Journal of Clinical Images & Reports

SCIENTIFIC Research and Community

Research Article

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Childhood Lennox-Gastaut Syndrome, Low Set Ears, Unilateral Cryptorchidism: A New Variant

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ABSTRACT

Background: Childhood Lennox-Gastaut syndrome is a heterogeneous epileptic encephalopathy with onset between the age of one and seven years. It is associated with more than one seizure type that are drug-resistant, a slow spike-wave activity in the EEG recording and mental retardation .The syndrome was first described by William Gordon Lennox in 1950, and later by Henri Gastaut in 1966. The condition was first called "Lennox-Gastaut syndrome" by Ernst Niedermeyer in 1968. The association of Lennox-Gastaut syndrome with low set ears and cryptorchidism has not been reported before.

Patients and Methods: A two and three months boy was referred late during February, 2022 because of seizures that started during the last week of December, 2021 and were not controlled with multiple anti-epileptic drugs. The diagnosis was made and an evidence-based therapeutic approach is described.

Results: When the boy was first seen he was still experiencing frequent generalized tonic clonic seizures that may last for about ten minutes and myoclonic seizures, despite he was receiving four anti-seizure drugs in good doses including valproic acid, clobazam, levetiracetam, topiramate. The drugs made the boy sleepy most of the day. Brain MRI was performed during August, 2021 for the evaluation of developmental retardation showed normal findings. The presence of more than seizure type, the EEG recording, and the developmental and retardation together with resistance of seizures to polytherapy allowed confident diagnosis of Lennox-Gastaut syndrome. Anti-epileptics were replaced with other drugs and evidence-based agents were used for neuroprotection and improving development and mental retardation. Treatment was associated with a significant improvement.

Conclusion: A new variant of childhood Lennox-Gastaut syndrome is reported and the experience with its early treatment is described.

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Received: March 16, 2022; **Accepted:** March 22, 2022; **Published:** March 29, 2022

Introduction

Childhood Lennox-Gastaut syndrome is an epileptic encephalopathy with onset between the age of one and seven years. It is associated with more than one seizure type that are drug-resistant, a slow spike-wave activity in the EEG recording and mental retardation [1-6]. The syndrome was first described by William Gordon Lennox (Figure-1A) in 1950, and later by Henri Gastaut (Figure-1B) in 1966 [1]. The condition was first called "Lennox-Gastaut syndrome" by Ernst Niedermeyer (Figure-1C) in 1968 [5].

Markand (1977) emphasized that Lennox-Gastaut syndrome is a heterogeneous condition resulting from a variety of pathologic processes (static or progressive) that are associated with more than one type of intractable seizures (commonly including tonic-clonic, minor motor, and absence seizures), a slow spike-wave activity in the EEG recording, in addition mental retardation. Markand reported 83 patients with Lennox-Gastaut syndrome; most of them had the onset of seizures during the first two years of life. 53 of the patients had identifiable cerebral insult [6].

Niedermeyer (1979) et al emphasized the occurrence of myoclonic seizures in Lennox-Gastaut syndrome [7].

Zimmerman and colleagues (1977) reported the Computerized axial tomography (CT) findings in 38 patients with Lennox-Gastaut syndrome. Twenty patients had normal imaging study, and 18 patients had abnormalities in CT-scan including diffuse cerebral atrophy eight patients, and cerebellar atrophy in two patients. Zimmerman and colleagues suggested increasing the possibility of increase of diffuse abnormalities with advancing age [8].

Synacthen Depot was used in the treatment of childhood Lennox-Gastaut syndrome during the 1970s [9,10], and the commonly used anti-epileptics included carbamazepine, clonazepam, and phenobarbital [11, 12, 13].



Figure 1A: William Gordon Lennox (July, 18, 1884-July, 21, 1960) was an American epileptologist who pioneered the use of electroencephalography (EEG) for the diagnosis and treatment of epilepsy

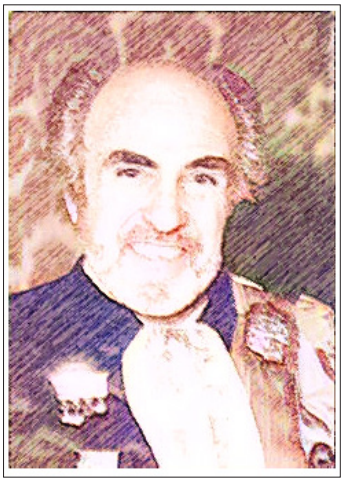


Figure 1B: Henri Jean Pascal Gastaut (April 15, 1915- July 14, 1995), a French epileptologist



Figure 1C: Ernst Friedrich Lepold Niedermeyer (1920-2012), a French electroencephalographer

Patients and Methods

A two and three months boy was referred late during February, 2022 because of seizures that started during the last week of December, 2021 and were not controlled with multiple anti-epileptic drugs. The diagnosis was made and an evidence-based therapeutic approach is described.

Results

When the boy was first seen he was still experiencing frequent generalized tonic clonic seizures that may last for about ten minutes and myoclonic seizures, despite he was receiving four anti-seizure drugs in good doses including valproic acid, clobazam, levetiracetam, topiramate. The drugs made the boy sleepy most of the day (Figure-2A).



Figure 2A: The anti-epileptic drugs made the boy sleepy most of the day

The boy had left undescended testis, and an operation was performed before about one year during February, 2021, but failed and the testis was removed. Biopsy showed well-defined testicular tissues with many seminiferous tubules containing only Sertoli cells, with thick basement membrane and atrophic epididymis.

The boy also had low set ears (Figure-2B), and significant developmental delay as he was able to sit alone (Figure-2C), but was not able to stand without support (Figure-2D). He was saying only Ba Ma, and not saying any word.



Figure 2B: The boy also had low set ears



Figure 2C: The boy was able to sit alone



Figure 2D: The boy had significant developmental delay and was not able to stand without support
The parents were not relatives.

EEG performed on the 11th of January, 2022, about two weeks after the start of seizures showed the awake state a fairly organized background with posterior dominant rhythm slower than the normal for the patient's age, and fairly reactive to eye opening and closure. During sleep, background showed with normal sleep architecture and sleep elements.

Intermittent photic stimulations before and after sleep were associated with a photo-paroxysmal (Waltz type 4) in the form of generalized spikes/polyspikes and wave complexes.

During EEG recording, the patient developed sudden jerking movements that were associated with generalized polyspikes/ wave complexes during the awake and sleep states, but mainly during the sleep state.

During the interictal period, there were frequent short runs of generalized spikes wave complexes and generalized polyspikes wave complexes.

The EEG report suggested generalized epilepsy of myoclonic type A second EEG during another time showed during the awake state, a poorly organized background with a slowing dominant posterior rhythm that was not reactive to eye opening and closure. Sleep record background showed abnormal sleep architecture. In this EEG record, there were frequent transient short runs of multi-focal spike wave discharges. The spikes varied from moment to moment in duration and location; appearing as focal occipital and few seconds later appear as originating from multiple foci. There were frequent and generalized runs of generalized spikes/ polyspikes wave discharges that were sometimes lateralized to the left with asymmetry of the epileptiform discharges.

The EEG report of this recording suggested an epileptic encephalopathy, both focal and generalized.

Brain MRI was performed during August, 2021 for the evaluation of developmental retardation showed normal findings.

The presence of more than seizure type, the EEG recording, and the developmental and retardation together with resistance of seizures to polytherapy allowed confident diagnosis of Lennox-Gastaut syndrome.

The decision was made to replace all the anti-epileptic drugs gradually over few days with carbamazepine (220 mg daily in three divided doses), clonazepam (0.25mg twice daily), and acetazolamide 125 mg daily). Injectable piracetam (200 mg given by intramuscular injection daily in the morning for 5 days), and oral citicoline (200 mg daily in the morning were added with aim of improving his developmental progress and overcoming excessive drowsiness associated with the use of multiple epileptic drugs based on our published extensive experiences with use of these drugs in mental and developmental retardation.

After one week, treatment reduced the frequency and duration of seizures, but didn't stop seizure completely. Oral citicoline was continued. In addition, Injectable piracetam (200 mg given by intramuscular injection on alternate in the morning; three doses over six days), and injectable cerebrolysin (1ml given by intramuscular injection on alternate in the morning; three doses over six days) based on our published extensive experiences with use of these drugs in mental and developmental retardation.

After two weeks, treatment significantly reduced the frequency and duration of seizures, but didn't stop seizure completely. The boy was more alert and was able to stand alone for few seconds (Figure-3), and the parents reported obvious improvement in vocalization.



Figure 3: After two weeks, the boy was more alert and was able to stand alone for few seconds

The decision was made to add Lamotrigine, 12.5 mg once in the morning. Oral citicoline increased to 300 mg daily and injectable piracetam (250 mg given by intramuscular injection on alternate in the morning; three doses over six days).

Discussion

Markand (1977) emphasized that Lennox-Gastaut syndrome is a heterogeneous condition. It has been reported to occur in association with Aicardi syndrome (Yamamoto et al, 1985) [14], organoid nevus syndrome (Clancy et al, 1985) [15], Dandy-Walker malformation (Hori, 1987) [16], Rett's syndrome, (Olmos Garcia de Alba, et al (1987) [17], Coffin-Siris syndrome (Alembik, et al 1988) [18], tuberous sclerosis (Gupta et al, 1989) [19].

The Lennox-Gastaut Syndrome is an important cause of drug resistant epilepsy, and anti-epileptics and non-anticonvulsant drugs have been used [13].

Pinder et al (1976) emphasized that clonazepam, a broad spectrum anti-epileptic is useful a many types of epilepsy including the Lennox-Gastaut syndrome and myoclonic epilepsies. Pinder et al also emphasized that clonazepam has been shown to be effective patients with resistant to other antiepileptic drugs. Initial success

with clonazepam can be followed by loss of effect, but benefit can often be restored, at least initially, by temporary interruption and re-institution of treatment. Common side-effects of clonazepam include drowsiness and fatigue which generally disappear with continuation of treatment [13].

Reiss and Oles (1996) recommended considering the use of acetazolamide (a carbonic anhydrase inhibitor) in refractory epilepsy including generalized tonic-clonic seizures, myoclonic [20].

Motte et al (1997) reported a placebo-controlled study which included 169 patients with Lennox-Gastaut syndrome. 79 patients aged 3 to 25 years were treated with lamotrigine for 16 weeks of lamotrigine, and 90 patients received placebo in addition to their other antiepileptic drugs. 33% of the patients treated with lamotrigine and 16% of patients who placebo experienced a reduction of at least 50% in the frequency of seizures (P= 0.01). Lamotrigine was well-tolerated. Motte et al suggested that lamotrigine can be used effectively in the treatment of Lennox-Gastaut syndrome [21].

The use of piracetam, citicoline, and cerebrolysin is associated with a neuroprotective effect, and has been increasingly reported to be used in repairing brain damage and improving cognition in a variety of neurological conditions including cerebral palsy and mental retardation [22-37].

injectable cerebrolysin solution contains free amino acids (85%) plus 15% biologically active low molecular weight amino acids including neuro-peptides (Brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, ciliary neurotrophic factor [22]. Injectable cerebrolysin has been used beneficially and safely in many childhood neurological and psychiatric conditions including idiopathic mental retardation [23,24], cerebral palsy [25,26], myelomeningocele [27], pediatric juvenile spinal muscular atrophy [28,29], pediatric Charcot Marie Tooth disease [30,31], kernicterus [32,33], agenesis of corpus callosum with colpocephaly [34,35].

Citicoline, which has been increasingly considered as new water soluble B vitamin, and is considered to be a form of the essential nutrient choline. It has been increasingly used with beneficial effect in the treatment of many childhood neurological and psychiatric disorders including, pervasive developmental disorders including Rett syndrome, and kernicterus [36-37].

The use of anti-epileptics alone in the treatment of Lennox-Gastaut syndrome is not expected to improve all the aspects of the disorder, and the use of evidence-based agents for neuroprotection and improving development and mental retardation is not only justified, but also recommended.

The association of Lennox-Gastaut syndrome with low set ears and cryptorchidism has not been reported before. In our patient, Testicular biopsy showed well-defined testicular tissues with many seminiferous tubules containing only Sertoli cells, with thick basement membrane and atrophic epididymis.

The work of Nistal and colleagues (1990) suggested that Sertoli-cell-only can be associated with cryptorchidism [38].

Conclusion

A new variant of childhood Lennox-Gastaut syndrome is reported and the experience with its early treatment is described.

Acknowledgement

The author would like to express his gratitude for the parents of the child who willingly accepted publishing his photos.

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