

CASE REPORT

Leucine-rich glioma-inactivated protein 1 (LGI-1) mediated limbic encephalitis associated with syndrome of inappropriate antidiuretic hormone secretion: a case report

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Abstract

Autoantibodies to leucine-rich glioma-inactivated protein 1 (LGI-1) are associated with inflammation of the limbic system. Faciobrachial dystonic seizures are pathognomonic for LGI1-antibodies and their treatment with immunotherapy is effective in seizure control with a potential to prevent cognitive decline. We report a 57-year-old man who presented to the emergency department with recurrent seizures, visual hallucinations and severe memory impairment over a seven-week period; he reported a background of alcohol excess. Initial investigations revealed hyponatremia, indicating syndrome of inappropriate anti-diuretic hormone secretion. Magnetic resonance imaging of the brain revealed bilateral asymmetrical high-T2 and low-T1 signal in the medial temporal lobes. Serum immunofluorescence assay tested positive for LGI-1 antibody. Patient responded to treatment with levetiracetam, intravenous methylprednisolone and five plasma exchange sessions. Patient remains on a maintenance dose of prednisolone and azathioprine. It is imperative that clinicians recognize signs of autoimmune encephalitis in order to curb long-term sequelae and improve clinical outcomes.

INTRODUCTION

Autoimmune Encephalitis (AIE) is an immunological response characterized by onconeural antibodies directed against intracellular proteins and a more recently discovered novel group of antibodies targeting cell surface neuronal receptors or synaptic proteins. This new group of antibodies may alter the target's function by receptor internalization and inhibition or disruption of ligand-receptor interaction [1]. The limbic system is a predilection in AIE. Clinical symptoms can be varied and include behavioral changes, memory deficits, psychosis and seizures. Leucine-rich glioma-inactivated protein 1 (LGI-1) is part of the

voltage gated potassium channel (VGKC) network and is involved in synaptic functions. We report a case of a LGI-1 mediated limbic encephalitis in an adult male associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH).

CASE REPORT

A 57-year-old male presented to the emergency department with first episodes of seizures. His wife reported 7 weeks of confusion, disorientation, visual hallucinations and severe memory impairment. He reported a background of excess alcohol

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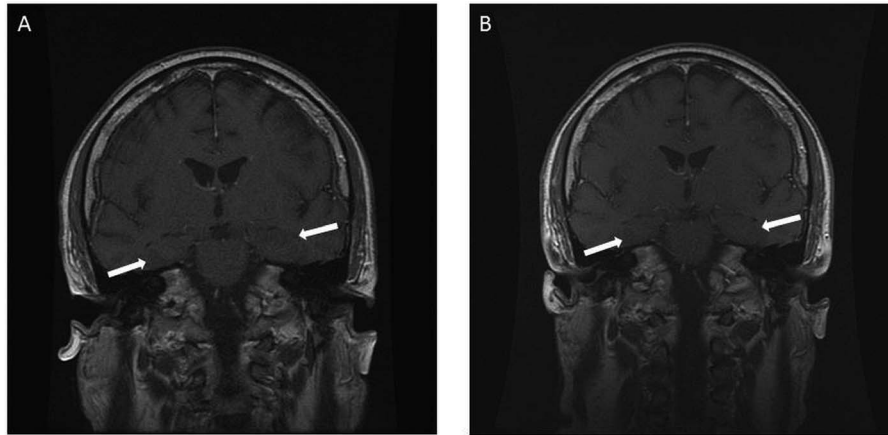


Figure 1: Magnetic resonance imaging of the brain coronal view showing bilateral and asymmetrical hypointensities on T1-weighted images in hippocampi with no change in intensity after intravenous contrast administration (image A, white arrows). Post immunosuppressive therapy there was partial resolution of the changes (image B, white arrows).

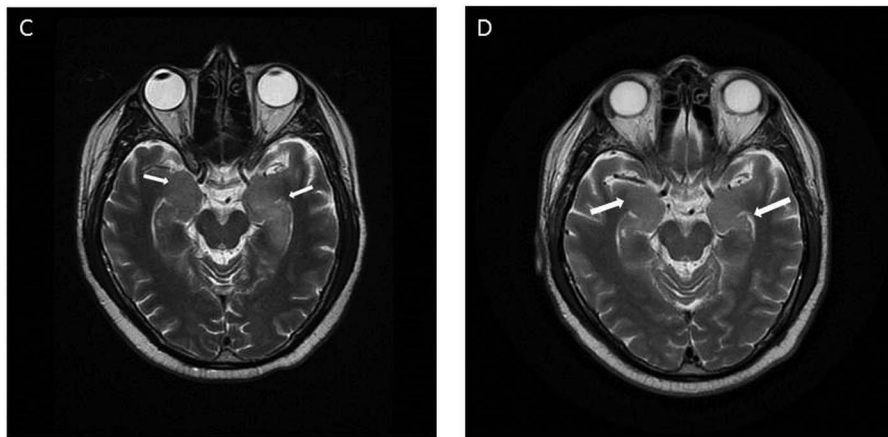


Figure 2: Magnetic resonance imaging of the brain axial view showing bilateral and asymmetrical increase in volume and T2 signal intensity in the medial temporal lobes (image C, white arrows) with partial resolution of changes post therapy (image D, white arrows).

intake of 150 units per week. On examination, he was disoriented in time and place, areflexic, ataxic and had a mild postural tremor. Laboratory values found significant hyponatraemia (127 mmol/L), hypo-osmolality (264 mOsm/Kg), raised urinary sodium (82 mmol/L) and raised urine osmolality (498 mOsm/Kg), all suggestive of SIADH. His renal, thyroid and adrenal function tests were normal. Computed tomography (CT) head found no acute intracranial pathology. CT chest, abdomen, pelvis revealed no underlying malignancy and a paraneoplastic antibody screen was negative. He was treated for alcohol-related seizures, placed on a 1 L fluid restriction and discharged to his general practitioner for serum sodium monitoring.

He had multiple additional attendances to the emergency department over the course of 2 months with further seizures. These consisted of 3–4 minutes of continuous rapid eye blinking together with 3–5 second episodes of tense, jerking movements of the right arm, followed by movement in the right leg. A diagnosis of autoimmune encephalitis was suspected. Cerebrospinal fluid sampling revealed normal protein with no evidence of oligoclonal bands. Electroencephalography showed muscle artifact. Video electroencephalography revealed a number of attacks consistent with faciobrachial dystonic seizures. Magnetic resonance imaging (MRI) of the brain demonstrated bilateral asymmetrical hyper-intensities in the medial temporal lobes on

T2-weighted images with low intensity signals on T1 (Figs 1 and 2). Immunofluorescence assay of the serum tested positive for LGI-1 antibody and a diagnosis of autoimmune limbic encephalitis was made.

Levetiracetam was given for seizures and 60 mg oral prednisolone for encephalitis. However, slow improvement prompted the need for intravenous methylprednisolone and five plasma exchange sessions. Follow-up was arranged in a neuroimmunology clinic where the patient was started on azathioprine. Repeat MRI showed partial resolution of original findings (Figs 1 and 2) and CT chest, abdomen, pelvis was normal. His sodium levels normalized accompanied by significant improvement in cognition and confusion (Fig 3). He remains on azathioprine and maintenance dose of prednisolone with regular follow-up in the clinic.

DISCUSSION

Limbic encephalitis has been long considered a paraneoplastic phenomenon, but autoimmune cases are being increasingly reported [2]. In AIE, antibodies are directed towards the intracellular or cell surface proteins. One such surface protein is LGI1, mainly present in the hippocampus and the temporal

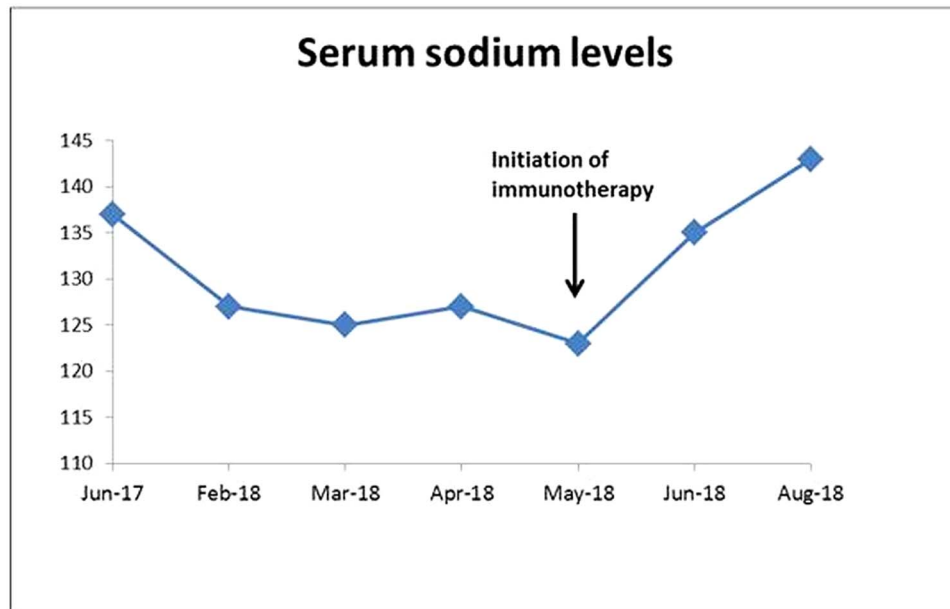


Figure 3: A graph showing improvement of sodium levels post initiation of immunotherapy treatment

Table 1: A table adapted from Hermetter *et al.* [9] illustrating the clinical features, MRI findings and male to female predominance in target proteins associated with limbic encephalitis

Target proteins associated with limbic encephalitis	Clinical features	MRI findings	Female:Male ratio
AMPA-R	Rapid progression, predominant psychosis, seizures	Hypertense signal in medial temporal lobes (90%)	9:1
GABAb-R	Early and frequent prominent seizures or status epilepticus, ataxia and opsoclonus-myoclonus syndrome	Hypertense signal in medial temporal lobes (>60%)	1:1
LGI-1	Highly repetitive, unilateral faciobrachial dystonic seizures, Hyponatraemia, sleep disorders, myoclonia	Hypertense signal in medial temporal lobes and basal ganglia (>80%)	1:2
GAD	Seizures, cerebellar ataxia, stiff person syndrome	Not known	Not known
CASPR2	Morvan syndrome, neuromyotonia, polyneuropathy, bulbar weakness	Normal or hypertense signal in medial temporal lobes (~40%)	1:4

cortex of the brain. Antibodies to LGI-1 are associated with limbic encephalitis and are characterized by disturbance of memory, behavior and spatial orientation [3]. There is 2:1 male predominance with median age of onset at 60 years. Seizures are common and include both partial and generalized tonic-clonic seizures. FBDS are specific for LGI-1 encephalitis; these are brief episodic (<3 s) unilateral contractions of the arm and ipsilateral hemiface that affect in descending frequency the arm, face or leg [4]. FBDS often precede the onset of cognitive decline [4]. In addition to FBDS, gelastic seizures, ictal bradycardia, sensory and autonomic seizures with piloerection and thermal sensations have also been recognized in patients with LGI-1 encephalitis [5]. Hyponatraemia is present in 60% of the anti LGI-1 patients. In 50% of the cases, MRI of the brain shows bilateral hyperintense signals in medial temporal lobes and basal ganglia [4]. Clinicians can make an early diagnosis of probable autoimmune encephalitis before antibody detection in the presence of subacute onset of symptoms (< 3 months) including personality changes, frequent focal seizures (FBDS), cerebrospinal fluid

pleocytosis, hyperintense signals on T2 weighted/FLAIR in both medial temporal lobes and no reasonable alternative diagnosis. Antibody detection is confirmatory but can be negative in 50% of cases with autoimmune encephalitis [6, 7]; measuring LGI-1 antibody levels may be more sensitive and specific in diagnosing AIE than the original method of using VGKC-complex antibody titers [8]. Table 1 illustrates features of non-FBDS associated limbic encephalitis [9]. The complications of autoimmune encephalitis if left untreated include coma, hyperkinesia, autonomic dysfunction, prolonged need for artificial respiration and intensive care treatment [9].

First line therapy for autoimmune encephalitis involves corticosteroids with intravenous immunoglobulins (IVIG) and/or plasma exchange (PLEX). Rituximab or cyclophosphamide is used as second line agents, with the former having the least side effects [6]. Long-term steroid sparing agents such as azathioprine or mycophenolate may be considered useful. The optimal duration of these treatments is unknown, however, frequent relapses in LGI-1 encephalitis require longer or

continuous treatment with serum antibody titer monitoring. Seizures can be difficult to control in certain situations and coma may need to be induced pharmacologically for the autoimmune process to regress.

Hyponatraemia secondary to SIADH has been noted in patients with LGI-1 antibodies. LGI-1 antibodies bind to the paraventricular nucleus neurons in the hypothalamus that produce ADH. This binding inadvertently may increase ADH secretion precipitating water retention and hyponatraemia [10]. Resulting SIADH may not respond to fluid restriction alone. Such patients require immunosuppressive therapy for normalization of serum sodium levels. Our patient showed minimal response to fluid restriction; however, a significant improvement was noted with methylprednisolone therapy clearly pointing towards a pathogenic role of the antibodies in the induction of SIADH.

Autoimmune encephalitis can be detected early with recognition of certain symptom constellations. Early treatment of FBDS with immunotherapy is key to optimizing clinical outcomes. Associated SIADH can be challenging to treat and often responds to immunosuppressive therapy.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

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ETHICAL APPROVAL

No ethical approval was required.

CONSENT

The patient has given written consent to publish features of his/her case and the identity of the patient has been protected.

GUARANTOR

Satyanarayana Sagi.

REFERENCES

1. Weissert R. Adaptive immunity is the key to the understanding of autoimmune and paraneoplastic inflammatory central nervous system disorders. *Front Immunol* 2017;8:336. doi: [10.3389/fimmu.2017.00336](https://doi.org/10.3389/fimmu.2017.00336).
2. Dalmau G. Antibody-mediated encephalitis. *NEJM* 2018;378:840–51. doi: [10.1056/NEJMra1708712](https://doi.org/10.1056/NEJMra1708712).
3. Finke C, Pruss H, Heine J, Reuter S, Kopp U, Wegner F, et al. Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with Leucine-rich, Gliom-inactivated 1 antibodies. *JAMA Neurol* 2017;74:50–9. doi: [10.1001/jamaneurol.2016.4226](https://doi.org/10.1001/jamaneurol.2016.4226).
4. Thompson J, Bi M, Murchison AG, Makuch M, Bien CG, Chu K, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. *Brain* 2018;141:348–56. doi: [10.1093/brain/awx323](https://doi.org/10.1093/brain/awx323).
5. Binks SNM, Klein CJ, Waters P, Pittock SJ, Irani SR. LGI1, CASPR2 and related antibodies: a molecular evolution of the phenotypes. *J Neurol Neurosurg Psychiatry* 2018;89:526–34. doi: [10.1136/jnnp-2017-315720](https://doi.org/10.1136/jnnp-2017-315720).
6. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. Clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404. doi: [10.1016/S1474-4422\(15\)00401-9](https://doi.org/10.1016/S1474-4422(15)00401-9).
7. Lee SK, Lee ST. The laboratory diagnosis of autoimmune encephalitis. *J Epilepsy Res* 2016;6:45–52. <http://dx.doi.org/10.14581/jer.16010>.
8. Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schenider SA, Pettingill P, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain* 2013;136:3151–62. doi: [10.1093/brain/awt212](https://doi.org/10.1093/brain/awt212).
9. Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis. *Front Neurol* 2018;9:706. doi: [10.3389/fneur.2018.00706](https://doi.org/10.3389/fneur.2018.00706).
10. Irani SR, Pettingill P, Kleopa K, Schiza N, Waters P, Mazia C, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol* 2012;00:000–0. doi: [10.1002/ana.23577](https://doi.org/10.1002/ana.23577).