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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 Lenox-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].

Literature Review

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 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

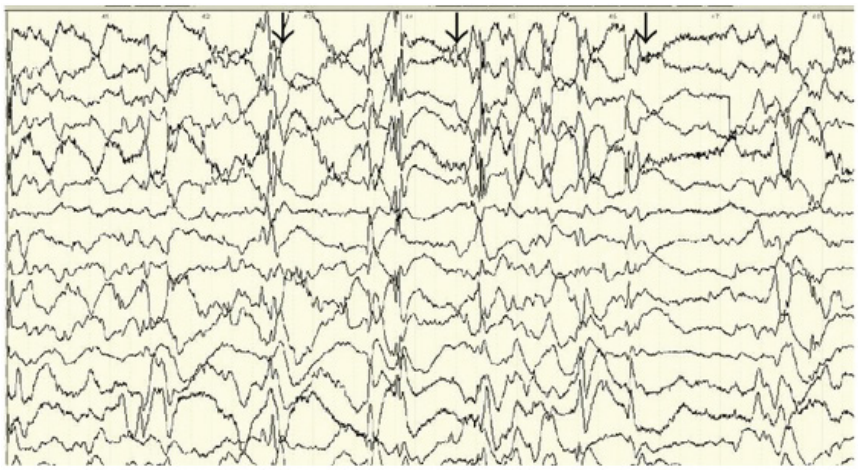

Figure 1: Paroxysms of fast activity and generalized slow spike and wave discharges (1.5–2 Hz) (arrows), in electroencephalogram of Lennox-Gastaut syndrome patient [1].

Syndrome	Age at onset	Seizure types	EEG features
Ohtahara Syndrome (epileptic encephalopathy)	First 3 months (usually within first 10 days of birth)	Tonic/clonic, clonic, myoclonic, atonic, absences, partial, complex partial (with or without secondary generalization)	Burst and suppression pattern during both waking and sleeping states.
West syndrome (epileptic encephalopathy)	Peak at 4–6 months	Epileptic spasms	Hypsarrhythmia
Dravet syndrome (severe myoclonic epilepsy)	First year	Focal or secondarily generalized with fever in infancy; myoclonus after 1 year of age	Often normal at onset; generalized spikes/polyspikes activated with photic stimulation
Pseudo-Lennox-Gastaut syndrome (atypical benign partial epilepsy)	Early childhood	Atypical absence, myoclonus, atonic, and focal seizures	Rolandic sharp waves, multifocal sharp waves, electrical status epilepticus in sleep
Doose syndrome (myoclonic-atonic epilepsy)	Early childhood	Myoclonic-atonic, myoclonus, and atypical absence	2–3 Hz generalized spike-waves, photo-paroxysmal response
Electrical Status Epilepticus during Slow Sleep (ESES)	2 months - 12 years (peak age 4 and 5 years)	Unilateral or bilateral clonic, generalized tonic-clonic, absences, complex partial seizures, with or without drop attacks	Spikes and waves occurring almost continuously during slow sleep (subclinical)
Acquired Epileptic Aphasia Landau-Kleffner Syndrome (LKS)	18 months – 13 years	Generalized tonic-clonic seizures	Paroxysmal electroencephalographic changes and little or no language development
Juvenile Myoclonic Epilepsy	Adolescence	Myoclonic jerks with or without generalized tonic-clonic seizures and/or absence seizures	3-5 Hz generalized spike waves and polyspikes with normal background activity

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

Drugs	Side effects	Remarks	Starting dose	Maximum dose
Valproate	Hepatotoxicity, pancreatitis, drug interactions.	Most effective for myoclonic, atypical absence, and atonic seizures.	Started at 7–10 mg/kg/day PO, weekly increased by 5 mg/kg/day as tolerated and necessary.	60 mg/kg/day or 3000 mg/day.
Lamotrigine	Skin reactions, drowsiness, nausea, anorexia, headache, and ataxia, exacerbate myoclonic seizures.	Effective for tonic-clonic seizures and drop attacks.	**Age < 12 yrs**: 0.3 mg/kg/day in 1 or 2 divided doses for the first 2 weeks **Age >12 yrs:** 25 mg/day for the first 2 weeks. Increased by up to 50 mg/day every 1–2 weeks.	300 mg/day in 2 divided doses.
Topiramate*	Anorexia, weight loss, renal stones, and slowing of cognition.		**Age 2-10 yrs**: 0.5–1 mg/kg/day for 1–2 weeks, increase gradually by 0.5–1 mg/kg/day every 1–2 weeks. **Age >10 yrs**: 25 mg nightly for 1 week, increase weekly by 25 mg/day over 2-4 weeks.	**Age < 16 yrs:** 18 mg/kg/day. **Age >16 yrs:** 600 mg/day, increase up to 1600 mg/day.
Felbamate*	Aplastic anemia, liver failure	Safety and efficacy not established for age <14 years.	1200 mg/day divided every 6-8hr, increases 2 weekly by 600mg, up to 2400 mg/day.	Maximum dose is 3600 mg/day.
Clobazam*	Sedation	Adjunctive treatment, decreasing drop attacks. Approved for 2 or more years old patient.	**Weight <30 kg:** 0.25 mg/kg/day in 2 divided doses. Increased by 5–15 mg every 5 days until seizures are controlled. **Weight >30 kg:** 5–10 mg/day, in 1–2 doses.	**Weight <30 kg:** 1 mg/kg/day. **Weight >30 kg:** 80 mg/kg/day.
Rufinamide*	Somnolence, vomiting, and weight loss. Contraindicated in patients with familial short QT syndrome.	Adjunctive treatment of seizures in 4 or more years old patient. Effective for drop attacks.	**Children (>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 every other day.	**Children (>4 yrs)**: 45 mg/kg/day or 3200 mg/day, whichever is less. **Adults:** 3200 mg/day.

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

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

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 possible number of drugs at a time, at their least effective doses. If first drug fails, while keeping the patient on monotherapy convert him on another drug, but if second drug is also not effective, add a second agent to the existing regimen [3]. Status epilepticus is a medical emergency and should be treated with benzodiazepines, like other patients with prolonged seizures. Non-convulsive status epilepticus is also responsive to corticosteroids and/or ketogenic diet [8].

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 severe mental retardation and treatment resistant seizures in 47-76% of the patients who need special home or institutional care [1].

Advances

Drug resistance and increased understanding of disease process has forced to look forward the novel methods of dealing with the disease. Lacosamide has found to be effective for focal and tonic-clonic seizures and is used as adjunctive treatment. What most concerning about lacosamide use, is that it may exacerbate tonic seizures in Lennox-Gastaut syndrome patient [4].

Other anti-epileptic drugs, which are suspected to be beneficial in these patients includes carisbamate (increases seizure threshold), fluorofelbamate (dicarbamate), ganaxolone (GABA-A receptor modulator), seletracetam (levetiracetam derivatives), and remacemide (NMDA receptor blocker). More clinical trials are needed to define the drug safety and their maximal tolerable doses [8]. Steroids along with antiepileptic drugs in these patients have shown promising results [3,8]. Global review has identified intravenous immunoglobulins (IVIG) effective in various infantile and childhood epilepsies including those with Lennox-Gastaut syndrome [3].

Neuroprotection is an emerging concept in the treatment of Lennox-Gastaut syndrome patients. Some trials have shown efficacy of melatonin and NMDA receptor antagonists in neuronal protection and control of epilepsy. Gene therapy is also fascinating option that needs to be pondering on, in cases of drug resistant epilepsies and in those patients who are not the suitable candidates for surgery [8].

Overall outcome of two double blinded well controlled trials have shown that cannabinoids are effective in patients with Lennox-Gastaut syndrome as compared to placebo at the dose of 10-20 mg/kg/day [10].

Discussion and Conclusion

Lennox-Gastaut syndrome is one of the encephalopathies develops as a result of epileptic activity, results into cognitive and behavioral disabilities. This syndrome is a clinical trial of drug-resistant seizures, pathognomonic electroencephalographic patterns along with mildly 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.

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