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ORIGINAL ARTICLE

Late infantile epileptic encephalopathy: A distinct developmental and epileptic encephalopathy syndrome

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Abstract

Objective: Within the spectrum of developmental and epileptic encephalopathy (DEE), there are a group of infants with features that are distinct from the well-recognized syndromes of early infantile developmental and epileptic encephalopathy (EIDEE), infantile epileptic spasm syndrome (IESS), and Lennox–Gastaut syndrome (LGS). We refer to this condition as late infantile epileptic encephalopathy (LIEE). Our objective was to highlight the characteristics of this group by analyzing patients who exhibit prototypical features.

Methods: From July 2022 to May 2023, we searched for LIEE features in pediatric patients who underwent epilepsy follow-up at the University of Chicago Comer Children's Hospital.

Results: Out of 850 patients evaluated, thirty patients (3.5%) were identified with LIEE based on electroclinical characteristics. These patients had an average onset of epilepsy at 6.8 months and an average onset of LIEE features at 18.1 months. The epilepsy etiology was most commonly genetic and metabolic (50%), followed by congenital cortical malformations (23%), acquired structural abnormalities (20%), and unknown (7%). The predominant seizure types were myoclonic–tonic (70%), spasm–tonic (50%), epileptic spasms (47%), tonic (43%), and myoclonic (43%) seizures. All patients reported a history of either spasm–tonic or myoclonic–tonic seizures in addition to other types. All patients had EEGs showing discontinuity, electrodecrements, or both along with diffuse slowing, background voltages between 100 and 300 μV, and superimposed multifocal, diffuse epileptiform discharges. Every patient, except one, fulfilled the definition of drug-resistant epilepsy, and all reported either moderate-to-severe or severe developmental delay.

Significance: Late infantile epileptic encephalopathy (LIEE) is characterized by several unique clinical and electrographic features. Typically, LIEE manifests in patients during the second year of life and occurs before two years of age, hence late infantile onset. The condition is commonly observed in infants with

This is an original work not presented at other meetings or conferences nor submitted for other publications.

symptomatic epilepsy. Myoclonic–tonic and spasm–tonic seizures are the quintessential seizure types. The inter-ictal EEG exhibits more organization and lower voltages than seen with hypsarrhythmia and lacks the defining EEG characteristics of EIDEE, IESS, or LGS. We propose that LIEE is a distinct electroclinical syndrome within the spectrum of developmental and epileptic encephalopathies.

KEYWORDS

developmental and epileptic encephalopathy, late infantile epileptic encephalopathy, late-onset spasms, myoclonic–tonic seizures, spasm–tonic seizures

1 | INTRODUCTION

Developmental and epileptic encephalopathy (DEE) is a term used to describe cerebral dysfunction resulting from the underlying cause, epilepsy, or both.[1] There is a subset of DEEs in which there is compelling evidence that the regression is directly tied to the epilepsy itself, where the "epileptic encephalopathy" component of DEE is most evident. Infantile epileptic spasm syndrome (IESS) is perhaps the clearest example. Professor Shunsuke Ohtahara proposed that these epileptic encephalopathies exist on an age-dependent electroclinical spectrum with clinical and electroencephalographic features that are influenced by the maturation of the nervous system.[2,3] These include early infantile developmental epileptic encephalopathy (EIDEE) formally known as Ohtahara syndrome, infantile epileptic spasm syndrome (IESS) formally known as West syndrome, and Lennox–Gastaut syndrome (LGS).

Throughout the past, several decades scattered publications have noted, however, that there are patients that present with apparent epileptic encephalopathies associated with spasms and other seizures in-between the common ages of presentation for IESS and LGS. For this, a separate condition has been proposed with various names including "Late-onset Infantile Spams," "Infantile Epileptic Encephalopathy with Late-onset Spasms," and "Late Infantile Epileptic Encephalopathy." There are differences in the nuances of the descriptions, but common features are onset of spasms, spasm–tonic, and myoclonic–tonic seizures beyond the first year of life with a lack of obvious pre-natal or perinatal causes in many cases.[4–8]

The authors of these papers have commented that these patients may be "overlooked" because of a lack of common familiarity with the presentation. This is important if the supposition is correct that older infants with this condition could benefit from prompt attention to address the underlying cause and effective medical treatment to reverse the epileptic encephalopathy.

This study aimed to analyze patients with prototypical features of these patients in order to evaluate the prevalence, demography, and specific clinical and electrographic characteristics. In this paper, we use the term late infantile epileptic encephalopathy (LIEE) to describe these patients, although the precise title is not of paramount importance.

Key points

- LIEE commonly presents during the second year of life often in patients with a genetic/metabolic or structural cause for epilepsy.
- Archetypical seizures of LIEE are either spasm–tonic, myoclonic–tonic seizures, or both in combination with other seizure types.
- EEG demonstrates an inter-ictal background with periods of discontinuity, electrodecrement, or both with diffuse slowing and superimposed epileptiform discharges.
- LIEE is associated with drug-resistant epilepsy and moderate-to-severe developmental delay.
- LIEE lacks the defining characteristics of neighboring DEE syndromes of EIDEE, IESS, and LGS.

2 | MATERIALS AND METHODS

We conducted a retrospective review of electronic medical records for 850 patients diagnosed with epilepsy, who sought evaluation and treatment at Comer Children's Hospital at the University of Chicago, Chicago, IL between June 2022 and May 2023. The study gathered demographic, clinical, and laboratory information from patients' medical records, including details of their epilepsy history such as seizure onset, types, and anti-seizure medication (ASM) regimens. Developmental milestones were classified based on self-reported information from a family member or guardian and categorized as mild (functional age < 33% below chronological age), moderate (functional age 34%–66% of chronological age), or severe

(functional age < 66% of chronological age) using standardized guidelines.[9] A board-certified clinical neurophysiologist reviewed the available EEG studies, assessing the background continuity, voltage, and organization, as well as the presence of epileptiform activity and seizures. For four patients, we relied on the EEG report available in the EMR as we were unable to directly review their EEG tracings.

3 | RESULTS

Out of 850 patients who underwent EEG studies and epilepsy follow-up, 30 patients (3.5%) were identified as having LIEE features. Among them, 15 (50%) were girls. The mean age of seizure onset was 6.8 months (range <1–19) and the average age of onset of LIEE characteristics was 18.1 months (range 12–23). The etiologies of epilepsy in these patients were genetic and metabolic (50%), congenital cortical malformations (23%), acquired structural abnormalities (20%), and unknown (7%) (reference Table 1). Among the genetic etiologies, the most common pathogenic variants were in *SCN2A* and *PAFAH1B1* gene which were present in 13% and 10% of total patients, respectively. The congenital cortical malformations included polymicrogyria and lissencephaly, while the acquired structural etiologies included hypoxic ischemic encephalopathy, perinatal stroke, and history of neonatal meningitis. Preceding the onset of LIEE symptomatology, a third of patients (10/30) had a previous clinical history supportive of IESS.

TABLE 1 Epilepsy demographics.

	Value ($n = 30$)
Female: male	15:15
Age (months) at epilepsy onset	6.8 (<1–19)
Age (months) at LIEE onset	18.1 (12–23)
Previously used ASMs (including dietary therapy)	2.9 (1–6)
Current ASMs (including dietary therapy)	2.7 (1–4)
Epilepsy etiology	
Genetic and metabolic	15 (50)
Congenital malformation	7 (23)
Acquired structural abnormalities	6 (20)
Unknown	2 (7)
Seizure types	
Myoclonic–tonic	21 (70)
Spasm–tonic	15 (50)
Epileptic spasms	14 (47)
Tonic	13 (43)
Myoclonic	13 (43)

Note: Values are presented as mean (range) or number (%) unless otherwise indicated.

Abbreviations: ASMs, anti-seizure medications; LIEE, Late Infantile Epileptic Encephalopathy.

The represented seizure types, including those documented on EEG or reported by the patient's guardians, include myoclonic–tonic (70%), spasm–tonic (50%), epileptic spasms (47%), tonic (43%), and myoclonic (43%) seizures. All patients were experiencing multiple seizure types. The most common combinations of seizure types observed were epileptic spasms accompanied by both myoclonic and myoclonic–tonic seizures (17%) and the combination of myoclonic–tonic and tonic seizures (17%). The second most common combination was spasm–tonic and tonic seizures (13%) (reference Table 1). It is noteworthy that among the patients who experienced epileptic spasms from both EEG tracings and self-reported symptoms, these spasms often exhibited a sporadic frequency, in contrast to the anticipated periodicity commonly observed in IESS.

All patients, except for one, met the definition of drug-resistant epilepsy proposed by ILAE with an average use of 5.7 ASMs (range 1–10) per patient.[10] Patients were taking an average of 2.7 ASMs (range 1–5) at the time of report and had previously tried an average of 2.9 ASMs (range 0–6). The most used medications were levetiracetam (70%), cannabidiol oil (60%), clobazam (53%), and phenobarbital (53%). The ketogenic diets were also used in 57% of patients.

EEG tracings were available to review in 26/30 (87%) of the patients and findings summarized in Table 2. The resting voltage was between 200 and 300 microvolts in 11/26 (42%) patients and between 100 and 200 microvolts in 15/26 (58%) patients. None of the patients exhibited voltages exceeding 300 microvolts in contrast to a common feature of hypsarrhythmia described in IESS.[11] All patients' EEG exhibited a diffusely slow background with periods of discontinuity, electrodecrement, or both. Additionally, all patients demonstrated either abundant or frequent multifocal and/or diffuse epileptiform discharges (Figure 1). The EEG recordings of 23/26 (88%) patients captured either a spasm–tonic or myoclonic–tonic seizure.

Myoclonic–tonic seizures were characterized by a sudden rhizomelic or global myoclonic jerk followed by a brief epoch of tonic posturing in the same distribution. The distinction between myoclonic–tonic seizures and spasm–tonic seizures is a subtle one and usually only distinguishable by the use of concurrent polygraphic recordings showing an EMG correlate more consistent with myoclonia rather than the more prolonged and rhomboid appearance of an epileptic spasm (Reference Figures 2 and 3). The rhomboid-shaped EMG correlation of epileptic spasms also aides in distinguishing spasm–tonic from

TABLE 2 EEG characteristics.

Patient	Available for review	Voltage (μV)	Background continuity	Background frequency	PDR	AP gradient	Inter-ictal epileptiform discharges	Recorded seizure(s)
1	No	–	Discontinuous	Delta	Absent	Absent	Frequent multifocal and diffuse	Myoclonic–tonic and spasm–tonic
2	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	Myoclonic and myoclonic–tonic
3	Yes	100–200	Discontinuous	Delta–theta	Absent	Present	Frequent multifocal and diffuse	Myoclonic, spasm–tonic, and tonic
4	Yes	200–300	Discontinuous	Delta	Absent	Absent	Abundant multifocal	Myoclonic, myoclonic–tonic, and spasm–tonic
5	Yes	200–300	Discontinuous	Delta–theta	Absent	Absent	Frequent multifocal and diffuse	Spasm–tonic
6	Yes	200–300	Discontinuous	Delta–theta	Absent	Present	Abundant multifocal	Spasm–tonic
7	Yes	200–300	Discontinuous	Delta	Absent	Absent	Abundant multifocal and diffuse	Spasm–tonic
8	Yes	200–300	Discontinuous	Theta–alpha	Absent	Absent	Abundant multifocal and diffuse	-
9	Yes	200–300	Discontinuous	Delta	Absent	Absent	Frequent multifocal	Myoclonic–tonic and tonic
10	No	–	Discontinuous	Delta–theta	Absent	Absent	Frequent multifocal	–
11	Yes	100–200	Discontinuous	Theta–alpha	Absent	Absent	Frequent multifocal and diffuse	–
12	Yes	100–200	Discontinuous	Theta–alpha	Present	Present	Abundant multifocal and diffuse	–
13	Yes	200–300	Discontinuous	Delta	Absent	Absent	Abundant multifocal and diffuse	Spasm–tonic and tonic
14	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	Spasm–tonic
15	Yes	100–200	Discontinuous	Delta	Absent	Absent	Abundant multifocal and diffuse	Myoclonic and myoclonic–tonic
16	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	–
17	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	Epileptic spasms, myoclonus, and spasm–tonic
18	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	Spasm–tonic and tonic
19	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal and diffuse	Myoclonic, myoclonic–tonic, and tonic
20	Yes	100–200	Discontinuous	Theta	Present	Present	Frequent multifocal and diffuse	Myoclonic–tonic
21	No	–	Discontinuous	Delta–theta	Absent	Absent	Frequent multifocal and diffuse	Myoclonic–tonic
22	Yes	200–300	Discontinuous	Theta	Present	Present	Abundant multifocal and diffuse	Myoclonic–tonic
23	Yes	100–200	Discontinuous	Delta–theta	Present	Present	Frequent multifocal and diffuse	Myoclonic, myoclonic–tonic, and spasm–tonic

TABLE 2 (Continued)

Patient	Available for review	Voltage (μV)	Background continuity	Background frequency	PDR	AP gradient	Inter-ictal epileptiform discharges	Recorded seizure(s)
24	Yes	200–300	Discontinuous	Delta–theta	Present	Present	Frequent multifocal	Myoclonic–tonic and tonic
25	Yes	100–200	Discontinuous	Delta–theta	Absent	Absent	Frequent multifocal	Epileptic spasms and spasm–tonic
26	Yes	100–200	Discontinuous	Delta–theta	Present	Present	Frequent multifocal	Myoclonic and spasm–tonic
27	No	–	–	–	–	–	–	–
28	Yes	200–300	Discontinuous	Theta	Absent	Absent	Abundant multifocal and diffuse	Epileptic spasms
29	Yes	200–300	Discontinuous	Delta–theta	Absent	Absent	Abundant multifocal	Myoclonic–tonic
30	Yes	100–200	Discontinuous	Delta	Absent	Absent	Abundant multifocal and diffuse	Spasm–tonic

Abbreviations: AP gradient, anterior–posterior voltage gradient; PDR, posterior dominant rhythm; μV, microvolts.

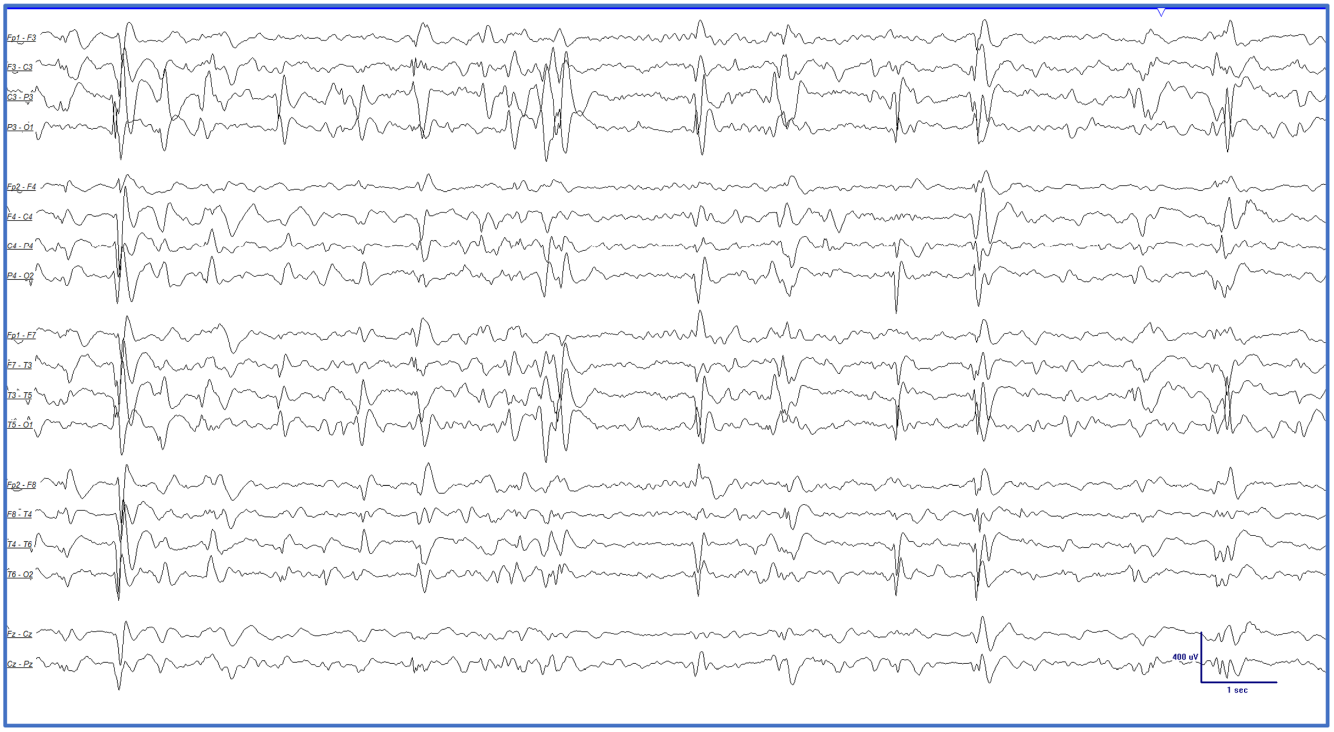

FIGURE 1 Sample of sleep background activity in patient 5 characterized by moderate voltage (between 200 and 300 microvolts), relative discontinuity, and superimposed epileptiform discharges. EEG recorded in longitudinal bipolar montage, sensitivity 20 uV/mm, HF 70 Hz, and paper speed 15 mm/s.

tonic seizures electrographically with standard placement of EMG leads overlying deltoid muscles. In spasm–tonic seizures, there is a distinctive rhomboid pattern observed during the spasm phase which precedes the prolonged and uniform increase in EMG activity characteristic of the tonic phase. Pure tonic seizures lack the rhomboid EMG signature of epileptic spasms.

The ictal electroencephalographic features of recorded myoclonic–tonic and spasm–tonic seizures were very similar. At the onset, both had prominent positive waveforms evident at the vertex, often with preceding electronegative epileptiform discharges in varying distributions and sometimes associated with brief spindle-like discharges – features in common with those described by Fusco and

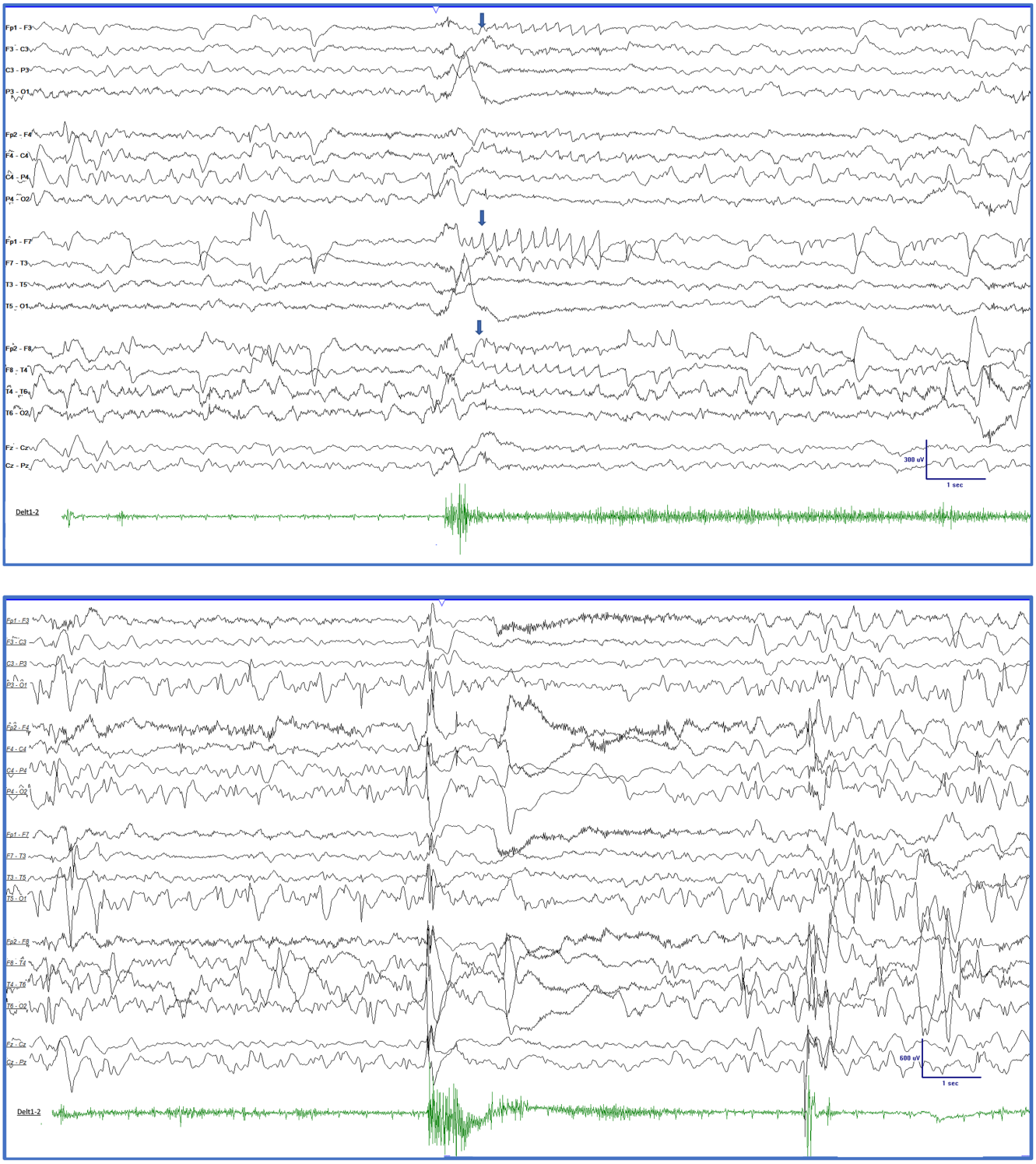

FIGURE 2 Example of a spasm–tonic seizure from patient #2 and #4, respectively, with a prolonged rhomboid appearance of the EMG correlate of the spasm component. An additional unique feature depicted in the first example is brief rhythmic vertical eye movement artifact (depicted by arrows) during the tonic portion of the seizure. EEG recorded in longitudinal bipolar montage, sensitivity 20 uV/mm (first tracing) and 30 uV/mm (second tracing), HF 70 Hz, and paper speed 15 mm/s; EMG leads placed over right deltoid.

Vigevano in the spasms of West syndrome.[12] Thereafter, there was a sudden electrodecrement lasting several seconds that was usually contaminated by over-riding EMG artifact from the tonic posturing. The concurrent polygraphic tracing reveals a typical tonic phase correlation. In many circumstances, evidence of brief rhythmic vertical eye movement artifact was present in the frontal derivations during the tonic phase of the seizures.

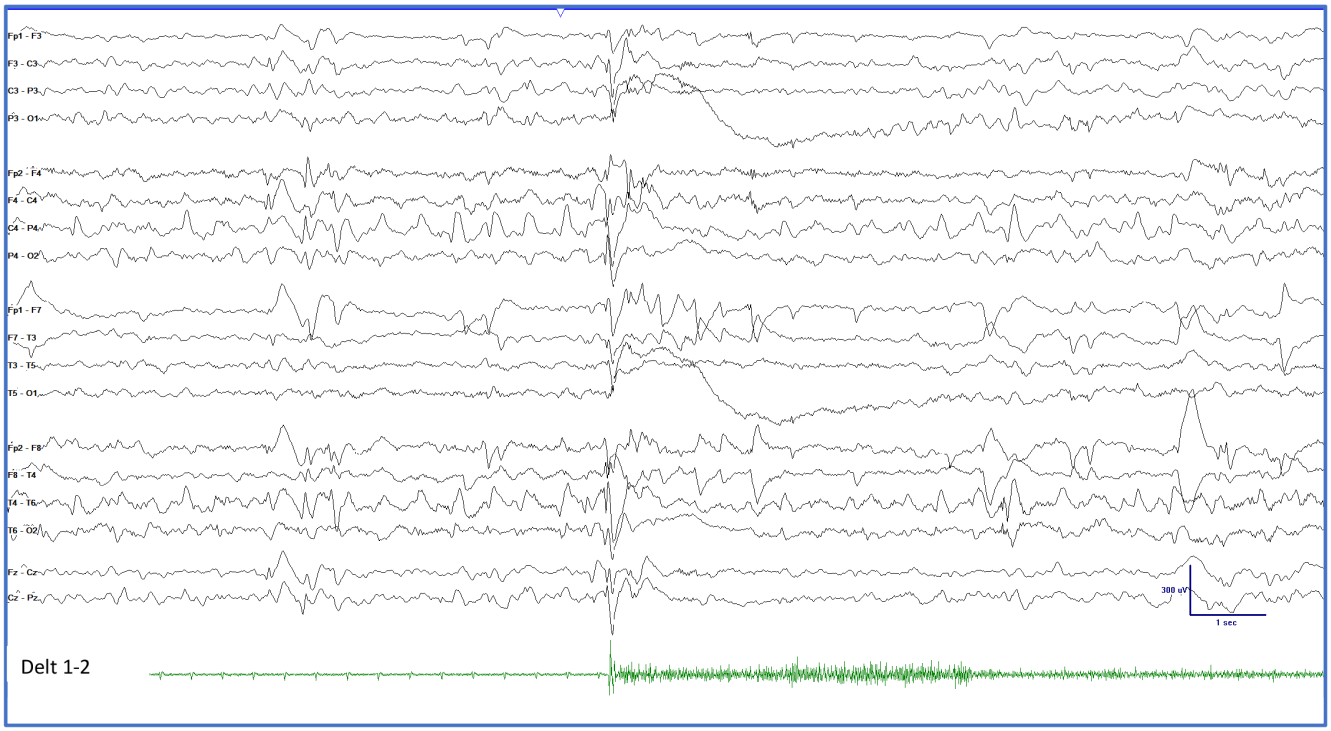

FIGURE 3 Example of a myoclonic–tonic seizure from patient #2 in longitudinal bipolar montage in which the EMG correlate is brief and consistent with myoclonia then followed by a tonic phase which contrasts the prolonged rhomboid appearance of the EMG correlate seen in epileptic spasms and spasm–tonic seizures. EEG recorded in longitudinal bipolar montage, sensitivity 20 μV/mm, HF 70 Hz, and paper speed 15 mm/s; EMG leads placed over right deltoid.

All patients in our study exhibited a reported developmental delay, which was classified as either moderate-to-severe (50%) or severe (50%) and was consistent with the documented clinical history and physical examination.

4 | DISCUSSION

Developmental and epileptic encephalopathies are a heterogeneous group of epilepsies with a common age of onset in neonates, infants, and children in which the degree of developmental or intellectual impairment is related to both the underlying etiology and the epileptic encephalopathy.[1] Some DEE syndromes could be considered likely epileptic encephalopathies including early infantile developmental epileptic encephalopathy (EIDEE), infantile epileptic spasm syndrome (IESS), and Lennox–Gastaut syndrome (LGS). However, within the spectrum of DEE exists a distinct syndrome which has been variously described as "late-onset infantile spasms," "cryptogenic late-onset epileptic spasms," "infantile epileptic encephalopathy with late-onset spasms," and "late infantile epileptic encephalopathy (LIEE)." In this paper, we use the term LIEE because pure epileptic spasms are not the sole seizure type found in the condition and the patients exhibited pronounced encephalopathy with the onset of their epilepsy. In the past, authors have noted the relative absence of obvious pre-natal or perinatal conditions in these patients and many were considered to have "cryptogenic" epilepsy. Modern genetic analyses and high-resolution neuroimaging have reduced the number of patients with unidentified cause to only 7% of the patients in our series.

While epileptic spasms are well described and often associated with IESS, their onset after one year of age should prompt consideration of other epileptic encephalopathies such as LIEE, which occurs after the typical period of IESS but before the onset of LGS. In our study, we found LIEE to be a relatively common and important diagnosis with a prevalence of 3.5%.

LIEE has several features highlighted in this case series and in previous reports which distinguish it as a separate entity among the DEE syndromes. These notable features include epileptic spasms with an onset in the second year of life, hence the namesake late infantile onset. The commonest and likely prototypic seizure types of LIEE are spasm–tonic and myoclonic–tonic seizures, though epileptic spasms are also noted in combination with these seizures. In contrast though to epileptic spasms in IESS, epileptic spasms in LIEE tend to cluster but lack the

TABLE 3 Patient characteristics

Patient	Epilepsy Onset	LIEE onset	Etiology	Seizure types	Current treatment	Past treatment	Developmental outcome
1	3 Mos	20 Mos	Polymicrogyria	Myoclonic–tonic and spasm–tonic	CBD, LEV, and VGB	CLB, OXC, PB, and TPM	Moderate to severe
2	6 Mos	15 Mos	Perinatal stroke	Epileptic spasm, myoclonic, and myoclonic–tonic	CBD, KD, and LEV	ACTH and PB	Moderate to severe
3	8 Mos	17 Mos	Polymicrogyria	Myoclonic and myoclonic–tonic	CBD and LEV	PRED	Moderate to severe
4	17 Mos	17 Mos	5q14.3 micro-deletion syndrome	Myoclonic, myoclonic–tonic, and spasm–tonic	CBD	FBM and PRED	Moderate to severe
5	13 Mos	13 Mos	Pathogenic variant in *SCN2A*	Epileptic spasms, myoclonic–tonic, and spasm–tonic	LEV and ZNS	FBM	Moderate to severe
6	8 Mos	20 Mos	Perinatal stroke	Spasm–tonic and tonic	CBD, CLB, and LTG	ACTH, PB, and VGB	Moderate to severe
7	4 Mos	23 Mos	Pyruvate dehydrogenase complex deficiency E1 alpha subunit	Epileptic spasms and spasm–tonic	KD	ACTH, CZP, LEV, and PRED	Moderate to severe
8	< 1 Mos	15 Mos	Hypoxic ischemic encephalopathy	Epileptic spasms and spasm–tonic	CBD and CLB	ACTH, LEV, OXC, PB, TPM, and VGB	Moderate to severe
9	18 Mos	18 Mos	Unknown	Myoclonic–tonic and tonic	TPM	LEV	Severe
10	16 Mos	16 Mos	Pathogenic variant in *SCN2A*	Myoclonic–tonic and tonic	CBD, CZP, FBM, and LEV	CLB, KD, OXC, and VPA	Severe
11	4 Mos	14 Mos	Kabuki syndrome (Pathogenic variant in *KDM6A*)	Spasm–tonic, and tonic	LEV and MCT	ACTH, CLB, PB, and VGB	Moderate to severe
12	6 Mos	16 Mos	Pathogenic variant in *PURA*	Myoclonic and spasm–tonic	FBM	PB and PRED	Moderate to severe
13	< 1 Mos	22 Mos	Pathogenic variant in *SCN2A*	Spasm–tonic and tonic	CBZ, KD, and LCS	LEV, PB, and OXC	Severe
14	< 1 Mos	22 Mos	Pathogenic variant in *SCN2A*	Spasm–tonic and tonic	CBZ, KD, and LCS	LEV and PB	Severe
15	3 Mos	17 Mos	*ARX* mutation-related syndrome	Epileptic spasms, myoclonic, and myoclonic–tonic	CLB, GBP, KD, PB, and VGB	ACTH and TPM	Severe
16	6 Mos	22 Mos	Unknown	Myoclonic–tonic and tonic	FBM and KD	CBD, CLB	Moderate to severe
17	7 Mos	23 Mos	Chromosome 15q duplication	Epileptic spasms, myoclonic, and spasm–tonic	CBD and CLB	ACTH, LEV, KD, PB, and TPM	Severe
18	< 1 Mos	20 Mos	Chromosomal translocation: 46,XX,t(16:17)(p13.3;p12.2)	Myoclonic–tonic and tonic	CBD, CZP, FBM, and LCS	PER, PHT, and ZNS	Severe
19	5 Mos	18 Mos	Pathogenic variant in *UBA5* gene	Myoclonic, myoclonic–tonic, and tonic	CBD, CZP, FBM, and GBP	ACTH, CLB, LEV, TPM, and VPA	Severe
20	17 Mos	17 Mos	Polymicrogyria	Myoclonic–tonic and tonic	CBD, CLB, KD, and ZNS	PRED and VPA	Severe

TABLE 3 (Continued)

Patient	Epilepsy Onset	LIEE onset	Etiology	Seizure types	Current treatment	Past treatment	Developmental outcome
21	1 Mos	16 Mos	*CDKL5* deficiency	Epileptic spasms, myoclonic, and myoclonic–tonic	CBD, KD, VGB, and VPA	GBP, LEV, PB, PHT, TPM, and RFM	Severe
22	6 Mos	14 Mos	Hypoxic ischemic encephalopathy	Epileptic spasms, myoclonic–tonic, and tonic	KD, LEV, and TPM	PB	Severe
23	7 Mos	22 Mos	Trisomy 21	Myoclonic, myoclonic–tonic, and spasm–tonic	CLB	–	Moderate to severe
24	19 Mos	19 Mos	Beta-propeller protein-associated neurodegeneration (BPAN) (pathogenic variant *WDR45*)	Epileptic spasms, myoclonic–tonic, spasm–tonic, and tonic	CLB	ACTH, LEV, and VPA	Severe
25	< 1 Mos	18 Mos	GBS meningitis with resulting encephalomalacia	Epileptic spasms, myoclonic, and spasm–tonic	CBD, CLB, and LEV	KD, PB, and PRED	Moderate to severe
26	8 Mos	12 Mos	Lissencephaly (*PAFAH1B1* pathogenic variant)	Myoclonic, myoclonic–tonic, and tonic	CBD, CLB, KD, and VGB	LEV, LTG, PB, and PRED	Severe
27	5 Mos	23 Mos	Lissencephaly (*PAFAH1B1* pathogenic variant)	Epileptic spasms, myoclonic, and myoclonic–tonic	CLB, FBM, KD, and VPA	CBD, LEV, VGB, and ZNS	Severe
28	4 Mos	14 Mos	Lissencephaly-pachygyria (chromosome 17 deletion including *PAFAH1B1* gene)	Epileptic spasms, myoclonic, and myoclonic–tonic	KD, LEV, PB, and RFM	ACTH and CLB	Severe
29	< 1 Mos	20 Mos	Hypoxic ischemic encephalopathy	Epileptic spasms and myoclonic–tonic	CBD, LEV, and PB	KD, TPM, and VGB	Moderate to severe
30	2 Mos	20 Mos	Bilateral polymicrogyria (*GRIN2B* pathogenic variant)	Epileptic spasms, myoclonic–tonic, and spasm–tonic	CLB, KD, and RFM	CBD, GBP, LCS, and TPM	Moderate to severe

Abbreviations: ACTH, adrenocorticotropic hormone; CBD, cannabidiol; CBZ, Carbamazepine; CLB, clobazam; CZP, clorazepate; FBM, felbamate; GBP, gabapentin; GBS, Group B Streptococci; KD, ketogenic diet; LCS, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MCT, medium-chain triglyceride; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; PRED, prednisone; RFM, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

predicted periodicity of epileptic spasms as seen in IESS and often have a co-existing tonic component at the start. A peculiar feature of spasm–tonic and myoclonic–tonic seizures in LIEE is frequent vertical eye movement artifact during the tonic phase which may be a helpful tool for EEG readers in identifying these seizures electrographically. The most common etiology among our patients is genetic and metabolic followed by congenital cortical malformations and acquired structural abnormalities.

In our study, the treatment of seizures in LIEE was varied consisting of 22 different ASMs (reference Table 3) and favored the use of broad-spectrum agents: levetiracetam (70%), cannabidiol oil (60%), ketogenic diet (57%), clobazam (53%), and phenobarbital (53%). Although this study was not designed to formulate treatment conclusions, in our experience we have found corticosteroids, and/or ketogenic diet to be the most efficacious for seizures in LIEE.

This study has some limitations, such as the relatively small sample size and short data collection period. Additionally, developmental status and seizures outside of those observed during EEGs were based on parent and guardian descriptions. While the developmental status reported in this study reflects the baseline at the onset of LIEE, it would be advantageous to also characterize the developmental status at the onset of epilepsy, considering the nature of developmental and epileptic encephalopathies. Future studies on LIEE would benefit from a larger sample size and a multicenter prospective design to assess its etiology, presenting seizure type(s), electroclinical features, and treatment options further including analysis on the role of dietary therapy, corticosteroids, felbamate, and vigabatrin.

5 | CONCLUSION

We propose the term late infantile epileptic encephalopathy (LIEE) as a distinct syndrome that unifies diverse prior reported descriptions, which fits within the spectrum of DEEs with unique clinical and EEG characteristics that are not uncommon in pediatric epilepsy. Typically, LIEE manifests in the second year of life or late infantile period, with myoclonic–tonic and spasm–tonic seizures. The inter-ictal EEG consists of periods of background discontinuity, electrodecrement, or both, with diffuse slowing, superimposed multifocal epileptiform discharges, and lacks the defining EEG features of EIDEE, IESS, or LGS. LIEE is almost invariably associated with drug-resistant epilepsy and moderate-to-severe developmental delay. Recognizing LIEE as a distinct syndrome within the spectrum of developmental and epileptic encephalopathies can expand our understanding and knowledge of DEE syndromes.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test Yourself

1. What is the most common age of onset of late infantile developmental epileptic encephalopathy?
   a. First few days of life
   b. Within the first year of life
   c. **Within the second year of life**
   d. Early childhood (ages 3–5 years old)
2. What are typical EEG findings seen in patients with an epileptic encephalopathy?
   a. Normal EEG background without epileptiform discharges
   b. Normal EEG background with stereotyped generalized spike and wave discharges
   c. Normal EEG with stereotyped focal epileptiform spikes
   d. Diffuse background slowing and pleomorphic focal inter-ictal epileptiform discharges
   e. **Discontinuous background with pleomorphic multifocal and diffuse inter-ictal epileptiform discharges**
3. What is the most common seizure type(s) seen in patients with late infantile epileptic encephalopathy?
   a. Rolandic
   b. Generalized tonic–clonic
   c. **Spasm–tonic or myoclonic–tonic**
   d. Myoclonic
   e. Absence

Answers may be found in the Supporting information.