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LGS (Lennox-Gastaut Syndrome)

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SUMMARY

Lennox-Gastaut syndrome (LGS) is a severe childhood form of epilepsy defined by multiple, often medication-refractory seizures (usually "drop attacks", atypical absence seizures and tonic seizures), a characteristic EEG pattern (slow waking background, slow spike wave) and paroxysmal fast rhythms in sleep) as well as cognitive, behavioral and psychiatric symptoms. This triad of mixed seizures, abnormal EEG and encephalopathy represents one of the most difficult to treat. LGS is also a physically dangerous epilepsy syndrome of childhood because of the frequent falls, injuries, and cognitive impairment that can severely limit quality of life. Neurologists are aware of different causes of LGS from cortical malformations to meningitis and almost any condition that causes brain injury or disrupts normal neural networks. New treatments are available, including medications specifically approved for the disorder. Complete end to all seizures is unusual.

Lennox-Gastaut syndrome (LGS) is a severe childhood form of epilepsy described by:

- multiple, often medically difficult to manage seizures
- a specific electroencephalography (EEG) pattern; and
- broad brain dysfunction or encephalopathy (causing cognitive, behavioral, psychiatric symptoms)

DESCRIPTION

Lennox-Gastaut syndrome (LGS) is a clinical condition which refers to a triad of signs and symptoms. These include (1) multiple seizure types, often medically refractory, with (2) a typical EEG pattern and (3) frequent moderate to severe cognitive disabilities. The most common seizure patterns are tonic, atypical absence, and "drop attacks" or atonic seizures, but generalized tonic-clonic and focal seizures can occur as well. The EEG abnormalities may vary,

but usually there is high voltage, generalized slow spike and wave activity (usually less than 2.5 Hertz) in addition to bursts of generalized paroxysmal fast activity (GPFA) during sleep; waking background is often slow and disorganized. The degree of cognitive delay and behavioral dysfunction vary, but are extremely common and often severe. These challenges represent an epileptic encephalopathy which weakens learning, social interaction and quality of life in general. Seizure types may change over time, slow spike wave and GPFA may not be appear on every EEG (especially routine waking studies), but cognitive and behavioral disabilities are permanent. There are children who fulfill the diagnosis for LGS whose seizures are well controlled and have minimal learning, social and behavioral challenges. However, many LGS patients wear protective headgear to prevent serious injuries from unprotected falls, and suffer from the long term effects of regular seizures and multiple drugs usage.
LGS is a clinical condition involving three specific signs and symptoms:

- Multiple seizure types, often difficult to medically manage. The most common seizure patterns are tonic, atypical absence and “drop attacks.” Generalized tonic-clonic and focal seizures can occur, as well.
- A specific EEG pattern that shows abnormal brain activity including:

1. high voltage (or increased activity),
2. generalized slow spike and wave activity (usually less than 2.5 Hertz),
3. bursts of specific activity called Generalized Paroxysmal Fast Activity (GFPA) during sleep waking background that is often slow and disorganized

- Moderate to severe cognitive disabilities are common. The brains of these children have existing encephalopathy (or brain dysfunction) that limits their ability to learn, social interactions, and their quality of life.

SYMPTOMS

LGS is a diagnosis based on the triad of seizure types plus EEG pattern as well as cognitive-behavioral dysfunction. None of these problems are specific to LGS, nor is there is single cause that leads to the syndrome, but it is important to make the diagnosis since it has great impact on treatment and prognosis. In sleep, the most typical seizure type in LGS is the generalized tonic seizure (often brief stiffening of all extremities). “Drop attacks” during wakefulness often occur dozens of times daily. They may include a brief tonic phase followed by loss of tone and falling. More subtle atonic seizures may present as head nods. Atypical absence seizures can be difficult to identify since they can have gradual onset and unclear termination; in other words, it is not always clear when they begin or end. Additionally, they are defined by brief episodes of loss of awareness, sometimes with head and eye deviation or subtle automatisms, such as eye flutter or muscle twitching. Not uncommon for children with LGS is to have periods of non-convulsive status epilepticus which can last for many minutes or days. This episode is characterized by altered awareness with almost continuous atypical absence seizures which may be interrupted by intermittent tonic or other seizure types. The presence of focal seizures may confuse the diagnosis, especially if the EEG does not show typical features of slow-spike wave or the decremental pattern called
GPFA (generalized paroxysmal fast activity).

The following define typical seizures seen in LGS patients:

- Generalized tonic seizures are often the brief stiffening of arms and legs in sleep.
- Atonic-akinetic seizures or “drop attacks” occur many times daily when a child is awake. They may include a brief tonic phase, loss of muscle tone, and a fall. Sometimes these seizures may present as head nods.
- Atypical absence seizures can be difficult to identify because they gradually begin and end. They can appear to be a loss of awareness, head and eye deviation (turn) or subtle automatisms, such as eye flutter or muscle twitching.
- Non-convulsive status epilepticus which can last for many minutes or days; and can look like altered awareness and continuous atypical absence seizures. These seizures may be interrupted by intermittent tonic or other seizure types.
- Focal or partial seizures may also be present.

Variable degree of cognitive delay is common in LGS. However, this may not be clear at the time of diagnosis. This can make it difficult to understand the reason for what may appear to be increasingly obvious failure to make progress or actual regression, as it could be due to:

- Underlying brain structure
- Epileptic encephalopathy caused by the frequent seizures
- Side effects of anti-seizure medication often prescribed as polypharmacy.

Unfortunately, almost all children with LGS have clear cognitive impairment within 5 years of diagnosis. The few LGS patients with normal intelligence usually continue to have major problems in daily life due to poor attention, hyperactivity, impulsivity, slow mental processing, and social difficulties.

LGS must be distinguished from other epilepsy syndromes, including:

- Early-onset childhood absence epilepsy does not have other seizure types, except for generalized tonic-clonic seizures. One difficulty may be caused by the fact that tonic seizures are inconsistent and may not be seen because they usually occur at night. Children with absence epilepsy should not have slow and disorganized EEG background and the frequency of spike-wave discharges are faster (approximately 3 Hertz) than those seen in LGS.
- Children with myoclonic-astatic epilepsy (Doose syndrome) are developmentally normal and typically have normal waking EEG background prior to onset of seizures and an epileptic encephalopathy.
- There is an overlap between LGS and Dravet syndrome , but the latter typically starts much earlier (within the first year of life) with atypical, prolonged febrile seizures followed by more focal seizures.
- Another important distinction is between LGS and atypical benign partial epilepsy. “Pseudo Lennox syndrome” can be distinguished by the persistently normal background, sleep activation of central-temporal spikes, and lack of tonic seizures.

LGS can be considered an age-related epileptic encephalopathy. It typically does not start in infancy, but other early onset epileptic encephalopathies may evolve into LGS. For example, it is not uncommon for infantile spasms, even if initially well-controlled, to subsequently demonstrate the variable seizure

types and EEG patterns, as well as developmental delays which define LGS. Eventually, as the child becomes an adolescent and enters adulthood, daytime seizures often improve with persistence of only sleep-related tonic seizures or development of focal seizures. In addition, the EEG may evolve and no longer fit the expected criteria with improved waking EEG background and absence of inter-ictal slow spike wave discharges. Interestingly, night-time tonic seizures often continue and still show the same diffuse fast rhythms of GPFA . It is important for adult practitioners to remember the life story of the individual and to put the current picture into context. It can be so common for adults to have focal epilepsy that a lack of awareness of the syndrome's presentation can lead to a wrong diagnosis and inadequate treatment. LGS should be considered in a patient with medically resistant seizures, especially if they include falling.

LGS should be considered as the diagnosis in all individuals with medically resistant seizures, especially if they include falling.

PHYSICAL ABNORMALITIES

There are no specific physical abnormalities that are associated with this epilepsy syndrome. However, LGS can be seen in a variety of chromosomal disorders, genetic-metabolic syndromes such as tuberous sclerosis and brain injury conditions (i.e. hypoxic-ischemic encephalopathy) that can help to determine the specific etiology of the disorder and lead to specific interventions.

CAUSATION

Since LGS is an age-related epileptic response to many different causes, the diagnosis suggests a broad differential diagnosis. Cerebral malformations, infections, hypoxic-ischemic injury, trauma, tuberous sclerosis and even progressive metabolic disorders are among the causes which can explain up to 75% of cases.

The following are examples of various conditions that explain 75% of seizure disorders:

- Cerebral malformations (abnormalities within child's brain structure)
- Infections (such as meningitis)
- Hypoxic-ischemic injury (brain injury that limits the amount of blood and oxygen delivered to certain areas of the brain)
- External trauma or injury
- Genetic – metabolic disorders (such as tuberous sclerosis)
- Other chromosomal disorders

Approximately 1 out of 4 children do not have a specific cause identified for their seizure disorder.

Age-related epilepsy often represents different stages of response to disrupted brain development. For example, Ohtahara syndrome which presents in the newborn period with tonic seizures, developmental delay, and an EEG showing burst suppression is caused by severe brain malformation or damage. This condition often evolves to West syndrome with infantile spasms and a chaotic EEG pattern (hypsarrhythmia) at 4-8 months of age. Over time, approximately

1/3 of children with West syndrome will eventually progress to LGS in childhood.

The diagnosis of LGS does not exclude other developmental or neuropsychiatric diagnoses. While some children with LGS have neurodevelopmental delays from the time of first diagnosis, even if they appear normal at the time when seizures are first recognized, the large majority of LGS patients are struggling with cognitive, behavioral, or social disabilities within several years. In addition to intellectual disability, many children will fulfill criteria for ADHD or autistic spectrum disorders. The diagnosis of LGS does not prevent medical treatment of these other conditions. Caregivers or providers should not be discouraged by theoretic concerns of seizure activity from stimulants or neuroleptics (typical treatment medications for ADHD and autism spectrum disorders).

ADDITIONAL CONCERNS AND COMPLICATIONS

Cognitive decline or intellectual disability (mental retardation) is present in 75-90% of children. Moderate to severe cognitive impairment is common in adults with LGS (96% in one study). Cognitive decline can occur over time, particularly in those with frequent seizures and many episodes of status epilepticus. However, it is unclear whether it is the frequent seizures causing worsening intellectual abilities or limitations that become more obvious due to lack of expected brain development. Behavioral disorders and psychiatric problems are also very common in children with LGS. These co-existing conditions further complicate the management of seizures and quality of life.

LABORATORY INVESTIGATIONS

Children present with seizures and developmental delays before they are eventually diagnosed with LGS. The work-up of epilepsy is discussed in another section. Obviously, the formal diagnosis of LGS requires a compatible EEG, but it is important to recognize that the characteristic features are inconsistent and may not be seen on every routine or even 24 hour video EEG. Once the diagnosis of LGS is made, it may be necessary to revisit the work-up for the child's epilepsy. For example, an MRI performed in the first year of life may need to be repeated with specific epilepsy protocols since a 3 Tesla study may now show abnormal myelination patterns or areas of cortical dysplasia not previously appreciated.

EEG and magnetic resonance imaging (MRI) are two tests neurologists use to diagnosis LGS. When thinking about the use of these tests, it is important to understand:

- While a LGS diagnosis requires a specific EEG pattern, the pattern may not be seen on every routine or even 24 hour video EEG.
- Once the diagnosis of LGS is made, it may be necessary to revisit the initial tests to see if the child's condition has changed. For example, an MRI performed in the first year of life may be repeated later to see if there have been any changes in the child's brain structure.

DIAGNOSTIC STANDARDS

As stated above, Lennox-Gastaut syndrome is a severe form of childhood onset epilepsy defined by (1) multiple seizure types, often medically refractory, with (2) a typical EEG pattern and (3) frequent moderate to severe cognitive disabilities. Most often it is the result of a brain insult during early life, but occasionally it can develop in an otherwise previously healthy child. Seizures associated with LGS may follow severe earlier seizure syndromes such as West syndrome or occur on their own. Any seizure pattern may be present, but typically include tonic, atypical absence and “drop attacks” or atonic seizures. The electrographic abnormalities may vary, but classically there is high voltage and generalized slow spike and wave activity (usually less than 2.5 Hertz) in addition to bursts of generalized paroxysmal fast activity during sleep; waking background is often slow and disorganized.

THERAPEUTIC INTERVENTION

There have been several new drugs recently approved by the Food and Drug Administration (FDA) for treatment of seizures associated with LGS. Until 2011 there were only four medications that were so designated including topiramate, lamotrigine,clonazepam and felbamate. Interestingly, none of these were the typical first choice of most clinicians who would start with valproate (which was never specifically tested for FDA registration in this population, so it has never been officially approved).Valproate can be effective for all of the seizure types typically associated with LGS. It is a complex drug which has significant side effects ranging from tremor to reduction in platelet count and function as well as hyperammonemi a. Rare life-threatening side effects include liver failure and pancreatitis.

Topiramate also has a broad spectrum of action which can help the multiple seizure types of LGS. It has been shown to reduce drop attacks and has a safety profile that many consider better than lamotrigine or felbamate. Even when dosages are increased slowly, there is a high rate of central nervous system (CNS) side effects, such as somnolence or sleepiness, mental slowing and ataxia (unstable gait) in addition to word-finding difficulties and weight loss. Lamotrigine has effects against multiple seizure types in addition to mood stabilizing properties, but unusual pharmacologic effects and interactions make it a challenging drug to use. It is rarely associated with life-threatening rash as long as the drug is introduced slowly and drug interactions (particularly with valproate) are considered.

Felbamate was effective for LGS when it was first introduced, and one of the first new agents that promoted alertness as well as weight loss; however, the risk of aplastic anemia and hepatic failure have relegated it to a last-ditch adjunctive drug for difficult to manage epilepsy. Clonazepam represented the most commonly employed representative of the benzodiazepine class of medications. It is particularly effective in myoclonic seizures, but it is limited by the common problem of tolerance as well as withdrawal seizures. In addition, sedation and drooling make it unappealing first line agents. Therefore, it is rarely used as a long term option, although various benzodiazepines (including clonazepam) are still used for short term relief at the time of seizure flurries.

Clobazam, a unique 1,5 benzodiazepine derivative long available in Europe, was finally introduced to the US in 2011. Its different structure appears to be responsible for a lower rate of sedation and broader spectrum of action as well as longer half-life than other benzodiazepines which all share a 1,4 structure.

In a short time it has proven itself to be a rapidly effective agent with an apparently lower rate of tolerance than other drugs in its class. It was shown to significantly reduce drop attacks and other seizure types. Rufinamide is the other newly approved drug. It is structurally unrelated to any other anti-seizure compound and has good efficacy against various seizure types associated with LGS.

Until 2011, only four medications were designated in the treatment of LGS:

1. Topiramate can help control the multiple seizure types of LGS. It has been shown to reduce “Drop Attacks”, and has a safety profile that many consider better than lamotrigine or felbamate. Side effects may include sleepiness (somnolence), mental slowing and unstable gait (ataxia) in addition to word-finding difficulties and weight loss.
2. Lamotrigine is effective with multiple seizure types, as well as being mood stabilizing. It is a challenging drug to use because of the varying ways it works in a person’s body, and the large number of medication interactions. It is rarely related to a life-threatening rash, as long as the drug is introduced slowly and drug interactions (particularly with valproate) are taken into account.
3. Clonazepam is the most commonly used benzodiazepine. It is very effective in myoclonic seizures, but it is limited by the common problem of tolerance, as well as withdrawal seizures. In addition, sedation and drooling stop many providers from initially prescribing it initially. It is rarely used as a long term option
4. Felbamate was very successful for LGS when it was first introduced, and one of the first medications that promoted alertness as well as weight loss. However, the risk of aplastic anemia and hepatic failure have reserved its use to a final drug choice for difficult-to-manage seizures.

There is no single treatment which provides complete or even satisfactory control of LGS. Seizures frequently persist even with multiple medications directed at the various seizure types. Furthermore, polypharmacy (multiple drug therapy) often contributes to side effects due to drug interactions. These interactions may worsen cognitive and behavioral abilities. Not only are the drug interactions between seizure medications responsible, but also interactions with other drugs used by psychiatrists and neurologists – such as antidepressants and neuroleptics — that may induce or inhibit the same mechanisms. Even if there are no significant drug interactions, the burden of multiple medications on various body organs may lead to side effects involving critical functions of central nervous system (CNS), liver, kidneys and bone marrow.

Since seizures are frequently refractory to all medications and combinations, it is important to consider other approaches. One of the most important alternative strategies is the ketogenic diet. This high fat dietary approach has been available for almost 100 years. Recent advances in understanding and creative thinking have improved its safety and tolerability. It has shown definite effectiveness against all of the seizure types associated with LGS at rates that meet or exceed any new medication. However, it is a rigorous treatment that requires the support of a comprehensive medical team (including nurses and dieticians), a major commitment by a family, and willingness of the child to avoid potentially dangerous loss of seizure control by cheating on the diet with excessive carbohydrates.

The vagus nerve stimulator (VNS) has similarly achieved a strong position as an adjunctive treatment for seizures associated with LGS, at rates comparable to those of the ketogenic diet. Although FDA-approved only for partial seizures in patients above 12 years of age, the VNS has evidence for safety and efficacy involving all seizure types at any age. Although a surgical intervention, it is a minor procedure usually performed as day surgery. It is a long-term commitment since the device must be ramped up slowly to avoid side effects such as coughing, voice alteration, and pain. The VNS has few side effects but it can cause dysphagia , increased drooling, or exacerbation of obstructive sleep apnea.

Resective surgery is an uncommon consideration in LGS because the cause of seizures is rarely restricted to an area of the brain able to be removed. However, corpus callosotomy is a reasonable treatment for refractory drop attacks. This is a disconnection of the bundle of nerve fibers that connect the two hemispheres; different technical approaches have been recommended which emphasize either partial or complete disconnection. Anterior two-thirds disconnection is the most frequently performed procedure, but complete callosotomy is often performed for those with drop attacks and severe mental disabilities.

Since seizures are frequently difficult to manage, it is important to explore treatments besides medication, including:

- Ketogenic diet
- Vagus nerve stimulator
- Corpus callosotomy or resective surgery

PROGNOSIS

Although it would be reassuring if one could provide an optimistic outlook on the future of a child with a new diagnosis of LGS, it more often has a devastating course and requires heroic team effort with many clinical resources. Up to 90% of children with LGS have developmental challenges including variable intellectual disability, behavioral abnormalities, and autistic features. Most have a static encephalopathy, but the disorder can be progressive depending on cause or it can appear progressive due to severity of seizures or side effects of medication. More than 80% will continue to have seizures as adults, although seizure types may evolve and the EEG patterns that helped to define the disorder may disappear. More than most other epilepsy syndromes, LGS carries a greater long-term mortality; several studies have estimated this as 3-7%. While it may not be true in the individual case, the diagnosis of LGS often means a life of dependency.

PREVENTION

There is no simple way to prevent the evolution of LGS since it is usually related to significant brain malformations or abnormalities, genetic-metabolic syndromes, or injuries. However, early and effective treatment may reduce the degree of disability caused by epileptic encephalopathy (either from potentially controllable frequent seizures or effects of polypharmacy).

CARETAKER AUGMENTATION

Since the probability of outgrowing epilepsy and becoming a fully independent adult is unlikely, it is especially important that parents and caregivers prepare for and coordinate transition to adulthood. The majority of children with LGS have refractory epilepsy, cognitive and behavioral disabilities, and some also have additional challenges such as cerebral palsy, blindness or hearing impairment associated with the particular cause of their epilepsy. Medical transition is only one part of a more complex process that ideally leads to maximal independence and optimal treatment.

Patients and their families may have grown up with a child neurologist and be unwilling to change a long-standing relationship. However, there are issues better managed by adult epileptologists, including drug-drug interactions with hormonal contraception, bone health, risks of long term obesity in adult-onset diabetes, and management of complex needs with far fewer resources than were available during childhood (i.e. special education, coordinated therapies and behavioral services). Furthermore, parents may be increasingly challenged by the care needs of their adult children even if they are not suffering from their own age-related conditions.

Transition should start very early with financial and legal considerations, such as estate planning, special needs trusts, and preparation of a will that includes "child care" for a disabled adult. These decisions are important to consider soon after an LGS diagnosis because of the risk of something happening to the parents before the child reaches adulthood. Parents must consider whether their child with LGS needs guardianship at the age of 18 years. This is a legal process that recognizes that the individual is incapable of making medical and financial decisions so that the parents can continue to help to make decisions for the individual. Living arrangements must be considered. It helps to have the youth with LGS on waiting lists for group homes or residential facilities even before they or the parents are ready since it may take years before one's name comes up.

Important quality of life considerations in planning for transitioning a youth with LGS to adult health care provider:

- Financial: estate planning or special needs trusts
- Legal: preparation of a will or guardianship
- Community-based services: child care, or respite care throughout the patient's life span
- Living arrangements: group homes or residential facilities

GLOSSARY/ DEFINITIONS

Atypical absence seizures – non-convulsive arrest of activity and staring, typically with slow onset and return to baseline often associated with irregular slow-spike wave on EEG.

Drop attacks – a combination of seizures with atonia (loss of motor tone) and myoclonic (sudden jerking of a group of muscles) that can lead to loss of muscle control. These unprotected falls are associated with injuries including chin lacerations, fractured teeth, concussion, etc. and may require protective head gear.

Non-convulsive status epilepticus – prolonged state of reduced awareness associated with epileptic EEG abnormalities often associated with abnormal

speech, intermittent eye deviation, automatisms or twitching. This can be difficult to identify in a child with delayed development.

Tonic seizures – rigidity without additional motor component, usually associated with generalized paroxysmal fast activity (electrodecremental response) on EEG; these are most common during non-REM sleep.

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www.lgsfoundation.org. This is the most comprehensive and independent patient advocacy voice for information and support of individuals with LGS.

www.livingwithlgs.com. This is a commercial website sponsored by Eisai which includes an excellent video that describes the challenges of living with LGS as well as video which focuses on other important topics including sleep hygiene, behavioral challenges, identifying a team of experts, and family dynamics.

www.lgstogether.com This is a commercial website sponsored by Lundbeck which offers a patient forum to share ideas and solutions.