Painful Itch in a Fidgety Girl

Dear Editor,

The anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis typically presents in the elderly male with faciobrachial dystonic features, hyponatremia, behavioral and cognitive features. Morvan syndrome (MoS) with CASPR2 mainly presents autonomic, hyperexcitability, and psychiatric disturbances. The literature has sparse reports of young female patients with LGI1 antibody positivity. Hence, we present a case of a young girl with LGI1 antibody-positive syndrome with unique clinical and magnetic resonance imaging (MRI) findings.

A 17-year-old female with no prior comorbidities presented with generalized body pain, crying spells, and backache for 2 months. Almost 1 month after the disease onset, she developed vaginal itching, with associated flushing and sweating. She became socially withdrawn and showed a lack of interest in studies and a lack of interaction with peers. She expressed death wishes and had reduced sleep. Two weeks later, she became confused with irrelevant talk.

On admission, her blood pressure was 160/100 mmHg and her pulse rate was 98/min. After correction of serum sodium to 130 mEq/L, her neurological examination was normal and Mini mental status examination (MMSE) and Montreal Cognitive Assessment (MoCA) were 30. There was no myokymia. Local pelvic examination was normal in this patient without any evidence of pelvic inflammatory disease or tumor.

The clinical differentials considered in this case were viral encephalitis, autoimmune encephalitis (LGI1, N - methyl- D - aspartate), new-onset nonorganic psychosis, and metabolic causes like toxic exposure, including indigenous herbal and Siddha medications.

The routine blood tests, including complete blood count, hematocrit, liver and kidney function tests, were unremarkable. Given hypertension, the following investigations were done: serum sodium (107 mEq/L corrected to 132 mEq/L), urine osmolality (417 mOsm/kg), serum osmolality (223 mOsm/kg), serum creatine phosphokinase 356 µg/L, serum cortisol normal, 24-h urinary protein 106 mg/day, urinary metanephrines 116 µg/24 h, and repeat urinary metanephrines 86 µg/24 h. Ultrasound of the abdomen was normal. Thyroid function test results were as follows: thyroid stimulating hormone (TSH) 4.5 mIU/L, T3 1.1 ng/mL, T4 7.34 µg/dL, with 4 IU/mL Anti-Thyroperoxidase. Antinuclear antibody (anti-TPO ANA) immunofluorescence with profile was negative. Cerebrospinal fluid (CSF) study showed no pleocytosis with protein 20 mg/100 mL and sugar 56 mg/100 mL. Electromyography showed normal insertional activity, no myokymia, no spontaneous activity, and Motor Unit Action Potential (MUAP) morphology. The electroencephalogram awake record showed a 9-Hz background activity with no epileptiform activity, and sleep showed no activation. The polysomnogram showed absence of deep sleep and high-frequency delta activity. Nerve conduction study showed normal Compound Muscle Action Potential and Sensory Nerve Action Potential (CMAP and SNAPs) in both upper and lower limb nerves.

Magnetic resonance imaging (MRI) brain showed diffusion restriction with the corresponding hypointensity on Apparent Diffusion Coefficient (ADC) in bilateral centrum semiovale extending into corona radiata. MRI brain T1, T2, Fluid Inversion Recovery (FLAIR), Gradient Echo (GRE), and contrast studies were normal.

Serum antibody testing using a cell-based assay showed LGI1-Ab (Voltage gated potassium channel [VGKC] type) to be positive, while CASPR2-Ab, AMPA1, and AMPA2 antibodies were all negative. Ultrasound of the neck showed colloid nodules in the left lobe of the thyroid gland (BIRADS I). MRI of the pelvis showed bilateral polycystic ovarian disease with no evidence of ovarian teratoma. Computed tomography (CT) thorax had no thymoma.

She was treated with pulse methylprednisolone, 1000 mg/day for 5 days, followed by oral prednisolone 50 mg daily. Pain was treated with gabapentin 300 mg and insomnia with lorazepam 0.5 mg. Hypertension was controlled with enalapril 10 mg. However, her pain, irritability, and resting tachycardia persisted. Hence, she was given the first dose of rituximab 500 mg. Her neuropathic pain, itching, and flushing symptoms significantly improved. Two weeks later, she was given the second dose of rituximab and oral prednisolone 40 mg was continued. We could not do the follow-up MRI on this patient.

The patient had a combination of central nervous system (irritability, fatigue, insomnia), peripheral nervous system (neuropathic pain and itching), and autonomic nervous system (excessive sweating, tachycardia, and hypertension) symptoms. The patient did not have clinical or electrophysiological evidence of neuromyotonia, despite her intractable neuropathic pain and itching.

This overlapping spectrum of symptoms is similar to that in patients with VGKC complex antibody-positive cases, where LGI1 and CASPR2 reactivity is negative.[1]

Our patient had symmetrical diffusion restriction with corresponding low signals on ADC in bilateral centrum semiovale extending to corona radiata with normal T1, T2, FLAIR, and GRE sequences. Only typical LGI1 antibody-positive encephalitis presenting with faciobrachial dystonic seizures has T2/FLAIR hyperintensities in the bilateral medial temporal lobe and deep gray matter on MRI brain. This contrasts with the MRI in CASPR2/VGKC complex, which is

usually normal. To the best of our knowledge, the presence of symmetrical diffusion restriction in centrum semiovale on MRI has not been described in LGI1/VGKC encephalitis till now.

Symmetrical diffusion restriction in bilateral centrum semiovale is usually seen in acute toxic or metabolic encephalopathy. However, such cases would have corresponding T2/FLAIR hyperintensity changes. Given the severe documented hyponatremia and its subsequent correction, the possibility of osmotic demyelination syndrome needs to be considered. However, osmotic demyelination syndrome can produce symmetric hypointensity on T1-weighted images and hyperintensity on T2/FLAIR images with or without diffusion restriction. It commonly involves the basis pontis and extends from the pontomedullary junction into the midbrain with characteristic sparing of the tegmentum. In the acute phase, restricted diffusion is observed on diffusion-weighted imaging (DWI) with corresponding low ADC values.

Although our patient had symptomatic hyponatremia, she never developed clinical signs of pontine or extrapontine myelinolysis. Hence, the possibility of osmotic demyelination syndrome causing MRI changes is unlikely. There was no toxic exposure to account for the same.

A rare possibility would be leukodystrophies; however, the absence of changes in T2/FLAIR images and the clinical presentation do not support this.

In the literature, white matter involvement in autoimmune encephalitis has been reported in anti-NMDA, CASPR2, GABA A, and anti-GAD encephalitis. The mechanisms responsible for the different propensities of involved brain regions remain unclear.[2]

Although dysautonomia is the defining feature in MoS with CASPR2 positivity, dysautonomia in LGI1 has been reported to be close to 23%.[3,4] The cause of autonomic dysfunction is thought to be small fiber neuropathy or the overlapping symptoms due to VGKC antibodies. Pruritus in isolated LGI1-positive cases is very rare and the mechanism is not clear.[5] Extreme pruritus has been described in anti-DPPX encephalitis. In CASPR2 antibody-positive cases, the downregulation of Caspr2/Kv1.1/1.2 complexes due to binding of CASPR antibodies leads to neuromyotonia, neuropathic pain, and autonomic dysfunction.[6]

Our patient is a young female diagnosed with LGI1 antibody-positive syndrome with overlapping features of both LGI1 and CASPR2 (hyponatremia, behavioral disturbances, insomnia, dysautonomia, and pruritus), suggesting involvement of VGKC antibodies.[7] Reports of young female patients with atypical overlapping features and isolated LGI1-Ab seropositivity are scarce. [8,9] We would also like to highlight our patient's atypical MRI brain findings. Our case also supports the view that non-neoplasm–associated patients respond well to steroids and rituximab.[10] A longer follow-up is essential to understand the manifestations of LGI1 and VGKC syndrome, especially in younger age groups.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 24-Jul-2023 **Revised:** 01-Dec-2023 **Accepted:** 17-Dec-2023
Published: 27-Jan-2024

DOI: 10.4103/aian.aian_651_23