Clinical commentary

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LGI-1 antibody encephalitis in a seven-year-old girl

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ABSTRACT – LGI-1 antibody encephalitis is a rare autoimmune limbic encephalitis which has been reported predominantly in adults. Seizures in LGI-1 antibody encephalitis exhibit significant semiological variability. Faciobrachial dystonic seizures are characteristically seen in this condition and have so far been described only in adults. Other seizure types have also been reported. We describe the case of a seven-year-old girl with LGI-1 limbic encephalitis who presented with acute new-onset seizures, and rapidly deteriorated over the course of a few weeks with very frequent seizures and encephalopathy, becoming non-verbal and non-ambulatory. The electroclinical presentation of this child with LGI-1 encephalitis makes this case unique and further highlights the importance of a high index of suspicion for diagnosis in young children. Early diagnosis can lead to prompt and appropriate treatment with immunotherapy, and potential harmful treatments such as pharmacological coma can be avoided. To the best of our knowledge, this is the youngest case ever reporter. [*Published with video sequences*]

Key words: leucine-rich glioma-inactivated 1 encephalitis, LGI-1, faciobrachial dystonic seizure, FBDS, VGKC

VIDEOS ONLINE

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Leucine-rich glioma-inactivated 1 (LGI-1) antibody encephalitis is a rare autoimmune limbic encephalitis. It has been reported predominantly in adults with a mean age at onset of around 63 years (Li *et al*., 2018a). The clinical presentation is variable with most patients presenting with characteristic faciobrachial dystonic seizures (FBDS), memory disturbance, cognitive impairment, and hyponatremia. To date, FBDS have not been reported in children (López-Chiriboga *et al*., 2018). Other seizure types have also been reported including generalized tonic-clonic, focal, and myoclonic seizures (Wang *et al*., 2017), and drop attacks (Vives-Rodriguez *et al*., 2017). Frequent focal seizures were found in LGI-1-IgG positive pediatric patients (Lopez-Chiriboga *et al*., 2018). The patients usually respond very well to immunotherapy (Wang *et al*., 2017).

We describe a case of a seven-year-old girl with LGI-1 limbic encephalitis in order to highlight the importance of having a high index of suspicion for diagnosis even in young children. Autoimmune encephalitis should be part of the differential diagnoses for any child who presents with acute frequent seizures, behavioral changes, hallucinations, cognitive impairment, and seizures resistant to anti-epileptic medications. Electroclinical data can be helpful in further identifying specific antibodies such as the presence of FBDS in LGI-1 antibody encephalitis and extreme delta brush on EEG in anti-NMDA receptor encephalitis.

Case study

A seven-year-old, previously healthy girl presented to an emergency department with events of awakening from sleep in which she was frightened and made monkey-like whooping sounds. She reported seeing scary faces without a mouth. After a few days, she developed a second type of seizure characterized as tonic flexion of the upper extremities, associated with deviation of the eyes and mouth to either right or left, lasting for a few seconds. She was diagnosed with benign Rolandic epilepsy at the hospital and was started on levetiracetam. Two weeks later, these events became more frequent and intense. Valproic acid was added. Brain MRI was performed and was unremarkable. Approximately three weeks later, her seizures became very frequent, almost 30-40 per day, and sometimes occurring in clusters lasting 3-4 hours. She also developed one generalized tonic-clonic (GTC) seizure. The patient became socially withdrawn and showed no interest in her surroundings. Valproic acid was discontinued due to worsening of seizures and carbamazepine was started without significant seizure control.

She was transferred to a secondary care hospital for a second opinion where she was admitted to the pediatric intensive care unit (PICU). The patient was intubated and put into pharmacological coma with midazolam and thiopental for two weeks. Her routine investigations were unremarkable. Computed tomography (CT) of the brain showed mild volume loss and EEG showed background slowing as per the report. Carbamazepine was discontinued. Phenobarbitone and phenytoin were added without significant improvement. She was managed there for a month before being referred to our hospital.

When we received the patient, the vital signs were stable and growth parameters were normal for age (head circumference: 52 cm). She was encephalopathic and mute. She responded to simple verbal commands by gestures. Cranial nerve examination was unremarkable. Motor examination showed normal muscle bulk and global hypotonia. She had generalized mild weakness with brisk reflexes. There was dysmetria on finger-nose testing and she was unable to walk. Systemic examination was unremarkable. She was on phenobarbitone, phenytoin, topiramate, and levetiracetam.

She was born from an uneventful pregnancy, weighing 3 kg, to consanguineous parents. Her developmental history was normal and she was an A student at school. There was no family history of any neurological, genetic, metabolic or autoimmune disease.

The patient was admitted to the Epilepsy Monitoring Unit (EMU) for 24-hour video-EEG, which showed severe diffuse background slowing, intermittent rhythmic delta activity in the bilateral occipital regions, left and right frontal-temporal high-voltage spike and wave and sharp wave transients (*figures 1, 2*), and intermittent rhythmic delta activity independently over the left and right frontal-temporal regions. During sleep, intermittent 12-14-Hz low to moderate-voltage fast polyspike bursts were present either diffusely (*figure 3*) or independently in the left and right frontal-temporal regions with shifting predominance. Brief periods of voltage attenuation were present diffusely and independently in the right and left hemispheres. During the 24-hour recording, more than 400 focal seizures were captured. These seizures were of three types: right focal unaware seizures with ipsilateral stereotypic movements (*video sequences 1, 2*), left focal unaware seizures with ipsilateral stereotypic movements (*video sequence 3*), and focal unaware behavior arrest seizures.

The patient was started on pulse methylprednisolone at 30 mg/kg for five days, followed by IVIG at 2 g/kg, given over two days. Phenobarbitone and phenytoin were weaned off, and lacosamide was introduced. Her routine blood tests, cerebrospinal fluid (CSF) analysis including a PCR neuro virus panel, and basic metabolic and immunological workup were unremarkable except for hyponatremia. The serum sodium level was 133 mmol/L (normal range: 135-147 mmol/L). The autoimmune epilepsy panel for CSF and serum was sent to the Mayo Clinic in the USA. The CSF sample was positive (reference value: negative) for LGI-1 IgG antibody. The serum sample was positive for LGI-1 IgG (reference value: negative) and neuronal (V-G) K+ channel (0.34 nmol/L; reference value: $\leq$ 0.02 nmol/L) and GAD65 (0.18 nmol/L; reference value: $\leq$ 0.02 nmol/L) antibodies. A CT scan of the chest, abdomen, and pelvis was performed to investigate paraneoplastic etiology and was unremarkable. Brain MRI with contrast was repeated in our hospital which showed only supratentorial brain volume loss. Positron emission tomography (PET) showed subtle hypometabolism in the right temporal and bilateral parietal cortices.

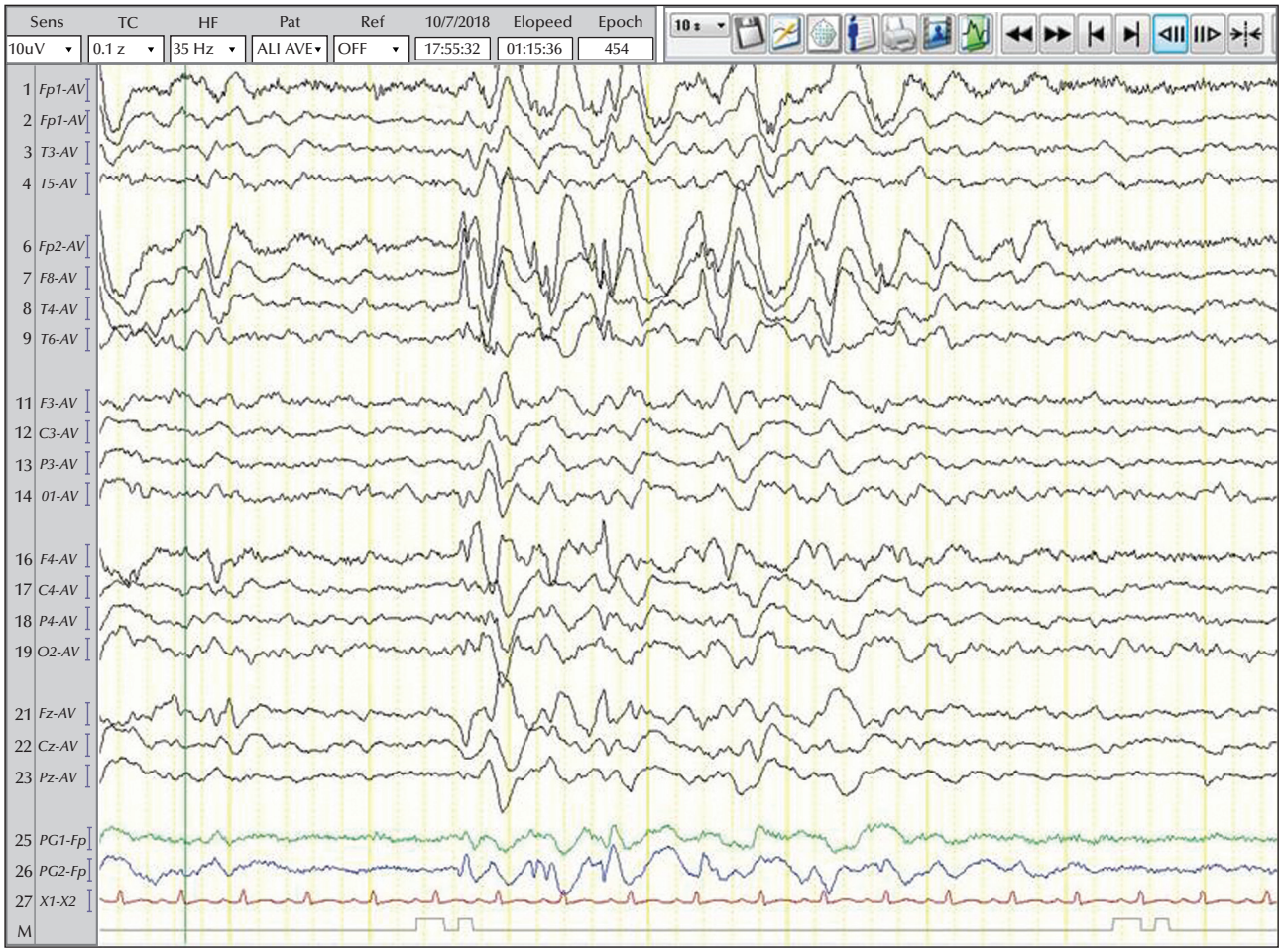

Figure 1. High-voltage spike and wave discharges at the right frontal-temporal electrodes.

The patient showed dramatic response to steroids and IVIG. Her seizures reduced significantly and she became more alert and oriented to her surroundings. She started to produce some sounds and later was able to say a few words at the time of discharge. The patient was started on oral prednisolone at 40 mg daily, to be slowly tapered over six months. Three weeks after the discharge from hospital, she was seen in the clinic. The seizures further reduced to 2-4/day. She became more interactive and more sociable with her siblings, and her mother reported improvement in her memory. She was readmitted three times to the EMU, each time for a 24-hour period, for better characterization and IVIG (2 g/kg given over two days). Our plan is to continue monthly IVIG for a total of six months to prevent possible relapse. Her EEG continued to improve significantly. The most recent EEG showed an occipital dominant rhythm within normal range for age, intermittent diffuse slow activity, and intermittent slow activity in the bi-temporal chains and the left temporal and left parietal-occipital regions. Slow wave transients were present either diffusely with bifrontal predominance or with shifting predominance over the left and right frontal regions during sleep. According to her mother, the patient's speech, cognition and memory returned to baseline levels. Serum sodium also returned to normal.

Cognitive functions, such as attention, learning, memory, problem solving, and executive function were improved based on the Cambridge Neuropsychological Test Automated Battery (CANTAB) (*table 1*) (Goveas *et al*., 2011).

Discussion

The voltage-gated potassium channel complex (VGKC) is present on the membrane of neurons in the central as well as peripheral nervous system. The VGKC helps neurons to return to the resting state after an action potential (Van Sonderen *et al*., 2016). LGI-1 is one of the proteins associated with VGKC and is mainly present in the hippocampus and temporal cortex (Van Sonderen *et al*., 2016). It plays an important role in synaptic

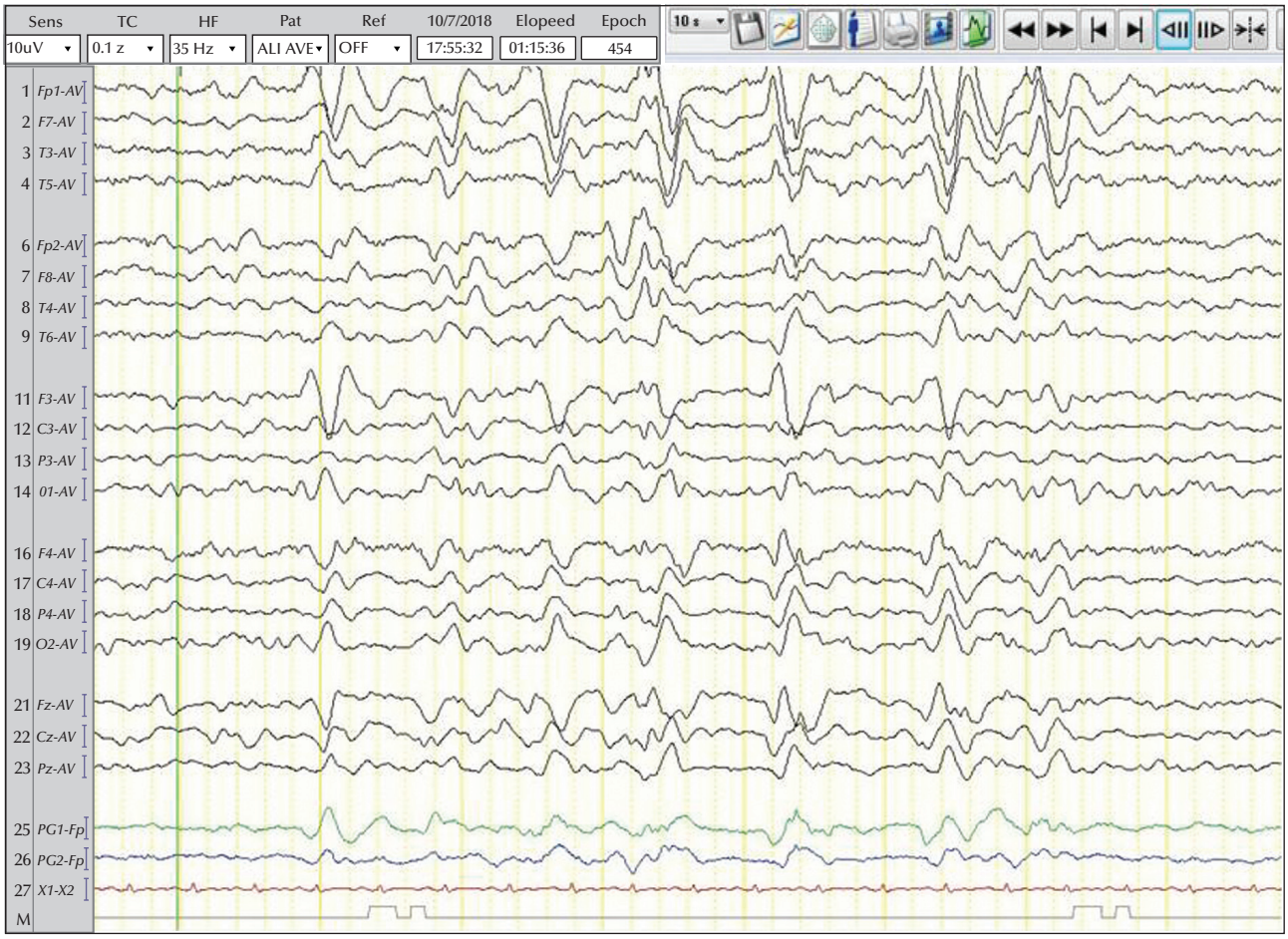

Figure 2. High-voltage sharp wave transients at the left frontal-temporal electrodes.

transmission and myelination (Kegel *et al*., 2013). Mutations in the LGI-1 gene, which is located on chromosome 10, cause autosomal dominant lateral temporal lobe epilepsy (Manna *et al*., 2014). Autoantibodies to the LGI-1 protein may give rise to limbic encephalitis. LGI-1 limbic encephalitis has been reported predominantly in adults with a mean age at onset of around 63 years (Li *et al*., 2018a). Janas-Kozik *et al*. reported a case of a 14-year-old adolescent girl with limbic encephalitis associated with LGI-1 antibodies who presented with seizures, autonomic instability, and psychotic symptoms (Janas-Kozik *et al*., 2017). To our knowledge, our patient is the youngest case ever reported in the literature and highlights the importance to consider this diagnosis also in children.

The clinical manifestations are diverse and typically comprise acute or sub-acute onset of seizures, memory deficits, cognitive impairment, autonomic dysfunction, psychosis, hallucinations, emotional disturbances, spatial disorientation, sleep problems, and hyponatremia (Wang *et al*., 2017; Li *et al*., 2018a). During the acute illness, our patient became completely mute and with treatment gradually regained her baseline speech. This has not been reported before in the literature. In one study, 14% of the patients were found to have paroxysmal dizziness spells which frequently delayed the diagnosis (Gadoth *et al*., 2017).

The electroclinical characteristics of seizures in LGI-1 encephalitis have mostly been described in adults. The patients usually present with multiple seizure types including characteristic FBDS, focal tonic or clonic seizures with or without loss of awareness, and myoclonic seizures (Wang *et al*., 2017; Li *et al*., 2018a; Steriade *et al*., 2018). Drop attacks have also been reported (Vives-Rodriquez *et al*., 2017). The initial seizure type of our patient, which was mistaken for Rolandic seizures, was considered compatible with FBDS. Faciobrachial dystonic seizures are present in almost two thirds of patients with LGI-1 encephalitis and are characterized by focal seizures with or without loss of awareness, mostly involving the face and arms (Li *et al*., 2018b).

FBDS are very frequent and brief seizures lasting less than 5 seconds may be associated with vocalization,

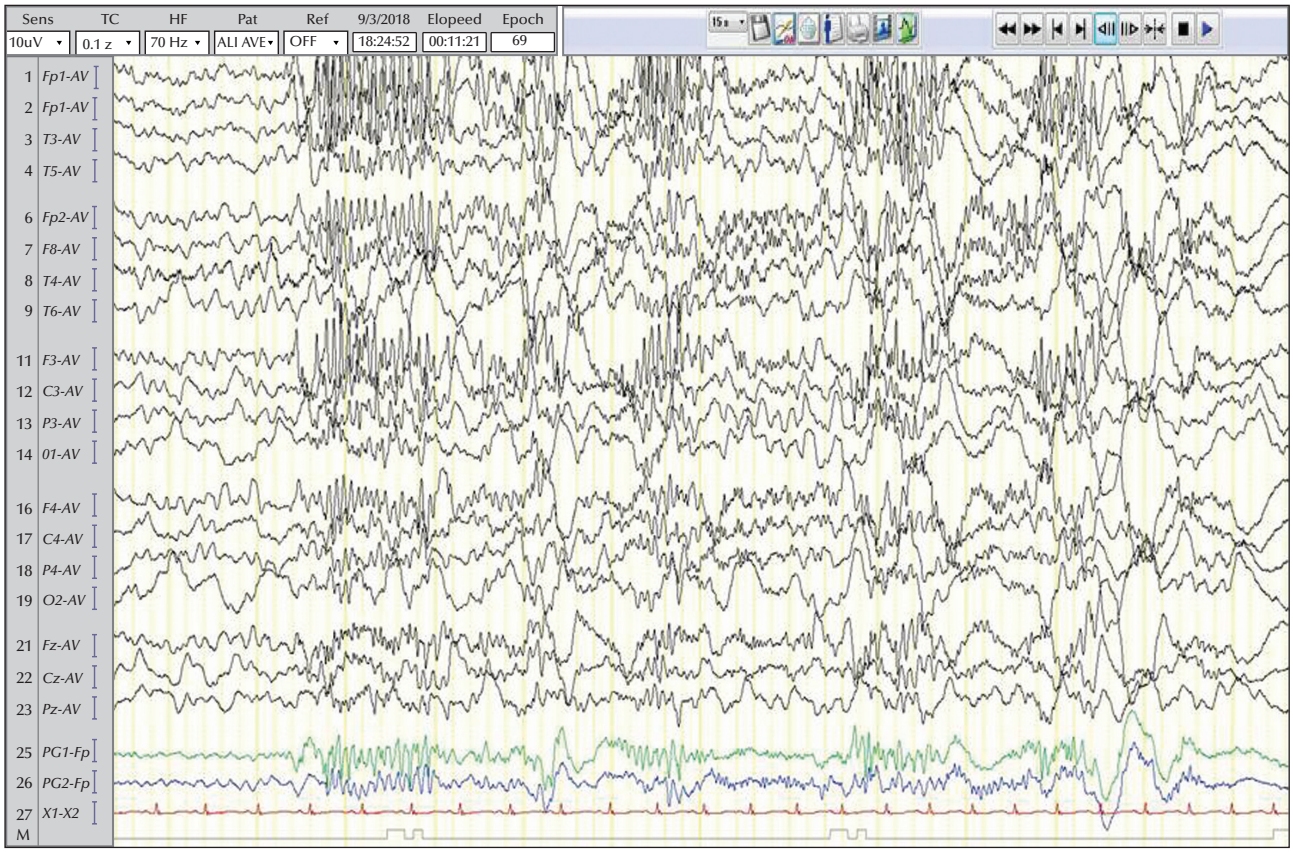

Figure 3. 12-14-Hz low to moderate-voltage diffuse fast polyspike bursts.

fear, automatisms or loss of consciousness (Li *et al*., 2018b). They can also present as unilateral or bilateral arm posturing or facial grimacing without loss of awareness (Vives-Rodriguez *et al*., 2017). FBDS have not been reported in children so far, but if present should not be confused with Rolandic seizures.

When the patient presented to our hospital approximately four months after seizure onset, her seizures were characterized as right or left focal-onset seizures with impaired awareness, followed by ipsilateral stereotypic movements of the arm. During some of the right-sided seizures, the patient also exhibited peri-ictal yawning and ipsilateral nose wiping. Peri-ictal yawning is known to occur in patients with right-sided non-dominant temporal lobe epilepsy (Kuba *et al*., 2010). Postictal nose wiping localizes to the ipsilateral

Table 1. Comparison between the presented case and controls (normative data from an age-matched control group) for cognitive function assessed using the Cambridge Neuropsychological Test Automated Battery.

CANTAB Parameter		Case	Control (*n*=62)
Spatial Recognition Memory (SRM)	Correct trial	60.0%	55-70%
Motor Screening Task (MOT)	Response time (ms)	857	700-880 ms
	Error rate	11%	8-18%
Spatial Working Memory (SWM)	Error rate	37%	35-55%
	Strategy and latency	32%	30-45%
Pattern Recognition Memory (PRM)	Correct response	95.83%	90-95%
Delayed Matching to Sample (DMS)	Correct response	87.5%	65-95%

temporal lobe (Leutmezer *et al*., 1998). In contrast to FBDS, which are usually reported not to be associated with abnormal ictal changes (Li *et al*., 2018a), these focal seizures associated with stereotypic movements exhibited a clear ipsilateral ictal EEG change.

We choose to describe the abnormal movements as stereotypic movements and not chorea because of the predictability of the phenomenology. In contrast, movements in chorea are more random due to variability in timing, duration or direction (Sanger *et al*., 2010). The stereotypic movements either on the right or left side were always ipsilateral to the side of the abnormal ictal electrographic changes. The ictal electrographic changes clearly lateralized to one hemisphere and localized to the frontal-temporal regions, but the lateralization and localization of the stereotypic movements could be challenging. One might assume that these movements are automatisms for three reasons: ipsilateral ictal electrographic changes, impaired awareness during the seizures, and frontal-temporal ictal onset (Tufenkjian and Lüders, 2012). Automatisms usually involve distal segments of extremities but in our patient, both distal and proximal segments were involved, making the automatisms atypical.

Lumbar puncture should be performed to rule out herpes encephalitis and CSF should be analyzed for autoantibodies. CSF in our patient was positive for LGI-1 autoantibodies but not for VGKC. Serum was positive for both LGI-1 and VGKC. In one study, VGKC Abs in the CSF, tested in five individuals, varied between <1 and 10% of serum values (Vincent *et al*., 2004). Autoantibodies to LGI-1 and VGKC can be detected in both CSF and serum but serum is more sensitive (Wang *et al*., 2017, Lopez-Chiriboga *et al*., 2018). Using both serum and CSF may increase the sensitivity of the test. Hyponatremia is present in approximately 40-60% of patients (Van Sonderen *et al*., 2016; Wang *et al*., 2017; Li *et al*., 2018a) and serum sodium levels increase as the condition improves (Wang *et al*., 2017).

3 Tesla MRI with contrast showed only supratentorial brain volume loss. Positron emission tomography (PET) showed subtle hypometabolism in the right temporal and bilateral parietal cortices. Avi *et al*. reported that in LGI-1 IgG-positive cases, 41% of patients showed mesiotemporal T2 hyperintensity, T1 hyperintensity in basal ganglia only in patients with FBDS, and abnormalities in almost three quarters of the patients based on PET (Vives-Rodriguez *et al*., 2017). PET could be more sensitive than MRI and may be helpful in the early diagnosis of the disease (Li *et al*., 2018a).

Antiepileptic drugs (AEDs) alone did not help our patient; she had seizures for four months and was put into pharmacological coma at the initial hospital with no benefit. First-line treatment includes glucocorticoids and IVIG, and combination of the two has been shown to be better. Patients show an excellent response to immunotherapy (Van Sonderen *et al*., 2016; Wang *et al*., 2017). Cyclophosphamide and rituximab could be used as second-line (Gastaldi *et al*., 2016). Early diagnosis can lead to prompt and appropriate treatment with immunotherapy and potential harmful treatments such as pharmacological coma can be avoided.

Prognosis of this condition is usually good with almost 70% of patients doing well after two years of follow-up and 30% of patients with recurrence mostly within the first six months (Li *et al*., 2018a). The major remaining symptoms are amnesia, spatial disorientation and insomnia (Li *et al*., 2018a). Data on prognosis is lacking in children. In our case, our findings indicated that the patient's speech, cognition and memory were back to baseline levels with immunotherapy. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

Legend for video sequences

Video sequence 1.

Right focal unaware seizure with ipsilateral stereotypic movements and peri-ictal yawning.

Video sequence 2.

Right focal unaware seizure with ipsilateral stereotypic movements and post-ictal nose wiping.

Video sequence 3.

Left focal unaware seizure with ipsilateral stereotypic movements.

Video sequence 4.

Left focal electrographic seizure.

Key words for video research on www.epilepticdisorders.com

Phenomenology: automotor seizure (video sequences 1,2,3), EEG ictal discharge (infraclinical) (video sequence 4)
Localisation: temporal lobe (right) (video sequences 1,2), temporal lobe (left) (video sequences 3,4)
Syndrome: focal non-idiopathic temporal (tle)
Aetiology: limbic encephalitis

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TEST YOURSELF

(1) LGI-1 limbic encephalitis can be seen in:
A. Adults
B. Children
C. Both adults and children
D. None of the above

(2) LGI-1 limbic encephalitis can present with which of the following seizure types?
A. Faciobrachial dystonic seizures
B. Focal seizures with automatisms
C. Generalized tonic-clonic seizures
D. All of the above

(3) What is the first-line treatment for LGI-1 limbic encephalitis presenting with very frequent seizures?
A. Antiepileptic drugs
B. Pharmacological coma
C. Combination of IVIG and steroids
D. IVIG

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".