Late-onset Lennox-Gastaut syndrome

Diagnostic evaluation and outcome

Kelsey M. Smith, MD, Jeffrey W. Britton, MD, and Gregory D. Cascino, MD

Neurology: Clinical Practice October 2018 vol. 8 no. 5 397-402 doi:10.1212/CPJ.0000000000000527

Correspondence

Dr. Cascino
gcascino@mayo.edu

Abstract

Background

We describe the clinical features and outcome in patients with late-onset Lennox-Gastaut syndrome (LGS).

Methods

Adult patients evaluated between January 1, 2000, and March 1, 2017, who presented with onset of LGS ≥ 10 years were identified. Data abstracted included age at seizure onset, seizure types, etiology, treatments, EEG and neuroimaging results, cerebrospinal fluid (CSF) findings, and autoimmune evaluation.

Results

Ten patients (8 females) were identified. The mean age at onset of seizures consistent with LGS was 16.5 years (range, 10–32 years). Seizure types included tonic, atonic, and tonic-clonic seizures (all), myoclonic seizures ($n = 3$), and atypical absence seizures ($n = 7$). Five patients had normal intellectual function at onset. Prolonged video-EEG monitoring recorded seizures and generalized interictal epileptiform discharges in all. All patients had drug-resistant epilepsy (range of anti-seizure drugs tried, 7–16). Two patients had a history of intrathecal methotrexate to treat acute lymphoblastic leukemia. Two patients had malformations of cortical development. CSF analysis ($n = 5$) showed a mild elevation in the protein level without other abnormalities. Autoantibody determinations in the serum ($n = 4$) or the CSF ($n = 5$) and genetic testing ($n = 5$) were negative. At final follow-up, all but 1 patient was disabled and required a caregiver, and none were driving. One patient died of probable sudden unexpected death in epilepsy (SUDEP).

Conclusions

Late-onset LGS represents a rare, treatment-resistant generalized epilepsy that is disabling and may be associated with progressive cognitive impairment. The elevated CSF protein level in our cohort could have been due to high seizure burden but increases the possibility of an inflammatory component to the pathophysiology of this disorder.

RELATED ARTICLE

Editorial

Inflammatory theory of diseases: What has it got to do with late-onset LGS?

[Page 375](#)

Lennox-Gastaut syndrome (LGS) is a potentially catastrophic epileptic syndrome accounting for 1%–10% of childhood epilepsies. It is characterized by multiple seizure types, including tonic, atypical absence, and atonic seizures. An underlying cause is identified in approximately 75% of patients, which may include malformations of cortical development or hypoxic-ischemic injuries, and the etiology is cryptogenic in the remainder.¹ Many patients with LGS develop the epileptic syndrome as a sequelae of infantile spasms.² Patients usually present by 8 years of age; the peak incidence is between 3 and 5 years. Seizures are often highly refractory to multiple antiseizure drugs (ASDs). The ASDs most commonly used in this disorder include

Department of Neurology, Mayo Clinic, Rochester, MN.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Lennox-Gastaut syndrome is a potentially catastrophic epileptic syndrome accounting for 1%–10% of childhood epilepsies.

clobazam, felbamate, lamotrigine, rufinamide, topiramate, divalproex sodium, and more recently cannabidiol.^{3,4} The characteristic EEG pattern in patients with LGS is diffuse background slowing, generalized 1.5- to 2.5-Hz spike-and-wave discharges, and generalized paroxysmal fast activity.⁴ Intellectual disability is common and may be progressive.

Late-onset LGS has been described in a few isolated reports, including in 2 patients with 15q duplication.^{5,6} The clinical features and outcome have not been well characterized previously. A previous study identified 3 patients who were considered to have late-onset LGS and demonstrated reduced fractional anisotropy in the white matter of the brainstem, suggesting that brainstem dysfunction may play a role.³ Our aim was to characterize the clinical features, laboratory and EEG findings, and outcome in a cohort of patients with late-onset LGS.

Methods

We retrospectively identified patients with epilepsy consistent with late-onset LGS from medical records of all patients with seizure disorders who underwent treatment at Mayo Clinic in Rochester, Minnesota, from January 1, 2000, to March 1, 2017. Patients aged 18 years or older were identified using the following search terms: Lennox-Gastaut, Lennox-Gastaut variant, intractable generalized idiopathic epilepsy, and drug-resistant generalized epilepsy. A total of 453 consecutive patients were identified. From this group, the following inclusion criteria were applied: (1) multiple seizure types that invariably included tonic and atonic seizures; (2) undergone a comprehensive epilepsy evaluation at our institution to include long-term video-EEG recordings in the inpatient epilepsy monitoring unit; (3) the electroclinical correlation supported the syndromic diagnosis of LGS; and (4) age at clinical onset of LGS at ≥ 10 years. Data extracted for purposes of this study included seizure types, etiologic factors, comorbidities, EEG results, neuroimaging findings, therapeutic interventions, and psychosocial outcome.

Standard protocol approvals, registrations, and patient consents

An institutional review board approved the use of humans for this study.

Data availability

Anonymized data will be shared by request to any qualified investigator.

Results

Demographics and clinic features

Ten patients (8 females) were identified (table). The mean age at onset of seizures consistent with LGS was 16.5 years (range, 10–32 years), and the mean age at seizure onset was 12.2 years (range, 5–19 years). Two patients had seizure onset before age 10 years but did not have the ictal semiology and electroclinical findings to support the diagnosis of LGS until age 14 and 32 years, respectively. One patient had absence seizures beginning at age 9 years and was seizure free on valproic acid until age 14 years. The other patient had generalized epilepsy beginning at age 5 years, which was well controlled on medication until age 32 years. The mean age at first appointment at Mayo Clinic was 27.8 years (range, 15–47), and patients were followed up for 36.2 months (range, 0–116 months). Two patients had a family history of epilepsy, and 1 patient had a history of “febrile-related” seizures. All patients had tonic, atonic, and generalized tonic-clonic seizures. Myoclonic seizures were reported in 3 patients and atypical absence in 7 patients. Five patients had normal intellectual function before LGS onset. Two patients had a history of status epilepticus, both after the onset of LGS.

EEG

All patients had inpatient video-EEG recordings in the epilepsy monitoring unit. Seizures were recorded in all patients. Seizure types included atonic ($n = 7$), tonic ($n = 6$), atypical absence ($n = 5$), generalized tonic-clonic ($n = 1$), myoclonic ($n = 1$), and focal ($n = 1$). The patient with focal seizures also had generalized atonic seizures. In all patients, the interictal and ictal EEG patterns supported the diagnosis of LGS (figures 1 and 2). Generalized paroxysmal fast activity was recorded in all patients, and slow spike and wave was identified in 2 (18%). Interictal generalized atypical spike or polyspike and wave discharges were recorded in all patients. In addition, interictal focal/multifocal epileptogenic discharges were recorded in 8.

Neuroimaging

All patients had a MRI head study (table). The brain morphology was normal in 7 patients. Two patients had malformations of cortical development. One patient had a congenital brain anomaly (colpocephaly).

Cerebrospinal fluid

Five patients underwent cerebrospinal fluid (CSF) analysis. The mean CSF protein level was mildly elevated at 54 mg/dL (range, 43–68 mg/dL; normal, 0–35 mg/dL). The remainder of the CSF findings were unremarkable—mean nucleated cell count: 1.6 (range, 1–4; normal value, 0–5); mean oligoclonal bands ($n = 4$): 0 (normal value, <4); and mean immunoglobulin G index: 0.54 (range, 0.48–0.6; normal value, <0.85).

Etiology

An underlying etiology was suggested by history in 3 of the 10 patients. Two patients had a history of acute lymphoblastic leukemia (ALL) as young children. They both received

Table Pertinent clinical information for each patient

Patient	Sex	Family history	Age at LGS onset	Age at seizure onset	Seizure types	Intellectual function at seizure onset	Brain MRI	Possible etiology	CSF protein level (mg/dL)	No. ASDs tried	VNS	Outcome
1	Female	N	16	16	T, A, G	Normal	Low-lying cerebellar tonsils just below the foramen magnum level		46	15	Y	Encephalopathy, continues to have persistent atonic seizures
2	Male	N	32	5	T, A, G, AA	Normal	Small probable arachnoid cyst in the left frontal region		66	12	Y	Able to maintain job, frequent subtle daily tonic seizures
3	Female	N	14	9	T, A, G, M, AA	Abnormal	Modest ventricular dilatation, colpocephaly	ALL with IT MTX and radiation		11	N	Encephalopathy, persistent daily seizure, behavioral dyscontrol
4	Female	Y	26	15	T, A, G, M, AA	Normal	Normal		43	12	Y	Encephalopathy, persistent seizures, died of presumed SUDEP
5	Male	N	19	19	T, A, G	Abnormal	Mild global cerebral volume loss, right cerebellar chronic infarct	Complex neuropsychiatric history with outside diagnosis of PANDAS		9	N	Continues to have persistent daily seizures
6	Female	N	15	15	T, A, G, AA	Abnormal	Single nonenhancing 6 mm focus in the paramedian inferior left cerebellum, some atrophy			12	Y	VNS helped with atypical absence. Had DBS placed, which originally helped with clusters of seizures, but continued to have daily atonic seizures
7	Female	N	11	11	T, A, G, AA	Normal	Gray matter of heterotopia in the lateral wall of the atrium of the right lateral ventricle with transmantle dysplasia	ALL with IT MTX and malformation of cortical development	68	12	Y	Encephalopathy, with persistent atonic seizures
8	Female	N	11	11	T, A, G, AA	Normal	Cerebellar atrophy, mild diffuse cerebral atrophy, small corpus callosum. Nonspecific T2 changes			16	Y	Encephalopathy, with persistent seizures
9	Female	N	11	11	T, A, G	Abnormal	Pachygyria, cortical developmental anomaly with diffuse bilateral posterior frontoparietal and temporooccipital lissencephaly and band heterotopia. Dilatation of the lateral ventricles bilaterally	Malformation of cortical development		7	Y	Continues to have persistent atonic seizures
10	Female	Y	10	10	T, A, G, M, AA	Abnormal	Mild generalized cerebellar and cortical cerebral atrophy		47	11	N	Continues to have persistent seizures

Abbreviations: A = atonic; AA = atypical absence; ALL = acute lymphoblastic leukemia; ASD = antiseizure drug; DBS = deep brain stimulation; G = GTC; IT = intrathecal; LGS = Lennox-Gastaut syndrome; M = myoclonic; MTX = methotrexate; N = no; PANDAS = pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection; SUDEP = sudden unexpected death in epilepsy; T = tonic; VNS = vagus nerve stimulation; Y = yes. Normal CSF protein level = 0–35 mg/dL.

intrathecal methotrexate as part of their treatment regimen, and one also received cranial radiation. One patient had a complex neuropsychiatric history with an outside diagnosis of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and underwent previous treatment with IV immunoglobulin. No definitive cause could be confirmed in 7 patients despite an extensive evaluation. Genetic workup was limited but uninformative. Two patients had unrevealing testing for *EPM2A* and *EPM2B* genes for progressive myoclonic epilepsy. One patient had normal *SCN1A* and *SCN1B* gene testing. Chromosomal microarray was normal in 2 patients. One patient had a comprehensive epilepsy gene panel revealing variants of uncertain significance in *KMT2D*, *SCN3A*, *FARS2*, *CLCNKA*, *SLC46A1*, and *ATP13A2* genes but no known pathologic mutation. Autoantibody determinations for autoimmune epilepsy were obtained in 5 patients; serum and CSF were checked in 4 patients and CSF alone in one. One patient did have potassium channel and acetylcholine receptor ganglionic neuronal antibodies in the serum, which on repeat testing 4 months later were not present. Testing for *LGI1* and *CASPR2* was not performed, likely due to the timing of this testing.

Treatment

The mean number of ASDs tried was 11.7, with a median of 12 (range, 7–16). Medications and treatment modalities used in the 10 patients included clobazam ($n = 9$), felbamate ($n = 8$), divalproex sodium ($n = 10$), rufinamide ($n = 10$), medical marijuana ($n = 2$), dietary therapy (ketogenic and/or modified Atkins diet) ($n = 5$), vagus nerve stimulation (VNS) ($n = 7$), and deep brain stimulation targeting bilateral

In the current patient series, the diagnosis of LGS occurred at a mean age of 16.5 years, much older than the typical presentation of this catastrophic epileptic syndrome.

centromedian and anterior nucleus of the thalamus ($n = 1$). None of the patients underwent corpus callosotomy.

Outcome

At final follow-up, 9 patients required a caregiver and did not live independently because of intractable epilepsy, including 4 who had normal intellectual function at onset. No patients were able to drive. Psychiatric comorbidities were identified in 4 during the follow-up period, including behavioral dyscontrol, obsessive compulsive behaviors, psychosis, and depression with hallucinations. One patient died of probable sudden unexpected death in epilepsy (SUDEP).

Discussion

LGS is a rare and disabling disorder that usually presents in early childhood with a peak age at onset between 3 and 5 years and is an epileptic encephalopathy with progressive

Figure 1 EEG with features of Lennox-Gastaut syndrome (LGS)

Generalized paroxysmal fast activity (first arrow) and generalized 2-Hz slow spike wave (second arrow) in a 35-year-old patient with late-onset LGS (patient 1).

Figure 2 Ictal EEG

Generalized high-amplitude sharply contoured slow wave (first arrow), followed by diffuse electrodecremental response (second arrow) in a 35-year-old patient with late-onset Lennox-Gastaut syndrome (patient 1) during an atonic seizure.

impairment in cognitive and behavioral abilities.^{1,2} The epileptic syndrome may be more difficult to diagnose in adults because of varied and atypical presentations.⁷ The clinical course of late-onset LGS has not been well described previously. Diagnostic and clinical features may evolve in patients over time and may not all be present at seizure onset.¹ In the current patient series, the diagnosis of LGS occurred at a mean age of 16.5 years, much older than the typical presentation of this catastrophic epileptic syndrome. Most patients were female in contrast to the male predominance of 5 to 1, which has been reported in LGS.⁴ All patients in the present study had drug-resistant generalized epilepsy with considerable progressive comorbidities. The treatment modalities commonly used in the management of patients with LGS, including ASDs and VNS, had limited efficacy in our patients. Seven of the patients required the placement of a VNS. Only 1 patient reported efficacy with VNS and this was only in regard to atypical absence seizures; drop attacks continued. The overall outcome was socially and physically disabling similar to what is reported in younger patients. Only 1 patient remained independent and able to maintain a job. This patient had normal intellectual function at LGS onset and seizures beginning at age 5, which were well controlled on medication until age 32 years. He had tried 12 ASDs and was on 4 medications at final follow-up continuing to experience frequent generalized tonic seizures. All other patients were essentially dependent, including the other 4 patients who had a normal intellectual function at onset. The dependency in the latter patients was due to the risks and falls posed by their disabling seizures. One patient died of suspected SUDEP. This patient had normal intellectual function at seizure onset. She had used 12 ASDs, ketogenic diet, and VNS. Despite these interventions, she continued to have difficulty to control seizures and progressive cognitive difficulties.

The etiology of LGS was cryptogenic in most of the patients in the present series. Two patients had a history of ALL as young children. They both received intrathecal methotrexate as part of their treatment regimen and one also received cranial radiation. Seizures are seen in 8%–13% of patients with ALL, usually during acute treatment of the disease.⁸ Intractable epilepsy resulting from treatment of ALL is less frequently described. A previous case series described 5 patients treated for ALL who all went on to develop epilepsy requiring trials of multiple AEDs.⁸ In addition, patients have been previously described who developed LGS during childhood after treatment.⁹ Late-onset LGS has been described in patients with genetic mutations, including 15q duplication and trisomy 21.^{5,6,10} In addition, late onset of atonic seizures have been described in 17 previously reported patients who had generalized epilepsy onset at a younger age.¹¹ Park et al.³ described 3 patients who were considered to have late-onset LGS with normal intellectual ability.³ In these patients, reduced fractional anisotropy in the white matter of the brainstem was present, suggesting that brainstem dysfunction may contribute to the pathophysiology of late-onset LGS.³ The authors speculated that late-onset LGS may have less damaging effects on cognition, given the brain has already gone through critical developmental stages.³ Despite this in our reported cases, progressive cognitive impairment was frequent.

The clinical and EEG features supported the diagnosis of late-onset LGS in all patients. Generalized paroxysmal fast activity was invariably present in this series. Slow spike wave was less frequently identified. These findings are typical of normal-onset LGS. Generalized paroxysmal fast activity is a feature that is likely to persist into adulthood in LGS.⁴ In a retrospective study of 27 patients with LGS followed into

adulthood by Ferlazzo et al.,¹² 44% had normalization of the background activity, with 74% having a reduction in epileptic discharges during wakefulness. However, diffuse fast rhythms in sleep persisted in all patients.¹² Generalized paroxysmal fast activity is associated with nocturnal tonic seizures.¹³

CSF analysis was performed in 5 patients. All cases demonstrated a mildly elevated CSF protein level without pleocytosis, suggesting a mild degree of inflammation. A previous study looking at CSF after epileptic seizures demonstrated an elevated CSF protein level in 60.9%.¹⁴ An elevated protein level was more common in patients with generalized seizures.¹⁴ It is hypothesized that a transient disturbance of the blood-brain barrier during seizure activity is what leads to the elevation of the protein level in the CSF. We do not have data in our study to demonstrate the time between the last seizure and CSF analysis. However, given the high seizure burden, it is plausible that ongoing seizure activity could have increased the CSF protein in our cohort. Nonetheless, the elevation of the CSF protein level raises the question whether an underlying inflammatory pathogenic mechanism is present in these patients.

There are important limitations of this study including the size of the patient cohort and the observational and retrospective study design. Two of our patients did have seizure onset before age 10 years but were well controlled on medications. The electroclinical correlation changed at an older age, justifying the diagnosis of late-onset LGS. This case series demonstrates the severity of this epileptic syndrome, even with onset at an older age, and the devastating psychosocial effects. Drug-resistant epilepsy was invariably present, and progressive cognitive impairment was a common feature.

Author contributions

K.M. Smith: acquisition of data and drafting and editing of the manuscript for intellectual content. J.W. Britton and G.D. Cascino: study concept and design and drafting and editing of the manuscript for intellectual content.

Study funding

No targeted funding reported.

Disclosure

K.M. Smith reports no disclosures. J.W. Britton receives research support from Grifols, GW Pharma, and from Mr. and Mrs. David Hawk charitable gift for epilepsy

TAKE-HOME POINTS

- Lennox-Gastaut syndrome usually presents between 3 and 5 years of age but rarely can have onset later in life.
- Late-onset Lennox-Gastaut syndrome is a disabling epileptic syndrome, which can be associated with progressive cognitive impairment.
- Elevated CSF protein levels were found in all patients tested in our cohort, which could be related to seizure activity but raises concern for an inflammatory component.

research. G.D. Cascino serves as an Associate Editor for *Neurology* and receives royalty payments for technology related to high frequency nerve stimulation to treat lower back pain (Nevro, 2013). Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received May 23, 2018. Accepted in final form July 16, 2018.

References

1. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia* 2011;52(suppl 5):3–9.
2. Hussain SA. Epileptic encephalopathies. *Continuum (Minneapolis)* 2018;24:171–185.
3. Park KM, Hur YJ, Kim SE. Brainstem dysfunction in patients with late-onset Lennox-Gastaut syndrome: voxel-based morphometry and tract-based spatial statistics study. *Ann Indian Acad Neurol* 2016;19:518–522.
4. Mastrangelo M. Lennox-Gastaut syndrome: a state of the art review. *Neuropediatrics* 2017;48:143–151.
5. Rocha J, Guerra C, Oliveira R, Doria S, Rego R, Rosas MJ. Late-onset Lennox-Gastaut syndrome as a phenotype of 15q11.1q13.3 duplication. *Epileptic Disord* 2012;14:159–162.
6. Orrico A, Zollino M, Galli L, Buoni S, Marangi G, Sorrentino V. Late-onset Lennox-Gastaut syndrome in a patient with 15q11.2-q13.1 duplication. *Am J Med Genet A* 2009;149A:1033–1035.
7. Pina-Garza JE, Chung S, Montouris GD, Radtke RA, Resnick T, Wechsler RT. Challenges in identifying Lennox-Gastaut syndrome in adults: a case series illustrating its changing nature. *Epilepsy Behav Case Rep* 2016;5:38–43.
8. Fasano RE, Bergen DC. Intractable epilepsy in patients treated for childhood acute lymphocytic leukemia. *Seizure* 2009;18:298–302.
9. Gonzalez-Otarula KA, Alvarez BM, Dubeau F. Drug-resistant epilepsy after treatment for childhood acute lymphocytic leukaemia: from focal epilepsy to Lennox-Gastaut syndrome. *Epileptic Disord* 2016;18:447–453.
10. Ferlazzo E, Adjien CK, Guerrini R, et al. Lennox-Gastaut syndrome with late-onset and prominent reflex seizures in trisomy 21 patients. *Epilepsia* 2009;50:1587–1595.
11. Lipinski CG. Epilepsies with atypical seizures of late onset. *Epilepsia* 1977;18:13–20.
12. Ferlazzo E, Nikanorova M, Italiano D, et al. Lennox-Gastaut syndrome in adulthood: clinical and EEG features. *Epilepsy Res* 2010;89:271–277.
13. Al-Banji MH, Zahr DK, Jan MM. Lennox-Gastaut syndrome: management update. *Neurosciences (Riyadh)* 2015;20:207–212.
14. Chatzikonstantinou A, Ebert AD, Hennerici MG. Cerebrospinal fluid findings after epileptic seizures. *Epileptic Disord* 2015;17:453–459.