as many as 30% of families.<sup>17</sup> Patients with the SCN1A gene mutation may rarely develop features suggestive of LGS.<sup>18,19</sup> It is important to note that multiple seizure types, cognitive decline, and slow spike wave EEG pattern may all be seen in children with Dravet or Doose syndrome.<sup>20</sup> Other characteristic clinical and EEG features should help in distinguishing between these syndromes, as will be discussed later in the differential diagnosis section.

**Electroencephalography.** Typical EEG features include slow background rhythm and slow (<3 Hz) spike wave discharges, which may not be present at seizure onset.<sup>21</sup> The characteristic slow epileptiform discharges are generalized and bilaterally synchronous, occurring intermittently in bursts of varying duration. Near continuous runs of generalized slow spike wave

discharges are less common, and could suggest non-convulsive status epilepticus. Focal and multifocal epileptiform discharges are also common. Generalized paroxysmal fast rhythm (>10 Hz) with frontal emphasis can be seen during sleep and is associated with nocturnal tonic seizures.<sup>22</sup> Patients with LGS are at a high risk of developing non-convulsive status epilepticus, which may be missed clinically, or diagnosed late.<sup>23</sup> A high index of suspicion should be maintained, and the parents should be instructed regarding the possible signs and symptoms for early recognition. The initial typical EEG changes may eventually evolve to a more focal type or disappear with time, particularly with better seizure control.<sup>24</sup>

**Differential diagnosis.** Table 1 summarizes the possible causes of drug resistant seizures. Every effort should be made to exclude an underlying treatable metabolic or structural pathology. Atonic seizures are also seen in patients with Doose syndrome.<sup>25,26</sup> These children tend to be younger at seizure onset and remain cognitively normal. However, cognitive decline may be noted if the diagnosis is missed or delayed, and the seizures continue. Tonic seizures are uncommon in Doose syndrome and drop attacks are the result of negative myoclonus. In addition, the EEG has normal background rhythms with relatively faster generalized spike wave discharges and central theta activity. The generalized paroxysmal fast rhythm that is seen in LGS is lacking.<sup>26</sup> Doose syndrome responds better to AED treatment and has a more favorable prognosis.<sup>26</sup> Dravet syndrome is another syndrome that may be confused with LGS. Patients usually present with prolonged febrile seizures and myoclonus is commonly encountered.<sup>27</sup> The diagnosis is usually poor. Therefore, accurate diagnosis is needed for better family counseling regarding the clinical course and outcome.

**Treatment update.** Every effort should be made to achieve complete seizure control; however, in many

**Table 1** - Differential diagnoses of drug resistant epilepsy.

Diagnosis	Examples
None epileptic events	Shuddering attacks, self-gratification, panic attacks, tics, pseudo seizures, dystonic dyspepsia
Improper management	Incorrect diagnosis or classification, poor compliance, under treatment
Intractable epilepsy syndrome	LGS, infantile spasms, dravet syndrome, Doose syndrome
Lesional epilepsy	Cortical dysplasia, mesial temporal sclerosis, cortical tumors, hamartomas
Treatable inherited metabolic epilepsies	Please refer to Table 2
Neuro-metabolic disorder	Amino acid or organic acid disorders, urea cycle disorders.
Neurodegenerative disorder	Progressive myoclonic epilepsy, neuronal ceroid lipofuscinosis, mitochondrial cytopathy
LGS - Lennox-Gastaut syndrome	

**Table 2 -** Treatable inherited metabolic epilepsies.

Disorder	Specific treatment
B6 dependent epilepsy	Pyridoxine
Pyridoxal phosphate responsive epilepsy	Pyridoxal phosphate
Folinic acid responsive seizures	Folinic acid
Glucose transporter 1 deficiency	Ketogenic diet
Biopterin synthesis disorders	L-dopa, 5-hydroxytryptophan, biopterin
Cerebral folate deficiency	Folinic acid
Biotinidase deficiency	Biotin
Serine biosynthesis disorders	Serine, glycine
Creatine synthesis defect	Creatine monohydrate

**Table 3 -** Doses of important antiepileptic drugs used for LGS.<sup>34</sup>

Drug	Dose
Valproic acid (Depakene)	15-40 mg/kg/day
Clonazepam (Rivotril)	0.02-0.2 mg/kg/day
Clobazam (Frisium)	0.5-2 mg/kg/day
Lamotrigine (Lamictal)	5-10 mg/kg/day 1-5 mg/kg/day with valproic acid 10-15 mg/kg/day with enzyme inducers
Topiramate (Topamax)	2-10 mg/kg/day
Levetiracetam (Keppra)	15-60 mg/kg/day
Rufinamide (Banzel)	25-45 mg/kg/day
LGS - Lennox-Gastaut syndrome	

cases only reduction in seizure frequency and severity is possible.<sup>28</sup> Better seizure control will lead to enhanced alertness, behavior, and reduced risks of injury, all leading to improved quality of life for both the child and the family.<sup>29</sup> While trying to do so, it is important to avoid drug related side effects and worsening of the associated comorbidities. This may be inevitable with polytherapy; therefore, careful monitoring of drug levels, side effects, and drug interactions is needed.<sup>30</sup> Table 2 summarizes some important causes of intractable epilepsy that should be considered when the seizures are resistant to multiple AED treatments. The seizures can respond dramatically when deficient vitamin or cofactor is supplemented.

**Pharmacological treatments.** To date, comparative drug studies in patients with LGS are not available. However, most practitioners agree that valproic acid is the first drug of choice.<sup>31,32</sup> Other helpful traditional AED treatments include benzodiazepines, such as clonazepam. The newer benzodiazepine, clobazam,

has also been effectively used.<sup>33</sup> Other traditional AEDs are less effective including ethosuximide and phenobarbitone, or may cause seizure worsening such as phenytoin and carbamazepines.<sup>34</sup> Newer AEDs that are useful for patients with LGS include lamotrigine, topiramate, levetiracetam, lacosamide, and rufinamide (Table 3). Gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin should be avoided because of lack of efficacy or possible worsening of myoclonic seizures.<sup>35,36</sup> In addition, lacosamide may also cause seizure worsening in some patients. Zonisamide and felbamate are available only in limited regions of the world and therefore are not discussed in this review. Two monotherapy trials are recommended before polytherapy is considered, however, most patients with LGS will eventually require AED combinations.<sup>37</sup>

**Valproic acid.** Valproic acid is highly effective for myoclonic, atypical absence, and atonic seizures.<sup>38</sup> Some patients respond only to higher doses (>30-40 mg/kg/day). In this situation, careful monitoring of the drug level is needed. Valproic acid is also a potent hepatic inhibitor and should be used with caution in patients on lamotrigine because of the increased risk of severe skin rash.<sup>39</sup> Serious hepatic toxicity is rare, but the drug should not be used if mitochondrial cytopathy is suspected. Tremor, hair loss, and weight gain are common side effects in older children. If the child becomes progressively sleepy or drowsy during treatment, serum ammonia should be obtained and L-carnitine should be started to treat any associated hyperammonemia. The drug has to be stopped if the condition does not improve, or the ammonia levels remain high.

**Benzodiazepines.** Clonazepam and nitrazepam are effective longer acting benzodiazepines, but tolerance and side effects limit their use. Clobazam is a newer 1,5-benzodiazepine that is better tolerated and effective for all seizure types including drop attacks.<sup>33,40</sup> It is associated with fewer side effects, which limited the use of older benzodiazepines, such as excessive drooling, lethargy, and sedation.<sup>33,40</sup> Clobazam was also observed to be more effective at higher doses (maximum 2mg/kg/day), but side effects limit such practice.<sup>41</sup> It is important to note that inducing excessive sedation and sleep with benzodiazepines may in fact, exacerbate the frequency of seizures.

**Lamotrigine.** Lamotrigine can be highly effective, particularly when combined with valproic acid. However, serious skin rash evolving to Stevens-Johnson syndrome is a significant risk.<sup>42</sup> This risk can be reduced by slower titration, however, leads to lowered antiepileptic effects.<sup>43</sup> Parents should be warned of the

risk of developing serious skin rash, and advised to report it promptly to the treating physician. Although the risk is small, it should be weighed against the potential benefits, particularly in children on valproic acid.

**Topiramate.** Topiramate appears to have multiple modes of action including sodium channel blockade, GABA enhancement, glutamate antagonism, and weak carbonic anhydrase inhibition.<sup>44</sup> These broad antiepileptic effects suggest an important therapeutic role. Topiramate was shown to be effective in randomized controlled trials.<sup>45</sup> Cognitive, language, and behavioral problems were the most common side effects, particularly with higher doses.<sup>46,47</sup> However, it has not been associated with any serious side effects. Poor appetite and weight loss can be a significant problem, particularly in young children.

**Levetiracetam.** Levetiracetam has a mechanism of action distinct from that of other AEDs.<sup>48</sup> The drug has a broad spectrum of antiepileptic properties and is highly effective for myoclonic seizures.<sup>49</sup> It was found effective against other seizure types in patients with LGS; however, no randomized controlled trial has been conducted to date. Except for irritability and behavioral disturbances, the drug is well tolerated.

**Rufinamide.** Rufinamide is a newer AED that was recently approved for the adjunctive treatment of seizures associated with LGS. It has a wide spectrum of antiepileptic effects; however, its mechanism of action is not fully known.<sup>50,51</sup> Rufinamide significantly reduced the frequency of generalized tonic clonic, absence, atypical absence, and atonic seizures. The drug can be quickly titrated to a maximum dose of 45 mg/kg/day.<sup>52</sup> Side effects include somnolence, headache, vomiting, and skin rash. No serious side effects or significant drug interactions were reported.<sup>52</sup> However, it is recommended to start rufinamide at a lower dose when combined with valproic acid.<sup>53</sup>

**Steroids.** Adrenocorticotrophic hormone, oral prednisone, and intravenous methylprednisolone were considered an option when other treatments fail or while preparing patients for non-pharmacological treatments. The efficacy and tolerability of steroids have not been fully established with a poorly understood mechanism of action.<sup>54</sup> A short pulse of IV methylprednisolone has been used with significant benefits.<sup>55</sup> In a recent study, IV methylprednisolone was given at 15 mg/kg/day followed by a weaning dose of oral prednisolone for one month.<sup>55</sup> One third of the children became completely seizure free. At 6 months post-treatment, improved seizure control was noted in 59% of the children. Patients with mixed seizures, including LGS, were

more likely to have a favorable response. The treatment was not associated with any major side effects. In fact, improvements in alertness and appetite were noted in 35% of the treated children.

**Non-pharmacological treatments.** Despite the availability of many AEDs for the treatment of LGS, most patients fail to respond and therefore the following modalities can be attempted.

**Ketogenic diet.** The ketogenic diet is an effective therapy for patients with LGS.<sup>56</sup> It consists of a high fat low carbohydrate ratio. However, it requires a supportive team and committed parents. Up to 50% of patients achieve significant seizure reduction.<sup>57</sup> However, the effectiveness may decline with time.<sup>58</sup> Side effects include renal stones, hyperuricemia, acidosis, metabolic disturbance, vomiting, diarrhea, and hyperlipidemia. The long-term side effects are not well known.

**Vagus nerve stimulation.** Vagal nerve stimulation has proven to have some effect in patients with LGS.<sup>59</sup> Although its exact mechanism of action not well known, it is a useful alternative for patients that are not candidates for epilepsy surgery.<sup>60</sup> The improvement in seizure control is gradual and continues over time with weekly increments of stimulation intensity.<sup>61</sup> In addition, improvements in cognition, and mood may be associated.<sup>62</sup> The occurrence of adverse events is low including laryngeal irritation, drooling, hoarseness, dysphagia, dyspnea, and cough.<sup>63</sup> No life-threatening side effects have been reported.

**Epilepsy surgery.** Partial or complete corpus callosotomy is a palliative procedure that results in significant reduction of the frequency of drop attacks. The improvements can be dramatic immediately after surgery with later recurrence. Potential side effects include decreased speech output, hemiparesis, gait disturbance, and disconnection syndrome. Partial corpus callosotomy (sectioning the anterior 2 thirds) involve better speech preservation; however, complete callosotomy is more effective.<sup>64</sup> The procedure was also shown to reduce secondary generalized tonic-clonic seizures.<sup>65</sup>

**Long-term outcome.** Lennox-Gastaut syndrome generally has a poor prognosis. Most patients will have drug resistant epilepsy, and up to 80% of patients may continue to have daily seizures.<sup>66</sup> In adult LGS, patients tonic seizures during sleep remain the major seizure type.<sup>67</sup> Risk factors for poor prognoses include history of infantile spasms, symptomatic etiology, severe cognitive dysfunction, and seizure onset before age 3 years. It remains to be proven how much of the cognitive decline is due to the underlying pathology versus the intractable epilepsy. There is some evidence

that the early use of newer AEDs could limit the cognitive dysfunction, but only when associated with significant seizure reduction.<sup>68</sup> In addition to multiple comorbidities, patients with LGS have an increased mortality rate of 5-17%. More than half of mortalities are a direct result of seizure related complications.<sup>66,68</sup>

In conclusion, Lennox-Gastaut syndrome typically results in drug resistant epilepsy of early onset and subsequent cognitive decline. Mixed seizures are associated with generalized slow spike and wave discharges on EEG and bursts of generalized fast poly spikes. The prognosis for complete seizure control is frequently poor. However, with the addition of newer antiepileptic drugs and other non-pharmacological therapies, improved hope is available for some of these patients and their families. Further long term randomized controlled trials are required, particularly to compare different therapeutic interventions in terms of efficacy and tolerability.

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