

# A rare case of antileucine-rich glioma-inactivated 1 encephalitis in a 14-year-old girl

Gökçen Özçifçi<sup>1</sup>, Tülay Kamaşak<sup>2</sup>, Derya Bako Keskin<sup>3</sup>

Departments of <sup>1</sup>Pediatric Intensive Care Unit and <sup>3</sup>Pediatric Radiology, University of Health Sciences Van Training and Research Hospital, Van; <sup>2</sup>Department of Pediatric Neurology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey.

## ABSTRACT

**Background.** Autoimmune limbic encephalitis in children occurs most frequently in those with antibodies against the N-methyl-D-aspartate glutamatergic receptor. We report the case of a 14-year-old girl who was diagnosed with antileucine-rich glioma-inactivated protein 1 limbic encephalitis.

**Case.** A fourteen years old, previously healthy girl applied to the emergency department with suspicion of dystonic seizure, ataxia, gait disturbance and speech disorders. Serum sample of the patient was positive for leucine-rich glioma inactivated protein 1 IgG.

**Conclusions.** Although it is a rare disease in childhood, in the presence of new onset psychotic symptoms or altered mental state, concomittant hyponatremia and unique type of seizures, anti leucine-rich glioma inactivated protein 1encephalitis should be considered in differential diagnosis.

**Key words:** leucine-rich glioma-inactivated 1 encephalitis, pediatric, faciobrachial dystonic seizure, autoimmune encephalitis.

Limbic encephalitis (LE) is an autoimmune neurological disorder associated with antibodies against various antigens.<sup>1,2</sup> In childhood, most patients with autoimmune LE develop with antibodies against the N-methyl-D-aspartate (NMDA) glutamatergic receptor.<sup>3</sup> The most common type of autoimmune encephalitis in adults is leucine-rich glioma-inactivated protein 1 (LGI-1)-associated encephalitis. Leucine-rich glioma-inactivated proteins 1–4 take a serious role in synaptic maturation, transmission, and myelination. One of the new autoantigens in autoimmune encephalitis is LGI-1.<sup>4</sup> The median age of patients with LE associated with the LGI-1 antibody is 60 years.<sup>5,6</sup> The clinical presentation is variable, including severe short-term memory loss, psychiatric disturbances, and various types of seizures such as faciobrachial dystonic seizures (FBDS).<sup>5,7</sup> Frequent focal seizures

were found in LGI-1-IgG-positive pediatric patients.<sup>7</sup> The condition may be complicated by severe hyponatremia in approximately 60% of cases.<sup>8</sup> Patients usually respond well to immunotherapy.<sup>9</sup> In this paper, we report the case of a 14-year-old girl who initially presented with ataxia and dysarthria, and was diagnosed with anti-LGI-1 LE.

## Case Report

A 14-year-old, previously healthy girl was brought to the emergency department because of suspected dystonic seizure, ataxia, gait disturbance, and speech disorders. The additional symptoms reported by the parents were personality changes, visual hallucination, intermittent disorientation, balance disorders, hyperanxiety, intermittent headaches, and vomiting for approximately one month.

On admission to the intensive care unit, a detailed neurological examination revealed dysarthria and 4/5 muscle strength in both the

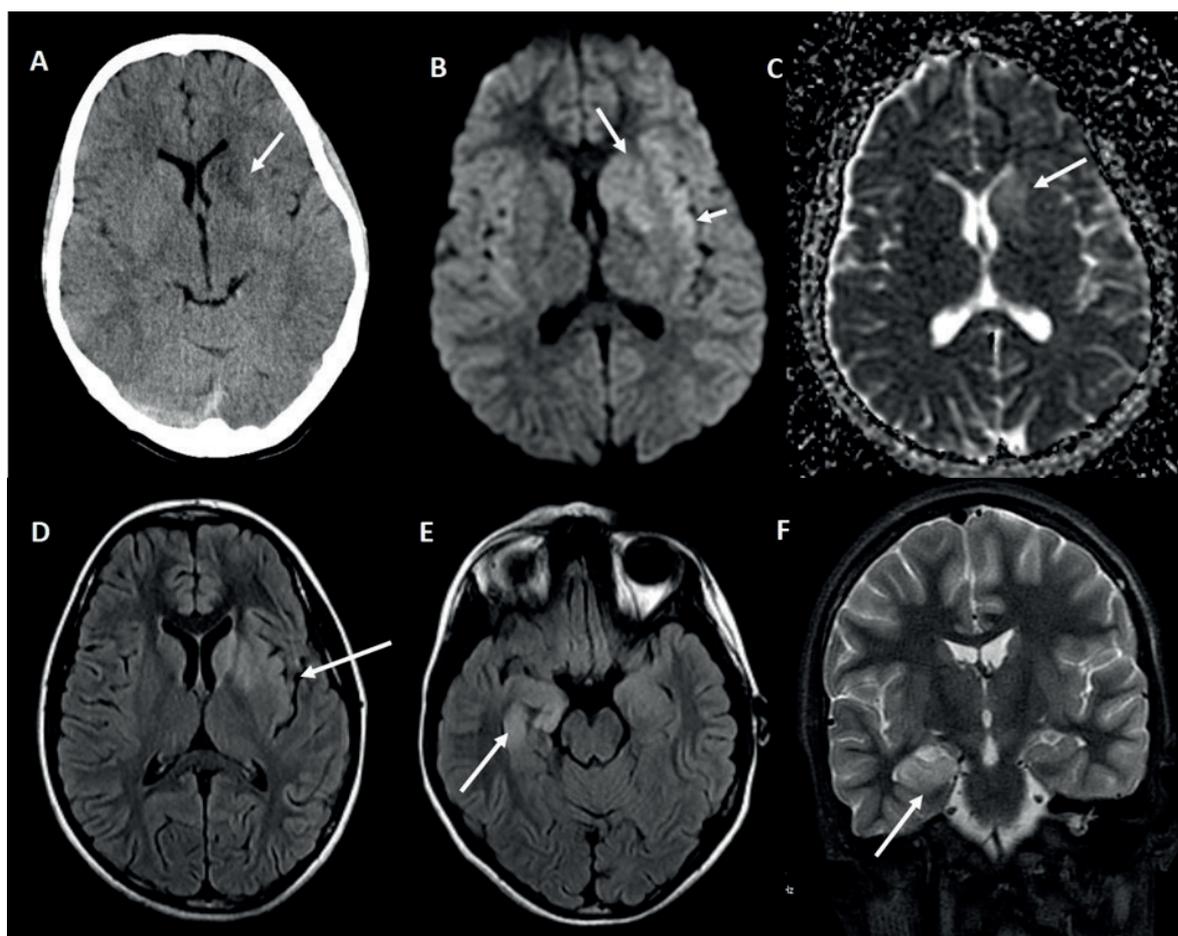
✉ Gökçen Özçifçi  
gkcnocifci@gmail.com

Received 6th April 2021, revised 21st June 2021,  
accepted 4th July 2021.

lower and upper extremities. Other components of the neurological examination were normal, mental orientation was good (Glasgow Coma Scale Score:15), and the cranial nerves remained intact. No signs of meningeal irritation were found. Other systemic examination results of the patient were normal. Except for hyponatremia (serum Na concentration, 125 mmol/L), no abnormalities were found in other laboratory tests neither in cerebrospinal fluid (CSF) examination.

Computed tomography (CT) of the head revealed a slightly hypodense area involving the left corpus striatum (Fig 1A). Consecutive

magnetic resonance imaging (MRI) of the brain revealed mild hyperintensity on the left corpus striatum and insula on diffusion-weighted imaging (Fig 1B) but no true restricted diffusion on the corresponding apparent diffusion coefficient map. Multifocal T2 fluid-attenuated inversion-recovery (FLAIR) hyperintensities and expansion were observed in the left frontal cortex, right medial temporal lobe, left insula and corpus striatum, right inferior frontal region, and left temporal lobe. We observed no hemorrhage on susceptibility-weighted images or contrast enhancement after administration of contrast media (Fig. 1).



**Fig. 1.** On non enhanced CT scan (A) slightly hypodense area involving left corpus striatum is seen (arrow). MR imaging of the brain demonstrates: mild hyperintensities in left corpus striatum (long arrow) and insula (short arrow) on DWI (B), but no restricted diffusion on the corresponding ADC map (C). On axial FLAIR images; hyperintensities and mild expansion involving left insula and corpus striatum (D), right medial temporal lobe, left temporal lobe and right inferior frontal lobe (E) is demonstrated. On coronal T2 image hyperintensity and expansion of right hippocampus is better visualized (F).

The typical involvement pattern on neuroimaging studies and clinical and laboratory findings were highly suspicious for autoimmune encephalitis. Although basal ganglia were involved and no hemorrhage was detected on the susceptibility-weighted images, which are useful for distinguishing from herpes simplex encephalitis, viral encephalitis were also included in the differential diagnosis because of similar appearance.

In accordance with the symptoms presented, administrations of maintenance fluid and sodium-correcting fluid, ceftriaxone (maximum, 4 g/d), acyclovir (maximum 1500 mg/d), and levetiracetam (20 mg/kg/d) were initiated. Administrations of pulse methylprednisolone were started at 30 mg/kg (maximum, 1 g/d) for five days. During the follow-up, the sodium level of the patient improved appropriately. The CSF culture and polymerase chain reaction (PCR) against herpes simplex type I and II viruses were negative. A serum sample was submitted for an autoimmune encephalitis panel and was positive for LGI-1 IgG (reference value: negative). Intravenous immunoglobulin (IVIG) treatment (2 g/kg for two days) was also given owing to the persistence of the brachial dystonic seizures and ataxia. The electroencephalogram performed on the patient was found to be normal. In addition, abdominal and thoracic imaging examinations were performed to rule out a paraneoplastic form of autoimmune LE.

The patient's symptoms completely improved, but short-term brachial dystonia recurred intermittently. The patient was discharged from the hospital with oral steroid therapy.

Written informed consent was obtained from the parents of the child.

## Discussion

Autoimmune encephalitis (AEs) are infrequent and various neurological diseases characterized by immune-mediated inflammation of the brain. AE phenotypes have mainly been reproduced from an antigen location.<sup>2,10</sup> With

increased research on autoimmunity, several new autoantibodies have been discovered and that expanded AE subtypes spectrum.<sup>10</sup> Antibodies targeting the extracellular matrix-associated components of the voltage-gated potassium channel complex (VGKC) can include those that target the proteins. Some of these proteins which coassociate directly or indirectly with the VGKC, are contactin-associated proteinlike 2 (CASPR2), contactin 2, dipeptidyl aminopeptidase-like protein 6 (DPPX), ADAM 22, ADAM 23, and LGI-1.<sup>4,11</sup> The VGKC is present on the membrane of neurons in the central and peripheral nervous systems. Leucine-rich glioma-inactivated protein 1 and CASPR2 are the proteins most frequently associated with the VGKC.<sup>4,10,12</sup> Leucine-rich glioma-inactivated protein 1 is mainly present in the hippocampus and temporal cortex.<sup>4,12</sup> LGI-1 LE has been reported predominantly in adults with a mean age at onset of approximately 63 years.<sup>6</sup> Our patient had one of the rare cases of LE with anti-LGI-1 antibodies in children in literature.

Patients with anti-LGI-1 encephalitis has often been misdiagnosed as a mental disorders since the disease progresses with acute or subacute onset of cognitive dysfunction. Its clinical manifestations are FBDS, cognitive disorder (mainly recent memory deterioration), epilepsy, mental disorder, hyponatremia, autonomic dysfunction, psychosis, hallucinations, emotional disturbances, spatial disorientation, and sleep disorders.<sup>6,9</sup> Our patient's initial symptoms were personality changes, hyperanxiety, and intermittent headaches. However, she was admitted to the hospital only when symptoms of dystonic seizure, ataxia, gait disturbance, and speech and balance disorders occurred, approximately one month after the onset of the initial symptoms.

In adults, an association between LGI-1 protein disturbances and abnormal seizure activity has been found in clinical and genetic studies.<sup>13,14</sup> Patients usually present with multiple seizure types, including the characteristic FBDS, focal tonic or clonic seizures, and myoclonic

seizures.<sup>6,9,15</sup> Focal seizures are common in a limited number of pediatric patients.<sup>7</sup> 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. Faciobrachial dystonic seizures are frequent but brief seizures lasting less than 5 seconds that may be associated with vocalization, fear, automatism, or loss of consciousness.<sup>16</sup> They can also present unilateral or bilateral arm posturing with facial grimacing lasting less than 3 seconds without loss of consciousness.<sup>17</sup> Our patient had brachial dystonic seizures lasting less than 5 seconds without loss of consciousness.

Lumbar puncture is essential in the diagnosis and exclusion of encephalitis. Autoantibodies to LGI-1 and VGKC can be detected in both CSF and serum, but serum tests are more sensitive.<sup>7,9</sup> Using both serum and CSF may increase the sensitivity of the test. In our patient, the lumbar puncture sample showed no abnormalities. However, we could not examine the antibodies in the CSF.

In several studies, hyponatremia has been observed in approximately 40%–60% of patients.<sup>6,9,12</sup> Serum sodium abnormalities correlate with the disease condition.<sup>8</sup> Our patient also had significant hyponatremia at the first admission.

Magnetic resonance imaging commonly, but not always, reveals hippocampal T2 hyperintensity.<sup>12</sup> Magnetic resonance imaging findings may be unilateral but are more commonly bilateral.<sup>18</sup> Neuroimaging findings may be absent in the early stages of the disease. Most patients with prolonged symptoms showed medial temporal MRI changes.<sup>18,19</sup> Furthermore, T1 hyperintensities in the basal ganglia have also been reported.<sup>7</sup> Positron emission tomography could be more sensitive than MRI and may be useful in the early diagnosis of the disease.<sup>6</sup> In our patient, MRI revealed T2-FLAIR hyperintensities and a mild expansion involving the left frontal cortex,

right medial temporal lobe, left insula and corpus striatum, right inferior frontal region, and left temporal lobe. No hemorrhage as well as contrast enhancement or a true diffusion restriction were observed.

The use of antiepileptic drugs alone for seizures and antipsychotic drugs for psychiatric symptoms is not generally effective. First-line treatment includes methylprednisolone and immunoglobulins, and a combination of these has been shown to be better. Patients show an excellent response to immunotherapy.<sup>9,12</sup> When methylprednisolone and immunoglobulins or plasmapheresis do not produce the desired therapeutic effect, the inclusion of pharmacotherapy in second-line therapy with rituximab or cyclophosphamide is recommended.<sup>20</sup> The condition usually has a good prognosis, with almost 70% of patients doing well after two years of follow-up. Disease recurrence, which can occur mostly within the first six months, accounts for 30% of patients. The major remaining symptoms are amnesia, spatial disorientation, and insomnia.<sup>6</sup> However, no clear data are available on the prognosis in childhood. In our patient, we used pulse methylprednisolone and IVIG therapy. Her symptoms completely improved, but short-term brachial dystonia recurred intermittently. Follow-up was continued with oral steroid therapy.

Consequently, though a rare disease in childhood, anti-LGI-1 encephalitis should be considered in the differential diagnosis in patients with new-onset psychotic symptoms or altered mental state, concomitant hyponatremia, and unique types of seizures.

### Acknowledgements

We thank the patient and her family for their participation in this study.

### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: GÖ;

data collection: GÖ, TK, DBK; analysis and interpretation of results: GÖ, TK, DBK; draft manuscript preparation: GÖ, TK, DBK. All authors reviewed the results and approved the final version of the manuscript.

### Source of funding

The authors declare the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

### REFERENCES

1. Tuzun E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. *The Neurologist* 2007; 13: 261-271. <https://doi.org/10.1097/NRL.0b013e31813e34a5>
2. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. *Lancet Neurol* 2011; 10: 759-772. [https://doi.org/10.1016/S1474-4422\(11\)70096-5](https://doi.org/10.1016/S1474-4422(11)70096-5)
3. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol* 2012; 27: 1460-1469. <https://doi.org/10.1177/0883073812448838>
4. Kegel L, Aunin E, Meijer D, Bermingham JR. LGI proteins in the nervous system. *ASN Neuro* 2013; 5: AN20120095. <https://doi.org/10.1042/AN20120095>
5. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010; 9: 776-785. [https://doi.org/10.1016/S1474-4422\(10\)70137-X](https://doi.org/10.1016/S1474-4422(10)70137-X)
6. Li W, Wu S, Meng Q, et al. Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. *BMC Neurol* 2018; 18: 96. <https://doi.org/10.1186/s12883-018-1099-z>
7. López-Chiriboga AS, Klein C, Zekeridou A, et al. LGI1 and CASPR2 neurological autoimmunity in children: LGI1 and CASPR2 Autoimmunity. *Ann Neurol* 2018; 84: 473-480. <https://doi.org/10.1002/ana.25310>
8. McQuillan RF, Bargman JM. Hyponatraemia caused by LGI1-associated limbic encephalitis. *Clin Kidney J* 2011; 4: 424-426. <https://doi.org/10.1093/ndtplus/sfr105>
9. Wang M, Cao X, Liu Q, Ma W, Guo X, Liu X. Clinical features of limbic encephalitis with LGI1 antibody. *Neuropsychiatr Dis Treat* 2017; 13: 1589-1596. <https://doi.org/10.2147/NDT.S136723>
10. Irani SR, Miller TD, Vincent A. Autoimmune encephalitis. In: Husain M, Schott JM (eds). *Oxf Textb Cogn Neurol Dement*. Oxford, United Kingdom: Oxford University Press, 2016: 299-314. <https://doi.org/10.1093/med/9780199655946.003.0028>
11. Griffith SP, Malpas CB, Alptsis R, O'Brien TJ, Monif M. The neuropsychological spectrum of anti-LGI1 antibody mediated autoimmune encephalitis. *J Neuroimmunol* 2020; 345: 577271. <https://doi.org/10.1016/j.jneuroim.2020.577271>
12. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology* 2016; 87: 1449-1456. <https://doi.org/10.1212/WNL.0000000000003173>
13. Manna I, Mumoli L, Labate A, et al. Autosomal dominant lateral temporal epilepsy (ADLTE): absence of chromosomal rearrangements in LGI1 gene. *Epilepsy Res* 2014; 108: 597-599. <https://doi.org/10.1016/j.epilepsyres.2013.11.011>
14. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol* 2011; 69: 892-900. <https://doi.org/10.1002/ana.22307>
15. Steriade C, Moosa ANV, Hantus S, Prayson RA, Alexopoulos A, Rae-Grant A. Electroclinical features of seizures associated with autoimmune encephalitis. *Seizure* 2018; 60: 198-204. <https://doi.org/10.1016/j.seizure.2018.06.021>
16. Li L, Ma C, Zhang H, Lian Y. Clinical and electrographic characteristics of seizures in LGI1-antibody encephalitis. *Epilepsy Behav* 2018; 88: 277-282. <https://doi.org/10.1016/j.yebeh.2018.08.019>
17. Vives-Rodriguez A, Sivaraju A, Louis ED. Drop attacks: a clinical manifestation of LGI1 encephalitis. *Neurol Clin Pract* 2017; 7: 442-443. <https://doi.org/10.1212/CPJ.0000000000000390>
18. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1-associated cognitive impairment: Presentation and long-term outcome. *Neurology* 2016; 87: 759-765. <https://doi.org/10.1212/WNL.0000000000003009>
19. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain* 2013; 136: 3151-3162. <https://doi.org/10.1093/brain/awt212>
20. Gastaldi M, Thouin A, Vincent A. Antibody-mediated autoimmune encephalopathies and immunotherapies. *Neurotherapeutics* 2016; 13: 147-162. <https://doi.org/10.1007/s13311-015-0410-6>