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Clinical evaluation and long term prognosis of patients with Lennox-Gastaut syndrome

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Summary

Aim: The aim of this study was to retrospectively evaluate clinical features, treatment and prognosis of 20 patients followed up as Lennox-Gastaut Syndrome in ESOGU in the Division of Pediatric Neurology.

Material and Method: Multiple different types of seizure, diffuse spike-wave pattern(<3 Hz) on electroencephalogram, psychomotor retardation were the diagnostic criteria for Lennox-Gastaut Syndrome. The patients who had no etiologic reason were described as the idiopathic type. Prenatal, natal and postnatal risk factors, seizure and clinical features, neurodevelopmental status, treatment and prognostic features were evaluated.

Results: Thirteen patients were female, seven were male; male/female ratio was 1,9. Nineteen patients were described as the symptomatic type. Hypoxic ischemic encephalopthy was the most common risk factor. Sixty percent of the patients had a history of infantile spasms. Generalized tonic, generalized tonic clonic and atonic drop attacks were the most common seizure types. Speech impairment and microcephaly were the most frequently seen neurologic findings. Diffuse spike-wave activity (1-3 Hz/s) on EEG, bioelectrical status epilepticus and 9-14 Hz/s fast activity discharges were the most commonly seen discharges. The most common neuroimaging finding was cerebral atrophy. Sixty percent of the patients suffered from a large number of seizures per day despite multiple antiepileptic drugs. The most commonly used antiepileptic drugs were valproate sodium, clobazam, lamotrigine and topiramate.

Conclusions: The prognosis of Lennox-Gestaut Syndrome is poor due to either recurrent seizures or mental deterioration. Seizure control can not be provided despite the use of multiple anti-epileptic drugs. New antiepileptic drugs are needed. *(Turk Arch Ped 2012; 47: 49-54)*

Key words: Antiepileptic drugs, EEG, Lennox-Gastaut Syndrome, prognosis, refractory seizure

Introduction

Lennox-Gestaut syndrome is an epileptic syndrome with poor prognosis which occurs in the childhood (1). It constitutes 3-10% of all childhood epilepsies (2,3). It is characterized by multiple different types of seizures which start in the childhood, cognitive dysfunction and diffuse slow spike-wave (1-3 Hz/s) complexes on electroencephalography (1). It is difficult to make a diagnosis, since clasical clinical and EEG findings are not present initially (4). Approximately half of the subjects have a history of infantile spasm (5). It is thought that autoimmunity plays a role, although the pathogenesis is not clear (6). Lennox-Gestaut syndrome may occur related to asphyxia, central nervous system infection, cranial trauma, congenital infection and brain malformation or may be idiopathic. The prognosis is poorer in subjects in whom the etiological cause is found (5,7). Although multiple antiepileptic drugs are used, seizures can not be controlled most of the time. Uncontrolled seizures and mental retardation effect the prognosis of LGS negatively (4).

The aim of this study was to retrospectively evaluate clinical features, treatment and prognosis of 20 patients followed up as Lennox-Gastaut Syndrome in ESOGU in the Division of Pediatric Neurology.

Material and Method

In this study, 20 patients who were followed up in Eskişehir Osmangazi University Medical Faculty, Division of Pediatric Neurology with a diagnosis of LGS were evaluated retrospectively. The following diagnostic criteria for a diagnosis of LGS were used: presence of multiple different types of seizures, diffuse slow (<3 Hz/s) spike-wave pattern on EEG and psychomotor retardation with different levels. Patients who had no risk factor, who had normal preseizure psychomotor

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development and normal neuroimaging findings and in whom no etiologic cause could be found were defined as idiopathic LGS and the others were defined as symptomatic LGS. Patients with a low apgar score in whom resuscitation was applied at birth and who were ventilated mechanically were considered as hypoxic ischemic encephalopathy (HIE). In all patients, prenatal, perinatal and postnatal risk factors, etiological cause, age of onset of seizures, seizure types, seizure frequency, neuromotor development, neurological examination, EEG, cranial imaging and metabolic tests (if necessary) were evaluated. Psychosocial-motor development in the patients below the age of 6 was evaluated with Denver II Developmental Screening Test and mental evaluation of the patients above the age of 6 was done using Stanford-Binet or Weshler Intelligence Scale. Seizure types were determined according to the history taken from the families and clinical observations during examination and EEG recording.

EEG recording was made using Nihon Kohden Neurofax 7310 F EEG device.

The efficiency of antiepileptic drugs (AED) used in the long-term follow-up of the patients, EEG findings and complications were evaluated.

Results

20 patients (13 male (65%) and 7 female (35%)) whose ages ranged between 1,5 and 16 years (mean 10.75) were evaluated retrospectively. The mean follow-up time of the patients was 7.5 (1-13) years. Mean age at onset of seizures was found to be 14.6 (1-3.5) months and mean age at the time of diagnosis of LGS was found to be 4,5 (1.5-5.5) years. In 17 of the patients (85%), LGS developed after three years of age. 19 patients (95%) were defined as symptomatic LGS and one patient (5%) was defined as idiopathic LGS. The most common etiologic cause was HIE (65%). The other etiologic causes were cortical dysplasia in 3 patients (15%), central nervous system infection in one patient (5%), neonatal sepsis in one patient (5%) and intracranial bleeding in one patient (5%). 2 of the patients (10%) had a history of abortus treath and one (5%) patient (5%) had a history of intrauterine hydrocephaly. Three of the patients (15%) had a familial history of epilepsy and one patient (5%) had a history of febrile convulsion. 60% of the patients (12 patients) had a history of infantile spasm. In 10 (83.3%) of 12 patients with a history of infantile spasm had multiple seizures daily and the age at diagnosis was 4.5 years.

All patients had moderate-severe mental retardation. Mental and motor retardation was less severe in patients whose seizures started later and who had normal neuromotor development before seizures. The most common neurological findings included speech disorder (60%) and microcephaly (35%) (Table 1). 7 (35%) of 12 (60%) patients who had speech disorder had no meaningful word and 5 (25%) had fonation disorder. 5 patients (25%) had spasticity and one patient (5%) was using wheelchair. 4 patients (20%) were bedridden. A total of 7 patients (35%) had neuropsychiatric findings (4 patients (20%) had autistic findings, 2 patients (10%) had nervousness and one patient (5%) had hyperactivity). All patients with neuropsychiatric findings had a history of infantile spasm. 2 of the patients with autistic findings had HIE and 2 had cortical dysplasia in the etiology.

75% of the patients (15 patients) had more than two different seizures and 25% of the patients (5 patients) had two types of seizures. The most common seizure types were diffuse tonic (80%) and diffuse tonic-clonic (75%) seizure. Atonic-drop attack was observed in 12 patients (60%), partial seizure was observed in 8 patients (40%), atypical absence was observed in 7 patients (35%) and myoclonic seizure was observed in 5 (25%) patients (Table 2). Convulsive status epilepticus developed in 3 patients (15%) during the follow-up period. It recurred two times in one patient. When EEG findings of the patients recorded at different times were evaluated, 1-3 Hz/s spike slow wave activity was observed in all patients (Figure 1), while bioelectrical status epilepticus was observed in 30% of the patients, 9-14 Hz/s rapid activity discharge was observed in 20% of the patients (4 patients), bitemporal and frontal spike-slow wave activity was observed in 15% of the patients (3 patients) and multiple spike discharges were observed in 10% of the patients (2 patients) (Table 2).

60% of the patients (12 patients) with Lennox-Gastaut syndrome had multiple seizures daily. In 4 patients (20%), seizures were controlled in a period ranging between 6 months and 4 years (one patient has had no seizure for 4 years, one patient has had no seizures for 3 years, one patient has had no seizure for 1 year and one patient has had no seizure for 6 months). The seizure frequencies of the patients are shown in Table 2. 10 (83.3%) of 12 patients who had more than one seizure daily had a history of infantile spasm and their seizures had started before the age of one.

Table 1. Neurological findings in patients with Lennox-Gastaut syndrome (n=20)

Finding*	Number	%
Mental retardation	20	100
Speech disorder	12	60
Microcephaly	7	35
Spasticity	5	25
Hemiparesis	4	0
Autistic findings	4	20
Dysphagia	3	15
Nistagmus	2	10
Ataxia	1	5
Hyperactivity	1	5

* More than one finding in one patient

15 patients (75%) had cranial MRI finding. Cranial magnetic resonance imaging (MRI) findings were as follows: brain atrophy in 7 patients (35%), cortical dysplasia (incomplete lissencephaly, pachygria, polymicrogria, colpocephaly) in 3 patients (15%), periventricular leucomalacia (PVL) in 3 patients (15%), corpus callosum dysgenesis in 3 patients (15%) and porencephalic cyst in one patient (5%) (Table 3). Intracranial bleeding was found on cranial tomography in one patient. The mental status of four patients (20%) with a normal cranial imaging was better compared to the others and they could walk without support. While seizures were controlled in 2 of the patients who had normal cranial MRI, two had multiple seizures daily.

Table 2. Seizure characteristics and EEG findings in patients with Lennox-Gastaut syndrome (n=20)

Seizure type	Number*	%
Diffuse tonic	16	80
Diffuse tonic clonic	15	75
Atonic-drop attack	12	60
Partial seizures	8	40
Atypical absence	7	35
Myoclonic	5	25
Seizure frequency		
More than one seizure	12	60
1-2 seizures every 1-3 months	4	20
Subjects with controlled seizures	4	20
EEG finding		
1-3 Hz/sn spike slow wave activity	20	100
Bioelektrical status epilepticus	6	30
Rapid activity decharges (9-14 Hz/s)	4	20
Bitemporal and frontal spike-slow wave activity	3	15
Multiple spike decharge (6-7 Hz/s)	2	10

Table 3. Cranial MRI findings in patients with Lennox-Gastaut syndrome (n=19)

MRI findings*	n=15	%
Normal	4	25
Brain artophy	7	35
Cortical dysplasia (pachygria, polymicrogria, lissencepahly, colpocephaly)	3	15
Periventricular leucomalacia	3	15
Corpus callosum dysgenesis	3	15
Porencephaly	1	5

* More than one finding in one patient
MRI: Magnetic resonance imaging

All patients were receiving multiple antiepileptic drugs. The most commonly used antiepileptic drugs included sodium valporate, clobazam, lomotrigine and topiramate. 8 patients (40%) were given intravenous gammaglobulin (IVIG). After IVIG treatment no change was observed in the number of seizures in 5 patients (62.5%), while seizures decreased by 50% for 2-6 months in three patients (37.5%). The frequency of seizures was evaluated, when clobazam, topiramate and lamotrigine were added to treatment while using multiple AEDs. The frequency of seizures did not change in 6 (40%) of 15 patients who were started clobazam. It decreased by 50% in 3 (20%) patients and seizures became frequent again approximately 4 months (1-9) later. Seizure-free status was provided in 5 patients (33.3%) for a mean period of 5.5 (1-12) months. Seizures decreased in 4 (50%) of 8 patients who received topiramate and two patients (25%) remained seizure-free for 8 months-2,5 years. The frequency of seizures did not change in 7 (77.8%) of 9 patients who received lomotrigine and seizures decreased by 50% in one patient (11%). Seizures were controlled for 6 months in one patient (11%) (Table 4).

A picture of hyperamonemia and encephalopathy related to valproate sodium developed in one patient. One patient was lost because of sepsis and diffuse intravascular coagulation. The long-term follow-up of the patients are shown in Figure 2.

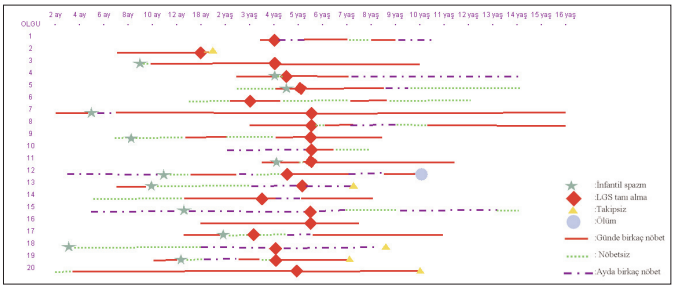

Figure 1. 1-3 Hz/s spike-wave activity on EEG

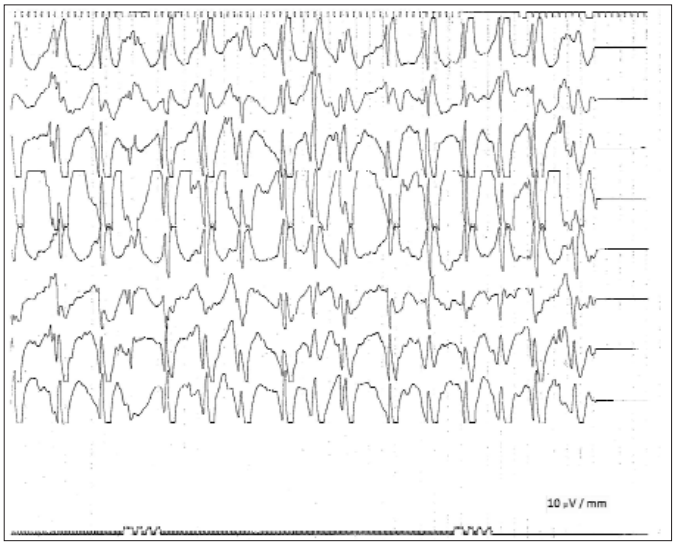

Figure 2. Long-term follow-up in patients with Lennox-Gastaut

Table 4. The effect of IVIG, Clobazam, Topiramate and Lamotrigine on the frequency of seizures

Antiepileptic drugs	No change (Number of patients	Decrease by 50% (Number of patients)	Cessation of seizures		Total (Number of patients)
			Number of patients	Tiem of seizure-free state	
IVIG	5	3	-	-	8
Clobazam	6	4	5	1-12 months	15
Topiramate	2	4	2	8 ay-2.5 years	8
Lamotrigine	7	1	1	6 months	9

IVIG: Intravenous gammaglobulin

Discussion

LGS which constitutes approximately 10% of childhood epilepsies occurs between the ages of 1 and 8 years and is most commonly observed at the ages of 3-5 years (3,8). Boys are affected more frequently than girls (5,9). In this study, 15% of the patients were diagnosed as LGS at the age of 1-3 years, 40% were diagnosed at the age of 3-5 years and 45% were diagnosed at the age of 5-8 years. Male/female ratio was found to be 1,9. Prenatal, perinatal and postnatal hypoxia, central nervous system (CNS) infections, CNS malformations, neurocutaneous and neurometabolic diseases and trauma play a role in the etiology of symptomatic LGS (3,4). In 30% of the patients, no etiology can be found (9). In this study, 19 of the patients (95%) had symptoms and one patient (5%) was idiopathic. The most common etiologic causes included HIE and cortical dysplasia. Lower rate of LGS in the literature might arise from the fact that the patients were evaluated retrospectively and the diagnosis of HIE was made by history. Since only one patient had idiopathic LGS, no comparison was made with the symptomatic group in terms of seizure frequency and prognosis. It has been reported that there is no significant difference between symptomatic and idiopathic LGS patients in terms of seizure type and frequency, EEG findings and response to treatment (10,11).

Brain demage plays a role in the etiology of Lennox-Gastaut syndrome with a higher rate and genetic causes are reported with a lower rate. 18-50% of the patients have a history of infantile spazm. LGS which develops after infantile spasm starts at a younger age and tonic seizures are observed more frequently. Neuromotor development is affected more severely (5). While the risk of development of Lennox-Gastaut syndrome is lower in patients with West syndrome who are given ketogenic diet, prednisolone and ACTH, it has been reported that no relation was found between the age at the time of diagnosis of West syndrome and the etiology (12). In our study, 60% of the patients had a history of infantile spasm and 83.3% of the patients with a history of infantile spasm had multiple seizures daily. The age of development of Lennox-Gastaut sydnrome was not different from the patients with no history of infantile spasm.

In patients with Lennox-Gastaut sydrome, mental retardation of different levels, behavior problems and neurological findings occur according to the underlying cause. Microcephaly, brain palsy, hypotonia, ataxia, pyramidal findings and dysphagia may be observed (13,14). Behavior problems, depression and autistic findings are observed frequently in patients with LGS in relation to brain demage, resistant seizures, lack of social stimulus and side effects of antiepileptic drugs used (4). In this study, all patients had moderate or severe mental retardation. Mental and motor retardation was less severe in patients whose seizures started at a later period. The most commonly observed neurological findings included speech disorder, microcephaly, hemiparesis, spasticity, dysphagia, ataxia and nistagmus. 20% of the patients had autistic findings, 10% had nervousness and 5% had hyperactivity. All patients with neuropsychiatric findings had a history of infantile spasm. West syndrome is reported to be related to Autistic Spectrum Disorders (15,16).

In this study, the most common findings on cranial MRI included brain atrophy, cortical dysplasia, corpus callosum dysgenesis, periventricular leukomalacia and porencephalic cyst. 25% of the patients had no abnormal MRI finding. Çalışkan et al. (14) found the most common cranial MRI finding as brain atrophy in 68 LGS patients. Goldsmith et al. (10) reported that MR findings had no value on the prognosis of seizures. In this study, cranial imaging was found to have no effect on seizure frequency. However, mental and motor status was better in patients who had normal cranial imaging.

While tonic, atonic, atypical absence seizures constitute the typical seizure types in LGS, myoclonic, myoclonic astatic, focal seizures and non-convulsive status epilepticus may also be observed. The most commonly observed seizures include tonic and atypical absence seizures (17). In this study, the most commonly observed seizure types included diffuse tonic, diffuse tonic clonic and atonic-drop attacks. The reason of lower frequency of atypical absence seizures may be the fact that families can not recognize seizures. In a total of three patients (15%), status epilepticus developed during the follow-up period (two times in one patient). Different EEG findings can be observed according to various seizure types. Typical interictal EEG finding in Lennox-Gastaut syndrome is diffuse slow spike-wave activitiy. During sleep 10-20 Hz/s rapid rythm can be

observed, but this is not specific for Lennox-Gastaut syndrome. In more than 50% of the patients, non-convulsive status epilepticus is observed (9). Non-convulsive status epilepticus was observed in 30% of the patients and rapid activity discharges were found in 20% of the patients.

Although multiple AEDs are used in Lennox-Gastaut syndrome, seizures can not be controlled. Therefore, a very diciplined approach is needed in treatment. The aim of treatment should be to decrease the number of drop attacks to a minimal, increase school success by decreasing daytime seizures and to prevent prolongation of seizures and non-convulsive status (18). Multiple drug treatment should be avoided, since multiple AED treatment increase some seizures and has cognitive and psychological side effects (4). Antiepileptic treatment should be selected according to LGS etiology and seizure type. Generally, the first option is valproic acid and lamotrigine, rufinamide, topiramate, clobazam, felbamat and levetiracetam are added to treatment (18). In children with Lennox-Gastaut syndrome, lamotrigine and topiramate is efficient in atonic and tonic clonic seizures and valproic acid is efficient in drop attack, atypical absence and myoclonic seizures (19-21). In studies performed in patients with Lennox-Gastaut syndrome, it has been reported that clobazamine leads to sedation with a lower rate, decreases seizures by 50-100% in more than 50% of the patients, maintains its efficiency of 42% after more than one year of use and provides seizure-free state for more than 6 months in 72% of the patients (22,23). It is reported that seizures of the patients with LGS are decreased with intravenous gammaglubulin treatment (24). In this study, the most commonly used AEDs included valproate sodium, clobazam, lamotrigine and topiramate. Seizures of three patients (37.5%) decreased by 50% for 2-6 months with intravenous gammaglobulin. The seizure frequency was evaluated, when clobazam, topiramate and lamotrigine were added to treatment, while using multiple AEDs and it was found that seizure-free state was provided for 1-12 months in 33.3% of the patients in whom clobazam was added, for 8 months-2.5 years in 25% of the patients in whom topiramate was added and for 6 months in 11% of the patients in whom lamotrigine was added.

The prognosis in LGS is poor because of mental retardation, behavior disorder and resistant seizures (4). Sympthomatic LGS, history of infantile spasm, a diagnosis made before the age of three, frequent seizures and presence of status attacts and persistence of diffuse spike-slow walve pattern indicate poor prognosis (9). In this study, history of infantile spasm, onset of seizures before the age of one year and retarded neuromotor development before seizures were found to be poor prognostic factors. Especially in symptomatic LGS, seizure resistance, neurological retardation rate and severity can vary according to the underlying cause. Autry et al. (25) reported that the risk of mortality increased 14 fold. Feeding difficulty and dysphagia may occur in relation to seizures and as a result aspiration penumonia may develop (15). In this study, dysphagia was present in three patients. A picture of hyperamonemia and encephalopathy developed in relation to valproate sodium in one patient and one patient (5%) was lost because of sepsis and diffuse intravascular coagulation.

Conlcusively, the prognosis of LGS which is an epileptic syndrome of the childhood is poor because of resistant seizures and disorder of mental function. Neurologic retardation may occur as a result of the underlying cause and resistant seizures and the patient may even become bedridden. Since seizures can be controlled in very few patients with present antiepileptics, new epileptics are needed. The aim of treatment should be to decrease the frequency and time of seizures and avoid multiple AEDs because of side effects. Patients with Lennox-Gastaut syndrome should be supported not only medically, but also socially together with their families and team work should be adopted.

Conflict of interest: Not reported.

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