Clinical characteristics and responsiveness to treatment in Lennox–Gastaut syndrome

A retrospective hospital audit

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ABSTRACT

Objectives: To describe the clinical profile of Lennox-Gastaut syndrome (LGS) patients and to assess the best antiepileptic drug combination.

Methods: Patient files of all children diagnosed with LGS at King Abdul-Aziz University (KAUH), Jeddah, Kingdom of Saudi Arabia between January 2000 to January 2005 were retrieved and analyzed. Details on clinical data, and disease related variables were collected. Treatment trial, last drug combination, maintenance dosage, seizure frequency, and duration before and after treatment, and the overall effect in reducing seizures were recorded.

Results: Fifty-four patients were identified with a male: female ratio of 2.4:1 with age range of 10 months–14 years. A history of febrile convulsion was found in 11 (20%) patients, history of infantile spasm was found in 14 patients (26%), mental retardation in 52 patients (96%), and hypotonia in 13 patients (24%). All patients had abnormal EEG that meets the diagnostic criteria. Brain CT scan was abnormal in 32 (65%) patients. Brain MRI was abnormal in 17 (23%) patients. Neuroradiological abnormalities varied from non-specific atrophy to hippocampal sclerosis and calcification. Metabolic screening carried out for 11 patients (20%) was normal. All patients were on a 3-drug combination at some stage of their disease. The most frequent combination was sodium valproate and lamotrigine. Intravenous immunoglobulin was used in 2 patients with temporary improvement; ketogenic diet was tried in one patient, which did not add much to fit control.

Conclusions: The severe nature and intractability of LGS emphasize the need for active and efficacious treatment, which can improve the prognosis as a whole. Different combinations of new anticonvulsants could achieve significant seizure control and could modify the quality of life for these patients. Each patient needs to be considered individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.

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Epilepsy occurs in 0.5-1% of the population and begins in childhood in 60% of the cases,[1] and approximately 10-20% are refractory to medical treatment.[1] Lennox-Gastaut syndrome (LGS) accounts for only approximately 4% of all childhood epilepsy, yet LGS is a very important epilepsy syndrome because of resistance of the seizures to treatment with routine anti-epileptic drugs (AEDs). Multiple types of seizures, mental retardation or regression, and abnormal EEG with generalized slow spike-and-wave discharges (1.5-2 Hz) characterize LGS. The most common seizure types are tonic-axial, atonic, and absence seizures, but we can observe myoclonic, generalized tonic-clonic, and partial seizures. Lennox

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and Gastaut[2,3] first described LGS. In most of the cases, it results from a previous encephalopathy and is primary in the rest of the cases. The optimum treatment for LGS remains uncertain, and no study to date has shown any one drug to be highly efficacious.[4] Different treatments have been tried including, phenobarbitone, sodium valproate, steroid, ketogenic diet, with patients still having seizures. We reviewed our cases of LGS to find out what drug combinations helped our patients in decreasing their seizure frequencies.

Methods. In a retrospective, open-label study, the patient files of all children diagnosed with LGS at King Abdul-Aziz University (KAUH), Jeddah, Kingdom of Saudi Arabia between January 2000 to January 2005 were retrieved and analyzed. Seizures were carefully documented, and a pediatric neurologist made the diagnosis after clinical examination and review of electroencephalograms. The diagnostic criteria used in this study depends on the presence of all of the following triad:[1] severe multiple seizure types including atypical absence, and seizures resulting in falls, axial tonic, massive myoclonic, and atonic seizures.[2] Abnormal EEG demonstrating slow spike and wave (< 2.5 hertz) and bursts of fast rhythms at 10-12 hertz during sleep,[3] and static encephalopathy and learning disabilities, associated with mental retardation. Details on the age of onset, sex, associated diagnosis, past medical history, family history, examination, laboratory results were recorded. Treatment trial, last drug combination, maintenance dosage, seizure frequency, and duration before and after treatment and the overall effect in reducing seizures were also recorded.

Results. Fifty-four patients were identified with a male:female ratio of 2.4:1 with age at onset ranging from 10 months to 14 years; mean age was 52 months. The majority (96%) was a product of full term pregnancy and spontaneous vaginal delivery with normal neonatal period. Positive consanguinity was found in 16 patients (30%), and positive family history of epilepsy was found in 12 patients (22%). Prior history of febrile convulsion was documented in 11 (20%) patients, and history of infantile spasm was found in 14 (26%) patients; associated diagnoses are shown in **Table 1**. Examination showed mental retardation in 52 (96%) patients, hypotonia in 13 (24%) patients. All patients had abnormal EEG that meets the diagnostic criteria. Brain CT scan was carried out for 49 (91%) patients, 17 (35%) were normal, 32 (65%) were abnormal. Brain MRI was carried out for 25 (46%) patients, 9 (15%) were

Table 1 - Etiology of Lennox-Gastaut syndrome (N=54).

Associated diagnosis	No. of patients
Spastic quadriplegic cerebral palsy	12
Post viral encephalitis	3
Down syndrome	2
Tuberous sclerosis	2
Congenital heart disease	1
Myelomeningocele	1
Road traffic accident	1
No associated diagnosis	32

Table 2 - Neuroradiological findings in Lennox-Gastaut syndrome (N=45).

Neurological abnormalities	No. of patients
Brain atrophy	24
Arachnoid cyst	4
Hippocampal-sclerosis	4
Calcification	3
Agenesis of corpus callosum	3
Agenesis corpus callosum + arachnoid cyst	2
Dandy Walker malformation	2
Demyelinating	2
Hemi-megalencephaly	1

Table 3 - Drug combinations used during treatment.

Drug combination	No. of patients
Sodium valproate + lamotrigine	25
Lamotrigine alone	6
Sodium valproate + lamotrigine + clonazepam	5
Phenobarbitone + lamotrigine	5
Sodium valproate + clobazam	4
Lamotrigine + clobazam	3
Phenobarbitone + clobazam	2
Carbamazepine + sodium valproate + lamotrigine	2
Sodium valproate + phenobarbitone	2

normal, 17 (23%) were abnormal. Neuroradiological abnormalities varied from non-specific atrophy to hippocampal sclerosis, isolated calcification, and arachnoid cyst as shown in **Table 2**. No surgical intervention was carried out for the arachnoid cysts. Metabolic screen carried out for 11 (20%) patients was normal. The mean follow-up duration was 30.1 months with a range of 8-59 months. All patients were on a 3-drug combination at some stage of their disease. The last drug combinations which achieved the best fit control, and more than 50% reduction in seizure frequency is shown in **Table 3**. The most frequent combination was sodium valproate and lamotrigine. Intravenous immunoglobulin was used in 2 patients with temporary improvement. Ketogenic diet was tried in one patient, which did not add much to fit control.

Discussion. Lennox-Gastaut syndrome is one of the intractable epilepsy syndromes that are difficult to treat; symptomatic cases are due to diverse cerebral conditions, which are usually bilateral, diffuse, or multifocal, involving cerebral gray matter.[5] In our retrospective study, we found 54 patients with the syndrome, the male:female ratio was 2.4:1 and we found this male predominance in other studies.[5,6] The prior history of febrile seizure we found in 11 patients (20%), corresponding with the well-known fact that some of the intractable epilepsies are preceded by a history of febrile seizure, especially a prolonged one.[7] Also, the prior history of infantile spasm we found in 14 patients (26%) is in agreement with previous reports projecting that LGS followed infantile spasm in 27-50% of cases.[8,9] The association between LGS and other syndromes such as Down syndrome and tuberous sclerosis is not new,[10,11] and may add to the difficulty in managing epilepsy in such conditions. Neuro-radiological finding in cases of LGS varies from non-specific atrophy to hippocampal sclerosis and calcification, in agreement with the fact that LGS is among the most common childhood epileptic syndrome associated with congenital malformations of the central nervous system.[12] One of the limitations of this retrospective study is that the responsiveness to the antiepileptic treatment was mainly focused on fit control and there was little data available in our records on the neuropsychological outcome. We tried different drugs regimen, 100% of our patients used a 3-drug combination at one stage. New AEDs such as lamotrigine used in this group, as an add on drug showed a very good response as 25% became seizure free, 50% of patients had more than 50% reduction in seizure frequency, and 25% remained to have seizure with same frequency. This agrees with Motte et al[13] that lamotrigine was an effective and well-tolerated treatment for seizures associated with LGS. We observed the best response with sodium valproate and clobazam, or lamotrigine, in agreement with other studies.[14-17] We tried intravenous immunoglobulin in only 2 patients with temporary improvement, in contrast to reports from other studies.[18-20] We tried a ketogenic diet in only one patient, which was poorly tolerated, and there was no change in seizure frequency, while some studies[21] showed a better response. The treatment of LGS has improved for some patients through the availability of vagal nerve stimulation. If adequate drug treatment and vagal nerve stimulation provide insufficient seizure control, partial callosotomy may be an option for the treatment of frequent, intractable, and disabling drop attacks based on the best available evidence.[22]

In conclusion, the severe nature and intractability of LGS emphasizes the need for active and efficacious treatment, which can improve the prognosis as a whole. Different combinations of new AEDs could achieve significant seizure control, and could modify the quality of life for these patients. We need to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.

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