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PHARMACOLOGICAL MANAGEMENT OF LENNOX-GASTAUT SYNDROME-A DIFFICULT -TO -TREAT FORM OF CHILDHOOD-ONSET EPILEPSY: AN OVERVIEW

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ABSTRACT

Lennox-Gastaut syndrome, or LGS, is a rare form of childhood-onset epilepsy which usually appears between the 2nd and 6th year of life. The syndrome is characterized by frequent seizures and multiple seizure types, behaviour issues, mental retardation, regression, and a resistance to medications or therapies.

The high frequency of seizures can take affect a patient's quality of life. Children are often required to wear a helmet due to the frequency of atonic seizures. Behaviour problems are a typical characteristic of LGS and can take a toll on the entire family. Individuals with Lennox-Gastaut syndrome are restricted from participating in certain activities such as some physical sports, driving, and various forms of employment. Changes in living quarters to accommodate the needs of a person with LGS are common. If an individual is wheelchair bound, an entire house or apartment may need to be remodelled for better accessibility. Shower bars and other equipment are often added in bathrooms to assist the individual. These improvements may be expensive, often leading to additional financial stress for a family. The side effects of many anti-epileptic drugs can also reduce the quality of life for a person with LGS. There is usually no single antiepileptic medication that will control seizures. Treatment for Lennox-Gastaut syndrome includes anti-epileptic medications such as valproate, lamotrigine, felbamate, or topiramate. Children who improve initially may later show tolerance to a drug or have uncontrollable seizures. In the present article, we have concentrated on characteristics, incidence, prevalence, mortality, causes, diagnosis, epidemiology, evolution and pharmacological treatment of Lennox-Gastaut syndrome. This article presents a brief review of Lennox-Gastaut syndrome with an emphasis on its possible pharmacological treatment.

KEYWORDS

Lennox–Gastaut syndrome, LGS, Lennox syndrome, tonic seizures and childhood-onset epilepsy, childhood epileptic encephalopathies, new antiepileptic drugs (AED).

INTRODUCTON

The term seizure refers to as an alteration of behaviour due to the disordered, synchronous and rhythmic firing of populations of brain neurons. The term epilepsy refers to as a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Seizures can be "nonepiletic" when evoked in a normal brain by treatments such as electroshock or chemical convulsants or "epileptic" when occurring without evident provocation[1, 2].

Lennox–Gastaut syndrome (LGS), also known as Lennox syndrome, is a difficult-to-treat form of childhood-onset epilepsy that most often appears between the second and sixth year of life, and is characterized by frequent seizures and different seizure types; it is often accompanied by mental retardation, psychological and behavioral problems. Lennox-Gastaut syndrome is a severe form of epilepsy. Seizures usually begin before 4 years of age. Seizure types, which vary among patients, include tonic (stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns), atonic (brief loss of muscle tone and consciousness, causing abrupt falls), atypical absence (staring spells), and myoclonic (sudden muscle jerks). There may be periods of frequent seizures mixed with brief, relatively seizure-free periods. Most children with Lennox-Gastaut syndrome experience some degree of impaired intellectual functioning or information processing, along with developmental delays, and behavioral disturbances. Lennox-Gastaut syndrome can be caused by brain malformations, prenatal asphyxia, severe head injury, central nervous system infection and inherited degenerative or metabolic conditions. In 30-35 percent of cases, no cause can be found.

In 1938, Gibbs *et al*. described the characteristics EEG pattern of spikes and slow frequency waves and proposed the term of "petit mal variant" to differentiate it from the petit mall absence seizures associated with rhythmic spike-and waves[3]. In 1950, Lennox and Davis found clinical correlation between this type of EEG and patients with multiple epileptic crisis[4]. Based upon the contributions of Lennox and colleagues, Gastaut[5] and Dravet and colleagues of the Marseille school, the term Lennox–Gastaut syndrome (LGS) was adopted.

CHARACTERISTICS OF LENNOX–GASTAUT SYNDROME

As a general rule, the age of seizure onset in LGS patients is between the ages of two and six; however, this does not exclude the possibility that seizures can begin before age two, or after age six. The syndrome shows clear parallels to West syndrome, enough to suggest a connection. Daily multiple seizures are typical in LGS. Also typical is the broad range of seizures that can occur, larger than that of any other epileptic syndrome. The most frequently occurring seizure types are: tonic, which are often nocturnal (90%); the second most frequent are myoclonic seizures, which often occur when the patient is over-tired[6].

Atonic, atypical absence, complex partial, focalized and tonic–clonic seizures are also common. Additionally, about half of patients will suffer from status epilepticus, usually the nonconvulsive type, which is characterized by dizziness, apathy, and unresponsiveness. The seizures can cause sudden falling (or spasms in tonic, atonic and myoclonic episodes) and/or loss of balance, which is why patients often wear a helmet to prevent head injury. In addition to daily multiple seizures of various types, children with LGS frequently have arrested/slowed psycho-motor development and behavior disorders.

The syndrome is also characterized by an interictal (between-seizures) EEG featuring slow spike-wave complexes.

INCIDENCE AND PREVALENCE

Approximately 5% of children with epilepsy have LGS, and it is more common in males than females. Whereas some children seem perfectly normal prior to the development of seizures, others already had some form of epilepsy, such as West syndrome, which is seen in 20% of patients before (symptomatic) LGS. West syndrome is characterized by Blitz Nick Salaam seizures, and typically evolves into LGS in the second year of life.

MORTALITY AND MORBIDITY:

The mortality rate ranges from 3% to 7%.

CAUSES

There is no uniform cause: in 20% of the concerned, the LGS develops from the West syndrome. The medical history frequently includes infantile spasms or focalized and generalized seizures.

The most common type of LGS (70–78%). This does not mean that LGS patients in other categories have no symptoms whatsoever; rather, it means that there is an identifiable underlying pathology responsible. This includes encephalopathy (brain damage) or another disease or developmental disorder. Frequent causes include tuberous sclerosis, hereditary metabolic diseases, inflammatory brain disease such as encephalitis, meningitis, and toxoplasmosis; hypoxia–ischemia injury and other birth injuries; and lesions of the frontal lobe. These patients tend to have a worse prognosis than the idiopathic ones.

In up to one-third of cases no cause can be found. These cases are referred as cryptogenic or idiopathic Lennox–Gastaut syndrome. Patients are considered to have idiopathic LGS if they were developing normally prior to the seizures, and cryptogenic if a cause is suspected by unknown. Not all investigators mention the second category.

Lennox–Gastaut syndrome, drug resistant/drug refractory epilepsy have been recorded with neurovisceral porphyrias including acute intermittent porphyria, hereditary coproporphyria and variegate porphyria. Care must be taken to avoid porphyrinogenic anti-seizure drugs in these cases. Diagnosis may be difficult in children who require enzyme or DNA testing.

DIAGNOSIS CRITERIA:

LGS belongs to the group of severe infantile epileptic syndromes (epileptic neonatal encephalopathy with suppression-burst, West syndrome, severe myoclonic epilepsy of infancy), which represent the most distressing epileptic encephalopathies of infancy. LGS is characterized by the following symptomatic triad: several epileptic seizures (atypical absences, axial tonic seizures and sudden atonic or myoclonic falls); diffuse slow interictal spike wave in the waking EEG (< 3 Hz) and fast mythmic bursts (10 Hz) during sleep; slow mental development associated with personality disturbances.

Although this last element is not indispensable for the diagnosis, it is manifested in a high percentage of cases[7].

LGS is a controversial entity due to the difficulty of establishing its semiological electro clinical features and some authors have considered that severe cases of myoclonic astatic epilepsy represent myoclonic variants of LGS. However the myoclonic phenomenon is not predominant in LGS and this review focuses only on Lennox-Gastaut syndrome, as strictly defined above. LGS is defined by the International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders as cryptogenic or symptomatic generalized epilepsy[8].

EPIDEMIOLOGY

Although the incidence is estimated to 0.1 in 100,000 inhabitants per year, the prevalence is high (5-10% of epileptic patients), representing 1-2% of all childhood epilepsies.

The onset occurs between 2 and 7 years. Cryptogenic cases have a later onset. Males seem to be more frequently affected. No family cases of LGS have been reported.

EVOLUTION

LGS, one of the most severe epileptic syndromes in childhood is refractory to treatment and tends to become chronic. Mental retardation, which is frequently associated with the condition[9], especially in symptomatic cases[10], tends to worsen as disease progresses, although it is not the absolute rule. Psychosis may manifest during disease evolution.

Patients with symptomatic LGS, especially with pre-existent West syndrome, frequent seizures and repeated episodes of status epilepticus, have the worse prognosis.

The mortality rate is around 5% but is rarely bound to the evolution of the epilepsy itself, as death is often related to accidents or episodes of tonic status epilepticus.

PHARMACOLOGICAL MANAGEMENT AND TREATMENT

LGS is essentially characterized by a lack of responsiveness to treatment, especially the classic anti-epileptic drugs (AED). LGS seizures are often treatment resistant, but this does not mean that treatment is futile. Options include anticonvulsants, anesthetics, steroids such as prednisone, immunoglobulins, and various other pharmacological agents that have been reported to work in individual patients.

PHARMACOLOGICAL

No scientific study has shown any drug to be highly efficacious for treatment of LGS, and its best treatment remains uncertain.

Rufinamide
(Banzel), lamotrigine, topiramate and felbamate may help as add-on therapy[11].

APPROVED FIRST-LINE DRUGS

- alproates (valproic acid, sodium valproate and valproate semisodium)
- felbamate
- benzodiazepines, specifically clonazepam, nitrazepam, and clobazam

Nitrazepam and Clobazam are not approved in the USA.

SECOND-LINE DRUGS

In 1999, Dr. Sachdeo and colleagues at the University of Medicine and Dentistry of New Jersey and the Robert Wood Johnson Medical School in New Brunswick reported that 33% of the patients in the topiramate group experienced a minimum 50% reduction in seizures (specifically drop attacks and tonic–clonics), compared with 8% in the placebo group[12]. It was also found to be effective as an adjunctive therapy in a review published by Drs. Edith Alva Moncayo and Antonio Ruiz in March 2003.

Dr. Motte and colleagues at the American Memorial Hospital at Reims, France reported in 1997 that lamotrigine was effective in the treatment of LGS, with the most common side effect in the treatment group relative to placebo being colds or viral illnesses. Two years later, it was approved by Health Canada for adjunctive therapy in Lennox Gastaut in adults and children[13]. The United States Food and Drug Administration approved it for that in August 1998[14]. Felbamate is indicated in the use of LGS in the event that everything else fails[15], and was found to be superior to placebo in controlling treatment resistant partial seizures and atonic seizures[16, 17]. However, it has been known to cause aplastic anemia and liver toxicity.

UNAPPROVED, OFF-LABEL, AND INVESTIGATIONAL DRUGS :

Vigabatrin was found by Feucht et al. to be an effective add-on in patients whose seizures were not satisfactorily controlled by valproate. Out of 20 children, only 1 experienced a serious side effect (dyskinesia)[18].

Zonisamide showed promise in an overview of controlled and uncontrolled trials conducted in Japan. However, in a physician survey conducted December 2004, only 28%

of Lennox–Gastaut and West syndrome patients improved on zonisamide.

SURGICAL : Surgical treatment is an exceptional option in cases of well-located lesions. Callosotomy has been shown effective in intractable atonic seizures, but it does not improve other seizure types and the focal crises can even increase.

OTHER

Ketogenic diet : A ketogenic diet is a diet that causes ketosis, a state in which there is an excessive amount of ketones in the body. It is becoming increasingly popular for treating intractable epilepsy. The ketogenic diet has been used in intractable infantile epilepsies[19].

Intravenous immunoglobulin therapy : Intravenous immunoglobulin therapy has been used in Lennox–Gastaut syndrome as early as 1986, when van Rijckevorsel-Harmant and colleagues used it in seven patients with ostensibly idiopathic LGS and saw EEG improvement and decreased seizure frequency in six of them[20]. Clinical trials of intravenous immunoglobins in high doses have been shown effectiveness in reduced series.

CONCLUSION

It may be concluded that Lennox-Gastaut syndrome (LGS) belongs to the group of severe childhood epileptic encephalopathies. The disorder is defined as cryptogenic or symptomatic generalised epilepsy, which is characterized by several epileptic seizures (atypical absences, axial tonic seizures, and sudden atonic or myoclonic falls). The disease is characterised by slow mental development with personality disturbances. Incidence is estimated in 1:1,000,000 inhabitants per year, and the prevalence to 5-10% of epileptic patients, 1-2 % of all childhood epilepsies. The onset occurs between 2 and 7 years. The most characteristic clinical manifestations in LGS consist of tonic seizures (17-92%), atonic seizures (26-56%) and typical absences (20-65%). Diagnosis is based on the presence of specific EEG recordings. Treatment is difficult as LGS is usually refractory to conventional therapy. Some of the new antiepileptic drugs (AED) (Felbamate, Lamotrigine, Topiramate) have proven efficient in the control of seizures in LGS.

Since the patient having Lennox-Gastaut syndrome is suffering from slow mental development, they need love and caring attitudes from family. The long-term management of the patient with LGS should evolve into a 'partnership-like' relationship between the attendees at the chronic care facility and/or the patient's family and the physician. Early education of the family and caregivers helps foster better decision making later in the course of this most severe of epilepsy syndromes. Children and adults with LGS are commonly referred to epileptologists with frequent daily seizures and significant dose-related side effects from multiple anti-epileptic drugs (AEDs). Parents and other caregivers often project unrealistic treatment objectives to their treating physician. These unrealistic therapeutic goals usually encourage polypharmacy and increased dose-related side effects of AEDs that can be as debilitating as the seizures. Once the physician makes the diagnosis of LGS, the time taken to educate the family and outline realistic treatment objectives usually pays dividends in the future by simplifying treatments, reducing dose-related.

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