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Case Report

A rare case of leucine-rich glioma-inactivated 1 and N-Methyl-D-aspartate receptor double-positive limbic encephalitis: Diagnostic and clinical implications

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Abstract

The co-occurrence of leucine-rich glioma-inactivated 1 (LGI1) and N-Methyl-D-aspartate receptor (NMDAR) antibodies in paired serum and cerebrospinal fluid (CSF) samples in limbic encephalitis is a rare occurrence and its clinical presentation is not known. We report a case of a patient with limbic encephalitis presenting the symptoms of both LGI1 and NMDAR components. This case highlights the significance of a thorough diagnostic evaluation in suspected autoimmune dementia in elderly. Autoimmune antibody panels testing in suspected limbic encephalitis may help in identifying treatable dementias. LGI1 and NMDAR case reports have been published in various journals, the concurrent occurrence of both conditions in a single patient has hardly been published before.

Keywords: Leucine-rich glioma-inactivated 1(LGI1), N-methyl-D-aspartate receptor (NMDAR), Limbic Encephalitis, Autoimmune encephalitis, Double-positive encephalitis.

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1. Introduction

Limbic encephalitis is a neurological disorder that involves inflammation of the limbic system, which includes the brain regions responsible for managing emotions, memory, and behavior.[1,2] This disorder results from autoimmune processes, with various autoantibodies targeting specific neuronal receptors. NMDAR encephalitis is a severe autoimmune nervous system disease, with the primary symptoms being abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorders or dyskinesia or abnormal posture, decreased consciousness, and autonomic dysfunction or central hypoventilation.[3]

NMDAR and LGI1 antibodies define the most recognized autoimmune encephalitis (AE) syndromes, although their co-occurrence in the same patient is extremely rare.[4] LGI1 is a secreted glycoprotein protein with strong expression in the hippocampus. The protein is secreted by neurons and functions trans-synaptically to modulate both presynaptic and postsynaptic structures, including potassium channel Kv1.1 and glutamate receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Dysregulation of these proteins by autoimmune damage to LGI1 results in the clinical manifestations of limbic encephalitis.[4,5]

In LGI1 encephalitis the most common symptoms include memory deterioration, facio-brachial dystonic seizures, psychiatric manifestations, and hyponatremia.[6,7] Notably, most cases of LGI1 encephalitis are not associated with malignancies.[8,9,10] This suggests a pathogenic role for the implicated antibodies, whose levels correlate with disease activity. This form of encephalitis is one of the factors contributing to subacute-onset dementia, and it has a favorable response to immunotherapy.[6]

In contrast, NMDAR antibodies which is the most common cause of autoimmune encephalitis, primarily affects young adults and manifests with fever, hallucinations, disorganized thinking, autonomic instability, and movement

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disorders.[11,12] Interestingly, in young females, NMDA encephalitis is frequently associated with tumors, whereas in males and older adults, such an association is less common.[13] However, it's imperative to note that symptoms are milder in patients over 45, and delay in diagnosis is very common.[14]

The simultaneous presence of both LGI1 and NMDAR antibodies is highly unusual. The underlying mechanisms and implications of this co-occurrence remain an area of ongoing research. To date, there has been only one documented case of LGI1 and NMDAR antibodies showing simultaneous positivity.[15] Here we present the second recorded case of this extraordinary co-occurrence.

2. Case Report

A 91-year-old Indian male with no prior co-morbidities presented with progressive memory loss over nine months. A computed tomography (CT) scan of the brain was performed initially by local physician, leading to a provisional diagnosis of degenerative dementia. Over the subsequent three months, the patient's condition worsened with new symptoms. He began experiencing hyperphagia and distressing visual hallucinations, particularly those of insects. Later, he started experiencing fever with altered sensorium. His lab investigations showed hyponatremia with sodium level of 123 meq/dL. While correcting his sodium levels, he experienced focal seizures on the right side, followed by generalized tonic-clonic seizures (GTCS). Thus, he was referred to our center.

He was admitted in a postictal state, necessitating intubation due to a low Glasgow Coma Scale (GCS) score E1VTM2 and desaturation. There were no signs of neck stiffness or meningismus. Blood cultures and sepsis markers were negative. Considering the clinical symptoms, encephalitis was suspected. A MRI brain plain revealed T2/FLAIR hyper-intense signals in the left medial temporal lobe, affecting the hippocampus and left insula, with no signs of diffusion restriction which lead to the suspicion of limbic encephalitis **(Figure 1)**.

CSF analysis showed a total cell count of 4 cells/cmm (reference range: 0–5 cells), with 100% lymphocytes. Glucose was 118 mg/dL, and protein was 58.1 mg/dL (reference range: 15–45 mg/dL), both within normal limits. EEG findings indicated mild; diffuse theta range slowing of the background activity **(Figure 2)**. Based on the MRI results suggesting limbic encephalitis, an autoimmune encephalitis panel [NMDA-NR1, AMPA GluR1, AMPA GluR2, and GABA B, VGKC (LGI1 and CASPR2)] was tested on both serum and CSF samples. Serum samples were analyzed using indirect immunofluorescence on human embryonic kidney cells 293 transfected with corresponding antigens of autoimmune encephalitis mosaic 6 (Euroimmun AG, Lubbock, Germany). Positivity was confirmed in undiluted CSF samples and at a 1:10 dilution for serum samples. The CSF sample displayed strong positivity for LGI1 antibodies **(Figure 3a,b)** and weak positivity for NMDAR antibodies **(Figure 3c, d)**. Serum samples also exhibited strong LGI1 positivity **(Figure 3e,f)** and mild NMDA positivity **(Figure 3g, h)**. The patient was treated with intravenous methylprednisolone (1gm daily) for five days, along with anti-epileptic therapy in the form of intravenous levetiracetam (500 mg twice daily). Following a week of treatment, his consciousness improved, and he was successfully weaned off from mechanical ventilation. Hyponatremia evaluation revealed (SIADH) of inappropriate antidiuretic hormone release.

The need for malignancy screening and consideration of second-line immunotherapy were discussed with the patient's relatives. However, due to his advanced age, they opted for a conservative management approach. Before discharge, the patient displayed significant improvement, walking with minimal support. Cognitive assessment indicated mild short-term and recent memory deficits, along with executive dysfunction. Consequently, he was started on an oral steroid.

Over the following one year follow-up, the patient made remarkable progress. At the last follow-up, he could walk with minimal support and exhibited only mild recent memory impairment, signifying a positive response to treatment and ongoing recovery.

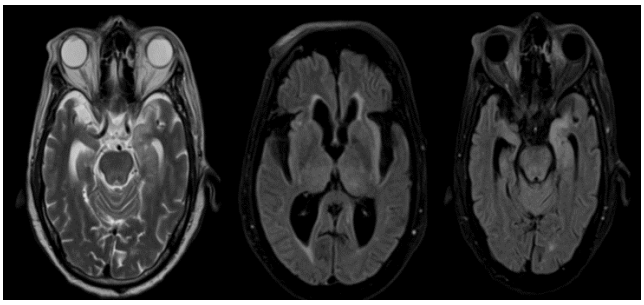

Figure 1: MRI images showing lesion left hippocampal and insular flair hyper-intensity

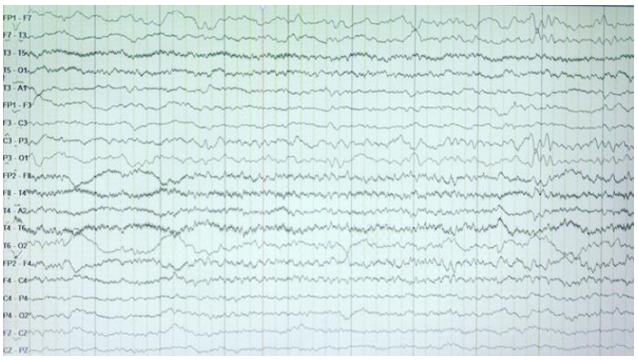

Figure 2: EEG showing theta range slowing

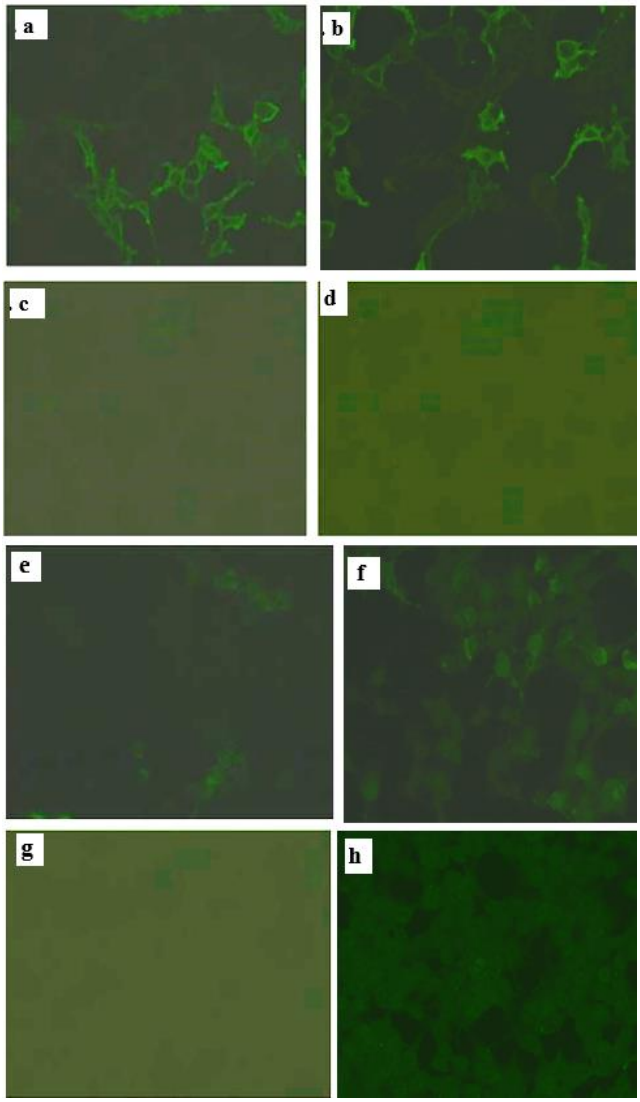

Figure 3: Immunology Report; **a:** Strongly positive for LGI1 Ab in undiluted CSF by cell-based Assay – recombinant, fixed transfected HEK cells using indirect immunofluorescence method. Apple green colour shows the positive resction; **b:** Very strongly positive for LGI1 Ab in 1: 10 diluted serumusing recombinant, fixed transfected HEK cells by cell based assay using Indirect Immunofluoresence method. Apple green color shows the positive resction. Magnification 40x; **c** and **d:** Negative reaction. No apple green color; **e:** Mildly positive for NMDA NR1 Ab in undiluted CSF by cell based assay – recombinant, fixed transfected HEK cells using Indirect Immunofluoresence method. Apple green color shows the positive resction. Magnification 30x; **f:** Moderately positive for NMDA (NR1) Ab in 1:10 diluted serumusing recombinant, fixed transfected HEK cells by cell based assay using Indirect Immuno fluoresence method. Apple green colour shows the positive resection. Magnification 40x; **g:** Negative reaction. No apple green color.

3. Discussion

There are various kinds of autoimmune encephalitis, each with a unique pathogenesis. Understanding the pathophysiology of these disorders is useful when performing diagnostic tests and selecting effective therapy. The first category includes classic paraneoplastic illnesses caused by antibodies to intracellular antigens, such as anti-Hu. The second group involves autoantibodies to extracellular epitopes of ion channels, receptors and other associated proteins, such as the NMDA receptor.[16]

Autoimmune encephalitis is rarely reported in nonagenarians.[17] This rarity can be due to several factors, such as a small percentage of nonagenarians (0.2%) in the global population, a lack of awareness among treating physicians, and a bias towards diagnosing degenerative diseases in the elderly.[17]

The coexistence of two antibodies in a patient with autoimmune neurological syndrome can be explained by the fact that the disease is caused by organ-specific autoimmunity, leading to the production of multiple antibodies.[18,19] It's crucial not to miss specific clinical symptoms that may be the tell tale signs of underlying autoimmune encephalitis.

The seizures in LGI1 encephalitis include typical medial temporal lobe events and more distinctive semiologies, including bradycardia, piloerection, and faciobrachial dystonic seizures (FBDS).[20,21] The high expression of LGI1 antigen in the hippocampus and limbic system makes epileptogenic areas vulnerable to these autoantibodies.[22] Seizures are also well-documented in anti-NMDAR encephalitis.[22] In our patient, the focal seizures and secondary generalization are likely due to the involvement of the left medial temporal lobe secondary to LGI1 encephalitis.

Our patient exhibited psychiatric symptoms in the form of recurrent visual hallucinations, a well-known occurrence in cases of NMDA encephalitis.[23] Studies suggest that patients who have low levels of NMDAR antibodies tend to have milder symptoms. In contrast, those with higher levels may present with severe psychiatric symptoms, including catatonia and hypoventilation, sometimes requiring mechanical ventilation.[24] In this case, the limited psychiatric symptoms might be due to low levels of anti-NMDA antibodies. Our patient did not exhibit any signs of hypoventilation, and intubation and ventilation were necessary due to generalized tonic-clonic seizures and post-ictal desaturation. Therefore, the probable cause of visual hallucinations is anti-NMDAR antibodies.

Initially, our patient experienced symptoms of hyperphagia and hyperthermia. Excessive craving for carbohydrate-rich foods is a well-known diagnostic criterion in frontotemporal dementia, with a multifactorial etiology involving hypothalamic dysfunction and peripheral hormonal imbalances.[25] Our patient was fond of carbohydrates and sweets, likely due to dysfunction in the hypothalamic appetite-satiety centers. The autonomic dysregulation in the hypothalamus is responsible for the hyperthermia seen in anti-NMDAR encephalitis. Hence, both hypothalamic

symptoms in our patient are likely due to anti-NMDAR antibodies. The hyponatremia in our patient was secondary to the syndrome of inappropriate antidiuretic hormone release (SIADH). Abnormal antidiuretic hormone secretion may be related to simultaneous LGI1 expression in the hypothalamus and kidney.[26]

Identifying these symptoms and localizing the neural substrate involved can aid in distinguishing autoimmune dementia from neurodegenerative dementia.While most cases of LGI1 encephalitis typically occur in adults over 60, this case demonstrates that age alone should not deter us from exploring treatable causes. Another valuable lesson is related to neuroimaging in dementia. Although the American Academy of Neurology recommends either a CT or MRI for dementia, replacing the initial CT scan with an MRI might have led to an earlier diagnosis in this case.

There are a few limitations to consider in this case. It is difficult to generalize from an isolated case, the CSF herpes simplex PCR test was not conducted due to an insufficient CSF sample, and the possibility of cross-reactivity cannot be ruled out. However, patient clinically improved without antiviral drugs. Additionally, a whole-body PET CT scan was not performed to screen for malignancies, as the family declined further investigations. Finally, the short duration of follow-up and immunotherapy is another limitation to consider.

4. Conclusion

This case underscores the need to investigate treatable forms of dementia, even in the elderly, as autoimmune etiologies like limbic encephalitis can present similarly to neurodegenerative diseases but respond favorably to immunotherapy. The significance of this case report lies in the fact that the population of nonagenarians is expected to increase in the coming decades, leading to a proportional increase in cases of dementia. It underscores the importance of conducting thorough investigations in all cases so that treatable forms of dementia are not overlooked.

5. Patient Consent

The authors certify that they have obtained appropriate patient consent. The patient has given their consent for their clinical information and images to be reported in the journal. The patient understands that their name and initials will not be published, and all efforts will be made to ensure their anonymity.

6. Source of Funding

None.

7. Conflict of Interest

None.

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