Medical and Research Publications
International Open Access

Case Report **Journal of MAR Neurology and Psychology (Volume 4 Issue 4)**

A Case of Immunotherapy Responsive LGI1 Limbic Encephalitis Previously Misdiagnosed as Alzheimer's Disease

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Received Date: March 17, 2022

Published Date: April 01, 2022

Abstract

Leucine-rich glioma-inactivated 1 (LGI1) protein, a vital component of the voltage gated potassium channel (VGKC) complex, is associated with rare autoimmune limbic encephalitis. Due to overlapping symptoms, there is a propensity to misdiagnose it as dementia or Alzheimer's disease. Here, we present case of an elderly gentleman having behavioral and cognitive dysfunction, who was initially misdiagnosed as having Alzheimer's and treated accordingly for 8 months. However, due to non-responsiveness to therapy and worsening clinical condition, he was referred to us. Our diagnostic work up revealed LGI1 autoimmunity. The patient was promptly put on immunotherapy. He showed significant clinical improvement. This an important case study which reinforces the need to test for autoimmune etiology. It is an important, but sometimes overlooked work up, which proves critical in early diagnosis, quick immunotherapy if required, and good prognosis. Cases like these can be frequently misdiagnosed as neurodegenerative disorders. It is therefore, imperative to determine autoimmune etiology early in the course of the illness in order to achieve near full recovery.

Keywords*: LGI1, autoimmune neurology, dementia, Alzheimer's, VGKC*

Introduction

Leucine-rich glioma-inactivated 1 (LGI1) is a scaffolding protein. It is a critical part of the voltage gated potassium channel (VGKC) complex on neural synapses, the other component being contactin-associated protein-like 2 (Caspr2). It is classified as an anti-neuronal surface antigen or anti-synaptic protein, associated with rare autoimmune limbic encephalitis. There are two pathogenic mechanisms involving LGI1 antibodies - reducing the formation of the LGI1-ADAM complex and altering the dendritic spine density of neurons located in the dentate gyrus and thalamus. [1,2,3]

LGI1 encephalitis patients are characterized by acute or subacute onset of cognitive dysfunction. This makes the disease vulnerable to be misdiagnosed as a mental illness. Recent publications have brought to light additional clinical features. These include neuropsychiatric symptoms and mental disorders including visual hallucination, paranoia, depression, anxiety and dysphoria; faciobrachial dystonic seizure (FBDS), refractory hyponatremia, Morvan syndrome (MoS) and acute psychosis. [4,5,6,7]

MRI tend to show abnormalities in the mediotemporal lobe and hippocampus. CSF evaluation is generally normal or non-specific. Unlike other limbic encephalitides, LGI1 antibody encephalitis is rarely accompanied by tumors. Most importantly, LGI1 encephalitis has been shown to be responsive to

immunotherapy and hence treatable. Definitive and early diagnosis and detection of LGI1 antibodies in serum and/or CSF is the key to avoid misdiagnosis and prevent long term sequalae.

Here, we present a case of an 80-year-old gentleman suffering from LGI1 encephalitis, who was initially misdiagnosed with Alzheimer's dementia because of his old age and clinical manifestations. The patient showed marked improvement on immunotherapy.

Case Report

Onset of Symptoms:

Symptoms started to appear eight months before the patient was brought into our hospital, a tertiary care multispecialty referral center in South India. He had slowly progressive behavioral disturbances and memory impairment. However, they were not simultaneous. The behavioral symptoms appeared first. His demeanor started to become aggressive, a complete deviation from his natural personality. He also started to move around restlessly in his room. These behavioral disturbances gradually worsened over last two months. Five months after the onset of behavioral problems, cognitive decline started to set in. He was unable to perform his routine activities like operating his computer and managing his finances. Other activities of daily living (ADL) were also impaired, resulting in complete dependency on his wife. These memory disturbances have been there for past three months and gradually worsening.

Previous Treatment:

Considering the onset of behavioral symptoms, the patient was initially treated by psychiatrists. He was managed as a case of Alzheimer's dementia. The possibility of this was considered because of his age and slowly progressive symptoms. He was being treated with Quetiapine for behavioral disturbances, Acetylcholine esterase inhibitors for memory loss and Memantine (NMDAR antagonist) for Alzheimer symptoms. However, despite being on these medications, the patient did not show any signs of improvement. His condition, in fact, deteriorated gradually over time. It is at this point in time, eight months after the initial onset of symptoms, that he was brought under our care.

Differential Diagnosis and Routine Investigations:

After clinical examination and a detailed review of his disease progression and response to therapy, we inferred that his case was slightly atypical for Alzheimer's. This was primarily for two reasons – a) onset of behavioral disturbances first, followed by memory loss, and not the other way round, which is usually the case in Alzheimer's and b) rapid transition from onset of symptoms to complete dependence on his

wife for ADL. His condition didn't mimic chronic meningitis or viral encephalitis because of the sub-acute onset and progressive nature of his disease.

We inferred that his condition was suggestive of autoimmune or paraneoplastic etiology (paraneoplastic encephalitis) and it was less likely that he was suffering from a neurodegenerative disorder. His Montreal Cognitive Assessment (MoCA) score was 7/30 on arrival. He was admitted for seven days and all initial investigations were conducted as an inpatient.

All parameters on his CSF were normal. However, his MRI revealed a small focal area of diffusion restriction in right amygdala. Subtle T2/FLAIR hyperintensities in bilateral hippocampi formation was seen. The final impression was suggestive of autoimmune or paraneoplastic limbic encephalitis due to the presence of slightly edematous bilateral hippocampal formation. [Figure 1] His EEG was normal.

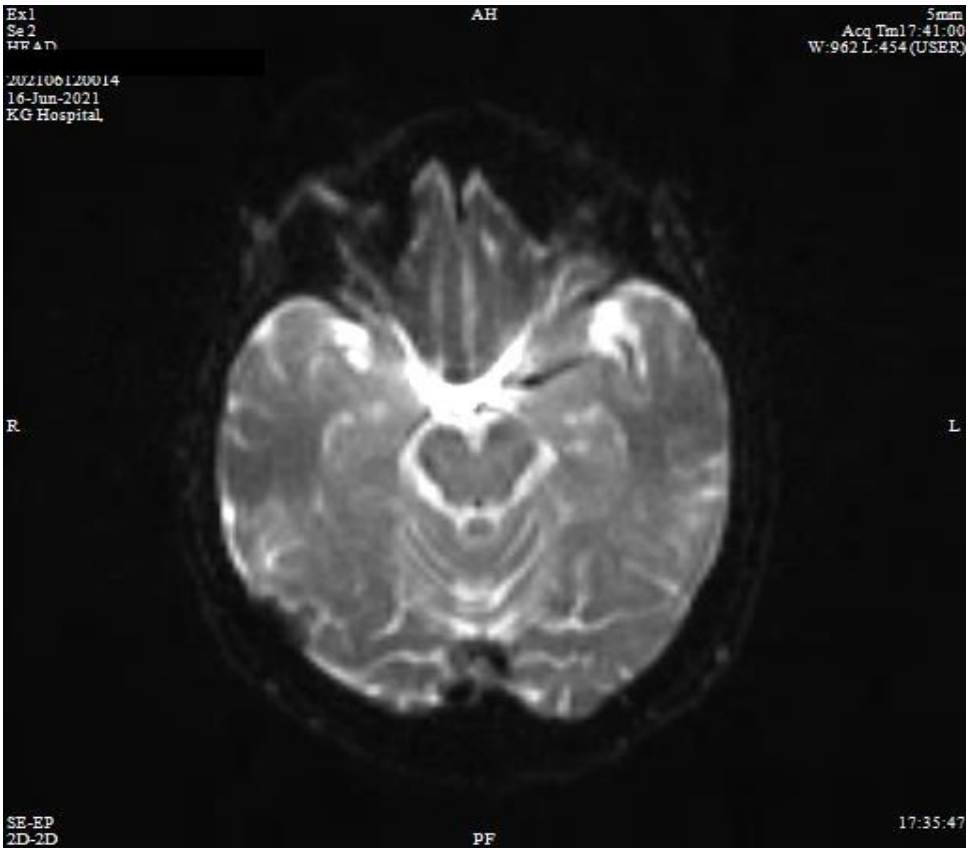

Figure 1: MRI showing a small focal area of diffusion restriction in right amygdala. The final impression was suggestive of autoimmune or paraneoplastic limbic encephalitis due to the presence of slightly edematous bilateral hippocampal formation.

Autoimmune and Paraneoplastic Work-up:

His serum sample was sent to neuroimmunology laboratory, Amrita Institute of Medical Sciences (AIMS) for evaluation of autoimmune encephalitis and paraneoplastic syndrome panels. It was strongly positive for LGI1 antibody [Figure 2] and negative for GABA-B receptor antibody, glutamate receptor (NMDAR) antibody, contactin-associated protein 2 (Caspr2) antibody, AMPA 1 and AMPA 2 antibody. In the paraneoplastic panel, his serum sample was negative for antineuronal nuclear antibodies (ANNA-1,2,3), purkinje cell cytoplasmic antibodies (PCA1,2, Tr), antiglial nuclear antibody (AGNA-1), amphiphysin, collapsin response mediator protein-5 (CRMP-5) and Ma/Ta antibodies.

LGI1, CASPR2 and NR1 subunit of NMDA receptor antibodies were tested by indirect immunofluorescence on human embryonic kidney (HEK) cell 293 transfected with corresponding antigens (Euroimmun AG, Lubeck, Germany). Paraneoplastic neuronal antibodies were tested on a substrate containing monkey cerebellum, sural nerve and intestine (neurology mosaic, Euroimmun AG, Lubeck, Germany) by indirect immunofluorescence. They were identified with immunofluorescence and confirmed with Euroline neuronal antigen profile 2 (Euroimmun AG, Lubeck, Germany). Immunofluorescence at a dilution of 1:10 was considered as positive as instructed by the manufacturer.

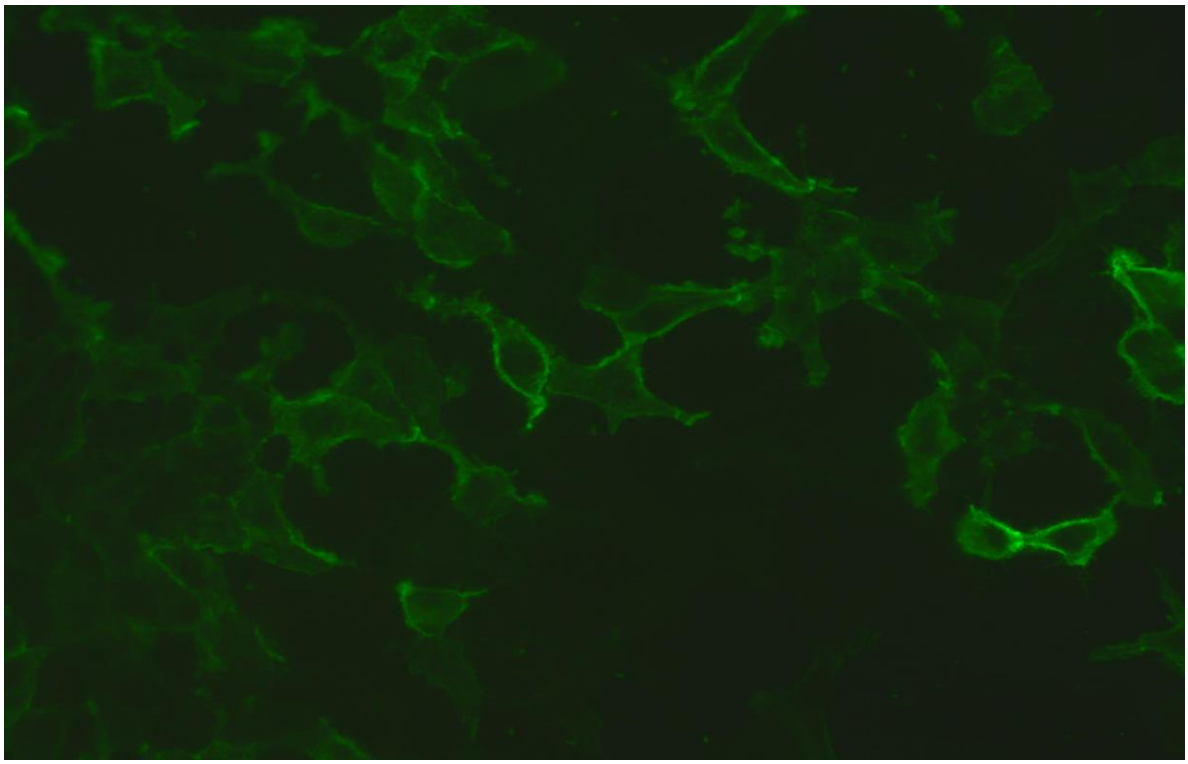

Figure 2: Immunofluorescence image showing LGI1 antibody strongly positive in serum at 1:10 dilution, 40x magnification.

Treatment:

We started the patient on monthly intravenous pulse methylprednisolone (IVMP) and intravenous immunoglobulins (IVIG). His 1st dose was administered as 1g pulse Methylprednisolone once daily (OD) plus 2g/kg of bodyweight IVIG for 5 days. In the subsequent doses, we administered 1g pulse Methylprednisolone OD for 3 days plus 1g/kg of bodyweight IVIG for 2 days. The total duration for his therapy was six months.

Outcome:

Significant clinical improvement was recorded after the first dose of immunotherapy. There was significant improvement in his memory functions within a month of administering the first dose. He was able to operate his computer independently and was able to manage his finances within two months. He started driving his car and insisted to be independent, even though we advised him to exercise caution. His dependency for ADL was reduced significantly. His MoCA score improved to 22/30, from 7/30 on arrival, after 3rd dose of immunotherapy, which is about 60 days from the start of treatment.

Discussion

Detection of LGI1 antibody prompted a complete change in the line of therapy. As a result, the patient not only returned to normalcy, but got his life back. If we wouldn't have done the test and treated him accordingly, the patient would have slowly deteriorated over a period of time, assuming it is a neurodegenerative disorder, the most common ailment in his age. He might have been left with permanent neurological deficits.

Previously, a rare case of anti-LGI1 limbic encephalitis with rapidly progressive dementia, psychiatric symptoms, and frequent seizures have been reported. [8] Unlike the aforementioned case, our patient did not have seizures. Similarly, a LGI1 autoimmune encephalitis case manifesting as rapidly progressive dementia and hyponatremia has also been reported. [9] Both these cases were reported from China. Many reports of LGI1 antibody encephalitis are from Europe and the US. Previous records of LGI1 from India include cases with 8 months' history of peripheral neuropathy followed by memory impairment, focal seizures with behavioral and psychiatric changes; ascending paresthesias with continuous twitching over the body, associated with insomnia; a patient treated with therapeutic plasma exchange; progressive cognitive decline and behavioral changes including apathy, episodes of confusion and anxiety. [10,11,12,13,14,15]

Our case reinforces the fact that recognition of specific symptoms and their onset patterns, as well as testing for autoimmune etiology will prove to be the most crucial factors in early diagnosis, prompt immunotherapy, and good prognosis. Early recognition and prompt initiation of immunotherapies are

of great importance. The clinical improvements often correlate with the antibody levels. As a case of treatable, rapidly progressive dementia with a good prognosis, early and accurate diagnosis is essential, particularly when such cases can be frequently misdiagnosed as neurodegenerative disorders. It is therefore, imperative to rule out autoimmune etiology in such cases. A misdiagnosis or lack of complete diagnostic work-up may deprive patients of complete recovery. In our case, the confirmative autoantibody detection prevented potential irreversible sequalae for the patient.

Conclusion

This case raises the awareness that Alzheimer's like presentation can be caused by autoimmunity. This case increases the gamut of LGI1 clinical features in patients from India, and establishes the increasingly appreciated fact that autoimmune disorders of the nervous system could be grossly underdiagnosed and may not be as rare as we have thought them to be.

Acknowledgment

We acknowledge Mr. VK Srinivasan, Founder & Director of ZeiniX Life Sciences for helping us with coordination during sample logistics, testing, proofreading, and publication process.

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