Child Neurology Open
Volume 9: 1-4

DOI: 10.1177/2329048X221105960
journals.sagepub.com/home/cno
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Faciobrachial Dystonic Seizures as a Sign of Relapse in a Child with LGI-1 Encephalitis

Wajd Alotaibi, MD[1], Shahid Bashir, PhD[2], and Ali Mir, MD[1]

Abstract

We report an interesting case of a young girl with LGI1-antibody encephalitis who presented at 7 years old with very frequent seizures and severe neurocognitive decline. She responded very well to high dose corticosteroids and intravenous immunoglobulin (IVIG) initially but relapsed after 7 months. The relapse included frequent faciobrachial dystonic seizures (FBDS) that were successfully treated with rituximab. This case report highlights a few important points about LGI1-antibody encephalitis in children to help clinicians recognize this condition early and start prompt treatment with immunosuppressants. Data is lacking about LGI1-antibody encephalitis in children as it is mostly reported in adults. Our patient presented with frequent drug-resistant seizures including FBDS, along with amnesia, confusion, medial temporal lobe involvement, and hyponatremia similar to the presentation in adults. In contrast, none of the patients in the recent systematic review had FBDS or hyponatremia, making our case unique and suggesting variability in clinical presentation in children similar to adults. To our knowledge, FBDS have never been reported in children and our patient was initially misdiagnosed as having Childhood Epilepsy with Centrotemporal spikes. Since receiving rituximab, our patient is seizure-free for 1 year and 9 months and was successfully weaned of topiramate. She is going to school and has normal attention, concentration, memory, and mood. We propose early consideration of rituximab to accelerate recovery and prevent relapse.

Keywords

leucine-rich glioma-inactivated 1 encephalitis, LGI-1, faciobrachial dystonic seizure, FBDS, rituximab, relapse

Received March 16, 2022. Received revised May 16, 2022. Accepted for publication May 20, 2022.

Introduction

Leucine-rich glioma-inactivated protein 1 (LGI1) is an antigen associated with voltage-gated potassium channel-complex (VGKC).[1] The LGI1-antibody associates limbic encephalitis with acute or subacute onset of frequent drug-resistant seizures including faciobrachial dystonic seizures (FBDS), as well as amnesia, confusion, medial temporal lobe involvement, and hyponatremia.[2] FBDS were first described as a distinctive adult-onset seizure type characterized by frequent, brief dystonic seizures predominantly affecting the arm and ipsilateral face.[3] The seizures were found to occur as a prodromal to the development of limbic encephalitis and were resistant to anti-seizure medications (ASMs) but highly responsive to immunotherapy.[3] Beneficial first-line treatment includes high-dose corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange (PLEX), or a combination of these therapies, similar to the treatment of all other autoimmune encephalitis.[4] In patients that do not respond to first-line therapies or in patients with relapses, second-line immunosuppressants like rituximab and cyclophosphamide are used. A weekly IV infusion of 375 mg/m^2 of rituximab for 4 weeks is effective as a second-line therapy. Previously, we reported a case of a 7-year-old girl with LGI1-antibody encephalitis who responded well to IVIG and steroids.[5] After a marked improvement for 7 months, she relapsed with frequent FBDS. Here, we present the same patient whose relapse was successfully and promptly treated with rituximab.

[1]Pediatric Neurology Department, King Fahad Specialist Hospital, Dammam, Saudi Arabia
[2]Neuroscience Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Corresponding Author:
Ali Mir, MD, Consultant Pediatric Neurologist & Epileptologist, King Fahad Specialist Hospital, Neuroscience Center, Ammar Bin Thabit Street, Dammam – 31444, Saudi Arabia.
Email: ali.mir@kfsh.med.sa

Case

The patient is a 10-year-old girl with a history of LGI1-antibody encephalitis. She presented at 7 years old with events of awakening from sleep and being frightened and making monkey-like whooping sounds.[5] After a few days, she developed a second type of seizure characterized by tonic flexion of the upper extremities with eye and mouth deviation, either left or right side, lasting for few seconds.[5] She was misdiagnosed at an outside hospital as having Childhood Epilepsy with Centrotemporal spikes. Her seizures became more frequent, almost 30-40 times per day. She was admitted to the pediatric intensive care unit (PICU) at the outside hospital, intubated, and put into a pharmacological coma for 2 weeks. Multiple ASMs were initiated and adjusted, including carbamazepine, phenytoin, phenobarbital, topiramate, and levetiracetam without significant improvement.

When we received the patient, she was encephalopathic and mute. The patient was admitted to the epilepsy-monitoring unit (EMU) and more than 400 left and right focal seizures were captured during 24 h of monitoring. She received 30 mg/kg pulse methylprednisolone for 5 days followed by IVIG at 2 g/kg over 2 days. The cerebrospinal fluid and serum samples were sent to Mayo Clinic Laboratories, Rochester, USA and were positive for the LGI1 IgG antibody [LGI1-IgG CBA, S – Positive (Reference value – negative)] and the serum sample also showed neuronal VGKC antibodies. Brain magnetic resonance imaging (MRI) with contrast revealed significant diffuse prominence of the supratentorial ventricles and extra-axial sulci related to diffuse supratentorial brain volume loss. There were no focal structural abnormalities identified. Magnetic resonance spectroscopy showed normal metabolite peaks. Positron emission tomography (PET) showed subtle hypometabolism in the right temporal and bilateral parietal cortices. A CT scan of the chest, abdomen, and pelvis was done to rule out paraneoplastic syndrome, and was unremarkable.

The patient showed a dramatic response to steroids and IVIG. Her seizures decreased significantly and she became more alert and oriented to surroundings. She started to verbalize some words before discharge. Upon follow-up three weeks after discharge, her seizures decreased to 2-4/day. She became more social and interactive with people and her speech was significantly better. Steroids were tapered over 6 months and she continued on IVIG monthly. Upon her 4-month follow-up, the patient had received a total of four doses of IVIG and her seizure frequency remarkably reduced to 1-2/month. The electroencephalogram (EEG) continued to improve significantly with a normal occipital dominant rhythm. Her cognition, attention, learning, memory, problem solving, executive functions, and memory were improved based on the Cambridge Neuropsychological Test Automated Battery (CANTAB).[5] Stanford-Benit Intelligence Scale, Fifth Edition was administered by psychologist to assess IQ and the patient scored 109 reflecting moderately high IQ. One month later, her seizures were exacerbated. She was admitted again to the EMU and started on 30 mg/kg of pulse IV methyl prednisone for 5 days and 2 g/kg IVIG over two days. She had no issues with cognition and speech. Seizures stopped after two days of initiating steroids and IVIG. She continued to be seizure-free for 7 months. Oral prednisolone was tapered and she continued on lacosamide, topiramate, and levetiracetam. A follow-up brain MRI after six months showed interval normalization compared to the initial MRI. She went to school with excellent school performance, normal attention, concentration, and memory, as per her mother's report.

After 7 months without seizures and returning back to neurocognitive baseline, she had a relapse in the form of frequent FBDS marked by dystonic posturing of the right arm and face (**Supplemental Video 1 and 2**). Some of the seizures were also associated with postictal urinary incontinence and incomprehensive speech and confusion. Sometimes these seizures had no manifestations on the face and only the upper extremity was involved. These seizures lasted for only a few seconds and reached up to 100 times a day. These seizures occurred in a cluster of two seizures with the first one being more intense than the second. Electrographically, the seizures were associated with diffuse spike-polyspike-wave bursts followed by 14 to 16 Hz moderate voltage activity and then diffuse voltage attenuation with overriding low-voltage fast activity (Figure 1A and B). Her ASMs were adjusted and she received two more doses of IVIG over a period of two months, but continued to have seizures and showed poor memory function on cognitive assessment. LGI1 IgG antibody was tested again and was positive. Rituximab was then used to treat the relapse. The initiation of rituximab was around 15 months from the initial seizure onset. A regimen of rituximab, which was given every week for 4 weeks, was used. She received 400 mg of rituximab per dose (435 mg/m^2 body surface area). The last dose of rituximab infusion was in January 2020. At the time of the fourth infusion, the patient had no seizures during wakefulness but she continued to have the same FBDS seizures, 3-4 times every night. During a follow-up visit 3 months later, mother reported that she became seizure free after the last dose of rituximab. She continued on carbamazepine, lacosamide, and topiramate. Her EEG also started to improve with the most recent EEG showing rare sharps in the left temporal-occipital regions, intermittent rhythmic theta in the left and right posterior temporal-occipital regions, intermittent sharply contoured theta slowing in the bilateral frontal regions, and a normal occipital dominant rhythm. A PET scan of whole body and CT of the chest, abdomen, and pelvis with contrast was repeated and was unremarkable. Her follow-up in July 2021 shows she has been seizure-free for 1 year and 9 months and was successfully weaned off of topiramate. Her mother reported normal attention, concentration, memory, and mood.

Discussion

LGI1-antibody encephalitis is rare in children and to the best of our knowledge; FBDS have never been reported in children. In this article, we present a 10-year-old girl with LGI1-antibody encephalitis relapse with FBDS, which were successfully treated with rituximab.

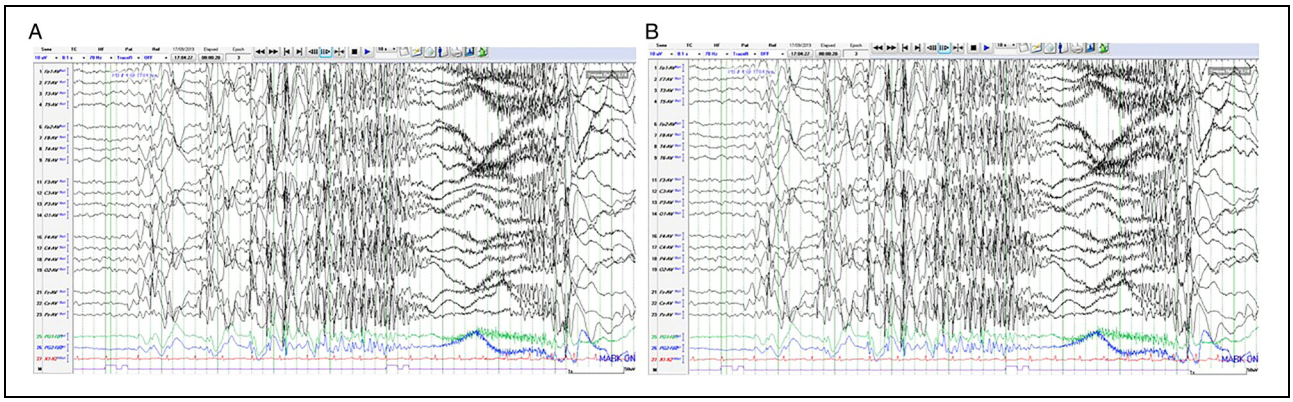

Figure 1. A: electrographic changes of FBDS 1 and B electrographic changes of FBDS 2.

LGI1-antibody encephalitis is mostly reported in adult patients and data are lacking in children. A recent systematic review in children found only 10 reported cases of LGI1-positive encephalitis.[6] This suggests the rarity of this condition in children. Our patient had FBDS and hyponatremia similar to the presentation in adult patients. In contrast, the systematic review showed that none of the patients had FBDS or hyponatremia, which makes our case very unique. FBDS were first described as an adult-onset, frequent, brief dystonic seizures and were found to occur as a prodromal to the development of limbic encephalitis.[3] In one adult study, FBDS were reported in almost 73% of patients.[7] Our patient's initial description of her seizures as reported from the referring hospital suggests that it was indeed FBDS that was misdiagnosed as Childhood Epilepsy with Centrotemporal spikes. When she relapsed, she presented with typical FBDS, which were never previously reported in children. This highlights the importance of early recognition of FBDS in children so that prompt immunotherapy can be started.

Relapses have been reported in around 27% of adult patients even after first-line treatments, and the predictors of a bad outcome included no response to initial treatment and clinical relapses.[8] In contrast to this, the systematic review done in children showed only one patient out of 10 cases of LGI1-positive encephalitis presented with relapse.[6] Rituximab and cyclophosphamide are the most commonly used second-line treatments for relapse of any antibody-mediated disease process. Rituximab, a B-cell depleting monoclonal antibody, is preferred over cyclophosphamide in children due to cyclophosphamide's potential serious side effect profile.[9] Rituximab also depletes the memory of the antibody-producing B-cells and has shown to be effective in anti-NMDAR encephalitis.[10] In patients with LGI1-antibody encephalitis, the Ab-immunoglobulin G (IgG) class was reported to be predominantly IgG4[8] and rituximab is considered particularly effective in IgG4-mediated disorders.[11] Our patient responded very well to rituximab. She continues to be seizure-free for 21 months. She is going to school and has normal attention, concentration, memory, and mood.

In conclusion, LGI1-antibody encephalitis is rare in children. To the best of our knowledge, we describe the first pediatric case with FBDS and highlight the importance of early recognition. Like in adults, relapse can occur in children, but is very rare. Prompt treatment with rituximab can accelerate recovery and prevent relapse. Larger studies are needed in children to better define the clinical spectrum of this condition.

Author Contributions

WA designed the study, collected the clinical data and wrote the main draft. SB collected the data and edited the main draft. AM designed the study, interpreted the clinical findings and wrote the main draft.

Consent for Publication

Written informed consent was obtained from the patient for publication of this research.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

ORCID iD

Shahid Bashir https://orcid.org/0000-0001-6286-6895

Trial Registration

Not applicable, because this article does not contain any clinical trials.

Supplemental material

Supplemental material for this article is available online.

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