Lennox-Gastaut Syndrome in a Nutshell

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Abstract

Lennox-Gastaut syndrome is one of the rare childhood onset epileptic encephalopathy, characterized by multiple type seizure disorder, typical pattern on electroencephalogram and intellectual disability. Tonic-type seizures are most commonly seen in these patients. Behavioral disturbances and cognitive decline are gradual onset and last long after the first episode of epileptiform activity. In most of the cases, there is some identifiable cause that has led to the clinical presentation of the patient. Various pharmacological and surgical procedures have been proposed for the treatment of Lennox-Gastaut syndrome and many more to come in very near future to overcome the drug resistance and to avoid the patient form life-long dependency.

Keywords: Childhood epilepsy; Encephalopathy; Intellectual disability

Introduction

Lennox-Gastaut Syndrome is one of the eight syndromes under epileptic encephalopathy as reported by International League Against Epilepsy (ILAE) Task Force [1,2]. The term “epileptic encephalopathy” is defined as a progressive decline of cerebral function and cognition along with behavioral regression or deterioration, caused by epileptogenic (ictal and electrical) activity during period of brain maturation [1-4]. Lennox-Gastaut Syndrome was first named by Lennox as "Petit mal variant", which was later named after him in 1966 by Gastaut and his coworkers, as Lennox syndrome. This was referred as childhood-onset tonic and absence type of seizures [3]. Lennox-Gastaut Syndrome accounts for approximately 1–10% of childhood epilepsies. The clinical picture of LGS is the triad of antiepileptic resistant seizure disorder, characteristic abnormality on electroencephalogram (EEG) and cognitive dysfunction. The epileptiform abnormalities contribute to the gradual onset intellectual disabilities along with psychiatric comorbidities like anxiety, depression and behavioral abnormalities. All the three criteria must not be present at the time of onset of seizure onset and diagnosis is established after following up the patient for several years [5].

Lennox-Gastaut syndrome is a typical childhood onset, severe epileptic encephalopathy associated with serious intellectual disability in 20–60% patients at the time of onset of seizures, the proportion of which will increase to 75-95% at 5 years of onset of seizures. Though some cases with normal intellectual and behavior have also been reported. The specific electroencephalographic pattern varies from either bursts of slow spike-wave complexes or generalized paroxysmal fast activity. Slow spike-wave complexes (<2.5 Hz) are not considered to be pathognomonic for Lennox-Gastaut syndrome, but some experts have found generalized paroxysmal fast activity on electroencephalogram to be an essential criterion for diagnosing Lennox-Gastaut syndrome [5,6].

Epidemiology

The prevalence of Lennox-Gastaut syndrome is 1–2% of the epileptic patients, and 1–10% (mean 4%) of the childhood epilepsies [3]. The age of onset ranged from tenth day of life to 9 years of age, with mean age of onset is 35.3 months [5]. The peak age of onset in patients with cryptogenic Lennox-Gastaut syndrome is less as compared to those with disease due to some identifiable etiology [1]. Lennox-Gastaut was once defined as any multiple seizure type epilepsy in children less than 11 years old. However late-onset syndrome has also been found in literature [3]. At the time of onset all patients suffer multiple seizures types, most commonly tonic seizures, followed by generalized tonic-clonic seizures. Almost all the patients are on 2-6 antiepileptic drugs (mean 3.4). 28% of the patients have been found to be seizure free after use of these drugs for at least 1.5 year [5].

According to prospective studies, 7-17% of patients with severe intellectual disability has Lennox-Gastaut syndrome. Lennox-Gastaut syndrome is found to be more prevalent in males than in females, for some undefined reason, with male to female ratio is 1:6 (relative risk, 5.31) [1,3]. The proportion of the patients with Lennox-Gastaut syndrome in European countries like Spain, Estonia, Italy, and Finland is found to be consistent across the studied populations and have demonstrated similarity to that in United States [1].

Etiology

In general, causes of Lennox-Gastaut syndrome has divided into two broader groups: [3,5]
1. Identifiable causes
2. Cryptogenic (non-identifiable) causes

Identifiable causes contribute to 67 to 75% of the patients with Lennox-Gastaut Syndrome. These include brain damage (e.g., head trauma), perinatal complications (e.g., birth asphyxia, intrauterine growth retardation, kernicterus), congenital central nervous system malformations (e.g., tuberous sclerosis), infections (e.g., meningitis, sepsis) or metabolic disorders. A retrospective study has shown that birth complications contribute to 25% of Lennox-Gastaut syndrome, while patients with this disease have history of central nervous system infections and head trauma in 3.7% and 1% of the cases respectively [3]. Cryptogenic Lennox-Gastaut syndrome has found in remaining

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25% to 35% patients. Many studies have tried to explain the mystery behind, by coupling the phenotypic description of the epileptic patients and their parents, with genetic studies of the pedigree. It has been seen in 16-20% of the patients with diagnosed West syndrome/infantile spasms that finally turned out to be Lennox-Gastaut syndrome [3].

Copy number variants have been found in 2.9 to 19% of the patients with Lennox-Gastaut syndrome. The mutation of other genes involved in human brain development (e.g., forkhead box G1 (FOXG1), chromodomain-helicase-DNA-binding protein 2 (CHD2) genes), and gene for presynaptic protein dynamin 1 (DNM 1) have also been found to be associated with this syndrome. The genetic heterogeneity of this syndrome identifies it to be one of the manifestations of other genetic disorders, rather being an independent entity [3,5].

Clinical presentation

The clinical picture is a triad of:
1. Seizure disorder
2. Specific abnormality in electroencephalogram
3. Cognitive impairment

Tonic type of seizures is seen in all the patients with Lennox-Gastaut syndrome but may not be present at the time of its onset. Atypical absence seizures (with gradual onset and termination) are the second most type of epileptic activity seen in these patients, but it is difficult to diagnose clinically in patients with diminished cognition. Prolonged atypical absences are seen in 66% of the patients with altered consciousness, which is periodically interrupted by episodes of tonic seizures. These non-convulsive episodes may last for hours to weeks in severe case, clinically named as 'non-convulsive status epilepticus' [3]. Atonic and myoclonic seizures have also been recorded in patients with Lennox-Gastaut syndrome. Drop attacks are also common (more than 50%) in these patients but is not a pathognomonic clinical manifestation. Other types of seizure more commonly seen in later stages of the disease; these includes focal seizures, generalized tonic-clonic seizures or unilateral clonic seizures [3].

Lennox-Gastaut syndrome seems to be the result of central nervous system network dysfunction, and sometimes refers as "secondary network epilepsy". The mostly seen EEG patterns are; slow spike-wave complexes (SSW) and generalized paroxysmal fast activity (GPFA) (Figure 1). These EEG patterns were studied while coupling them with functional magnetic resonance imaging (fMRI) findings, which revealed the fact that patients with generalized paroxysmal fast activity on EEG had increased blood oxygen level-dependent (BOLD) signals in cortical "association" areas, brain stem, basal ganglia, and thalamus, while in patients with slow spike-wave pattern on EEG had primarily decreased BOLD signals in "primary cortical areas". This concludes that GPFA is the result of more diffuse activation of cortical and subcortical neuronal networks. However, cortical and subcortical activations and deactivations are associated with SSW complexes [2,3]. Single-photon emission computed tomography (SPECT) during peri-ictal phase, in the patients with Lennox-Gastaut syndrome with tonic seizures have shown the activity in bilateral frontal and parietal association areas and the pons [2] (Figure 1).

According to a case-control study, what increases the odds of having intellectual disability in the patients with Lennox-Gastaut syndrome include, history of non-convulsive status epilepticus, diagnosed case of West syndrome, any identifiable etiology of having epilepsy and early age of onset. Cognitive decline is secondary to epilepsy itself, like all other epileptic encephalopathies or may be due to abnormal neuronal connections and the side effects of medications [3].

Diagnosis

The following test can be considered to diagnose Lennox-Gastaut syndrome [1,3,4]:
1. Complete blood panel (rule out the metabolic causes)
2. Magnetic resonance imaging brain
3. Electroencephalogram
4. Genotyping; chromosomal array, Sanger sequencing, next generation sequencing panels

Differential diagnosis

Other medical diagnoses to be kept in mind, include following infantile/childhood epileptic encephalopathies (Table 1).

Treatment

Various pharmacological and surgical options are now available to
and should be treated with benzodiazepines, like other patients with status epilepticus. Status epilepticus is a medical emergency; if a first drug fails, while keeping the patient on monotherapy convert him on the least effective doses of other anti-epileptics reported to be effective are; clobazam, felbamate, and rufinamide [2,3] (Table 2). It’s a general principle to prescribe the least number of drugs at a time.

Table 1: Differential diagnosis of Lennox-Gastaut syndrome [1,3,6,7].

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at onset</th>
<th>Seizure types</th>
<th>EEG features</th>
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<tbody>
<tr>
<td>Ohtahara Syndrome (epileptic encephalopathy)</td>
<td>First 3 months (usually within first 10 days of birth)</td>
<td>Tonic/clonic, atonic, myoclonic seizures and drop attacks</td>
<td>Burst and suppression pattern during wake and sleep states</td>
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<tr>
<td>West syndrome (epileptic encephalopathy)</td>
<td>Peak at 4–6 months</td>
<td>Epileptic spasms</td>
<td>Hypsarrhythmia</td>
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<tr>
<td>Dravet syndrome (severe myoclonic epilepsy)</td>
<td>First year</td>
<td>Focal or secondarily generalized seizures</td>
<td>Often normal at onset; generalized spikes/polyspikes with photic stimulation</td>
</tr>
<tr>
<td>Pseudo-Lennox-Gastaut syndrome (atypical benign partial epilepsy)</td>
<td>Early childhood</td>
<td>Atypical absence, myoclonic seizures</td>
<td>Rolandic sharp waves, multifocal sharp waves, electrical status epilepticus in sleep</td>
</tr>
<tr>
<td>Doose syndrome (myoclonic-atonic epilepsy)</td>
<td>Early childhood</td>
<td>Myoclonic-atonic, atypical absence</td>
<td>2–3 Hz generalized spike-waves, photoparoxysmal response</td>
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<tr>
<td>Electrical Status Epilepticus during Slow Sleep (ESES)</td>
<td>2 months - 12 years (peak age 4 and 5 years)</td>
<td>Unilateral or bilateral clonic seizures</td>
<td>Spikes and waves occurring almost continuously during slow sleep (subclinical)</td>
</tr>
<tr>
<td>Acquired Epileptic Aphasia Landau-Kleffner Syndrome (LKS)</td>
<td>18 months – 13 years</td>
<td>Generalized tonic-clonic seizures</td>
<td>Paroxysmal electroencephalographic changes and little or no language development</td>
</tr>
<tr>
<td>Juvenile Myoclonic Epilepsy</td>
<td>Adolescence</td>
<td>Myoclonic jerks with or without generalized tonic-clonic seizures and/or absence seizures</td>
<td>3-5 Hz generalized spike waves and polyspikes with normal background activity</td>
</tr>
</tbody>
</table>

Table 2: Anti-epileptic drugs and their application [2,3].

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Side effects</th>
<th>Remarks</th>
<th>Starting dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Hepatotoxicity, pancreatitis, drug interactions.</td>
<td>Most effective for myoclonic, atypical absence, and tonic seizures.</td>
<td>Started at 7–10 mg/kg/day PO, weekly increased by 5 mg/kg/day as tolerated and necessary.</td>
<td>60 mg/kg/day or 3000 mg/day</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Skin reactions, drowsiness, nausea, anorexia, headache, and ataxia, exacerbate myoclonic seizures.</td>
<td>Effective for tonic-clonic seizures and drop attacks.</td>
<td>Age &lt; 12 yrs: 0.3 mg/kg/day in 1 or 2 divided doses for the first 2 weeks Age &gt;12 yrs: 25 mg/day for the first 2 weeks. Increased by up to 50 mg/day every 1–2 weeks.</td>
<td>300 mg/day in 2 divided doses</td>
</tr>
<tr>
<td>Topiramate*</td>
<td>Anorexia, weight loss, renal stones, and slowing of cognition.</td>
<td>Effective for tonic-clonic seizures.</td>
<td>Age &lt; 16 yrs: 18 mg/kg/day. Age &gt;16 yrs: 600 mg/day; increase up to 1600 mg/day.</td>
<td></td>
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<tr>
<td>Felbamate*</td>
<td>Aplastic anemia, liver failure Safety and efficacy not established for age &lt;14 years.</td>
<td>Safety and efficacy not established for age &lt;14 years.</td>
<td>1200 mg/day divided every 6–8 hr, increases 2 weekly by 600 mg, up to 2400 mg/day.</td>
<td>Maximum dose is 3600 mg/day</td>
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<tr>
<td>Clobazam*</td>
<td>Sedation Adjunctive treatment, decreasing drop attacks. Approved for 2 or more years old patient.</td>
<td>Adjunctive treatment, decreasing drop attacks.</td>
<td>Weight &lt;30 kg: 0.25 mg/kg/day in 2 divided doses. Increased by 0.5–1 mg/kg every 1–2 weeks.</td>
<td>Weight &lt;30 kg: 1 mg/kg/day. Weight &gt;30 kg: 80 mg/kg/day</td>
</tr>
<tr>
<td>Rufinamide*</td>
<td>Somnolence, vomiting, and weight loss. Contraindicated in patients with familial short QT syndrome.</td>
<td>Adjunctive treatment of seizures in 4 or more years old patient.</td>
<td>Children (&lt;4 yrs): 10 mg/kg/day, in two equally divided doses, and increases by 10 mg/kg every other day up to target doses. Adults: 400–800 mg/day, in two equally divided doses, and increased by 400–800 mg/kg every other day.</td>
<td>Children (&lt;4 yrs): 45 mg/kg/day or 3200 mg/day, whichever is less. Adults: 3200 mg/day.</td>
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</table>

*Recently approved anti-epileptics drugs for Lennox-Gastaut syndrome [2].

Treat these patients. Most of the patients with epileptic encephalopathies are resistant to anti-epileptic drugs and most of them are on more than two medication for seizure control [7].

Anti-epileptics: Valproate, lamotrigine, and topiramate are declared to be the first-line. According to randomized control trials other anti-epileptics reported to be effective are; clobazam, felbamate, and rufinamide [2,3] (Table 2). It’s a general principle to prescribe least number of drugs at a time.

Ketogenic diet: It is left over option for those patients who are poorly responding to medical treatment [1]. It is found to be effective in childhood refractory seizures in specific genetic disorders e.g., Glut-1 deficiency syndrome [2]. Common side effects of ketogenic diet are; constipation, vomiting, abdominal pain, apathy, increase appetite, hypercholesterolemia, mineral deficiencies, acidosis, and growth retardation. Some studies have shown that use of low glycemic index diet and modified Atkins diet (containing nuts/seed, fruits or dairy products) are also effective in these patients [3].

Surgery: Surgical options for Lennox-Gastaut syndrome include...
corpus callosotomy, vagus nerve stimulation, and focal cortical resection [1].

**Corpus callosotomy:** Corpus callosum comprises of ‘rostrum’, ‘genu’, ‘body’ and ‘splenium’ (anterior to posterior). According to its topographical representation, resection of anterior 4/5th is sufficient to produce effective results in these patients, though 10% lesser response rate as compared to those with total resection of corpus callosum. Keeping splenium preserved will preserve some of the fibers for interhemispheric perceptual information to transfer and to lessen the complications of ‘disconnection syndrome’ [3].

**Vagus nerve stimulation:** The exact mechanism how vagus nerve stimulation is effective in patients with epilepsy is yet to be known. It has been suggested it might interrupt the synchronicity of electrical activity or might cause changes in metabolism or blood flow to various cortical and sub-cortical areas of the brain. It is reserved for those medical treatment is not effective and respective surgery is not the option. It is effective in all types of seizures and adverse effects are much less as compared to corpus callosotomy. The most common side effects are hoarseness of voice, dysphagia, dyspnea, and coughing [3]. Meta-analysis have shown significantly better results after callosotomy as compared to vagus nerve stimulation, in seizures control in patients with Lennox-Gastaut syndrome [9].

**Cortectomy/Lobar dissection:** Selective dissection of cortex may produce immediate and spectacular results in disabling seizures [8]. Other options are; gamma knife callosotomy, deep brain stimulation and multiple sub-pial transection [8].

**Prognosis**

Various prospective studies have shown that features of typical Lennox-Gastaut syndrome will evolve over time and it will difficult to identify if remain undiagnosed in childhood. The variety and frequency of seizures decreases over time, same in case of their severity. Generalized paroxysmal fast activity on EEG will typically persist in adulthood, while slow spike-wave complexes will remain in minority of patients. Cognitive and behavioral disturbances will remain in most of the patients with Lennox-Gastaut syndrome as an adult [3]. Long-term outcome of the disease is variable from normally functioning individuals to severely decreased intelligence quotient (IQ). Lennox-Gastaut syndrome is a rare pediatric diagnosis and comparatively more prevalent among males than in females. The etiology of this syndrome is broadly divided into identifiable and non-identifiable causes. Identifiable causes comprise the major portion of this classification (65-75%) and include various diseases of structural, genetic, or metabolic in origin.

The patient of Lennox-Gastaut syndrome like all other epileptiform encephalopathies is multi-drug resistant. Many experts think valproate, lamotrigine, and topiramate as first-line drugs while managing this syndrome. Various recently approved drugs are being used as an adjunctive therapy. Steroids, immunomodulation or dietary restrictions have proved their roles in treatment of these patients. Severely damaging seizures which are not responsive to medical treatment are treated by complete or partial (preferably) resection of corpus callosum fibers. Those who are not an ideal candidate for surgery, vagus nerve stimulation is providing a promising result. Overall, prognosis of Lennox-Gastaut syndrome is debilitating both for the patient and the family of the patient.

**References**