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Anti-LGI1 autoimmune encephalitis mimicking rapidly progressive dementia in an elderly patient: a case report and review of the literature

Carmine Siniscalchi,[1] Nicoletta Cerundolo,[1] Giuseppa Jolanda Rosa,[2] Natasa Mojovic,[1] Beatrice Prati,[1] Tiziana Meschi[1]

[1]Internal Medicine Ward, Parma University Hospital; [2]Neurology Unit, Fidenza Hospital, Italy

Abstract

Autoimmune encephalitis is increasingly recognized as a major cause of potentially reversible encephalopathy and rapidly progressive dementia, yet it remains frequently underdiagnosed in elderly patients, particularly outside specialist neurological settings. Among these disorders, anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis represents a rare but distinctive entity, typically characterized by subacute cognitive decline, behavioral disturbances, seizures, and hyponatremia, often associated with mesial temporal lobe involvement on magnetic resonance imaging.

We report the case of an 80-year-old man who presented with an acute confusional state and recurrent bilateral tonic-clonic seizures following a 2-month history of progressive cognitive and behavioral deterioration that had initially been misinterpreted as the onset of a neurodegenerative dementia. Laboratory testing revealed severe hyponatremia, whereas the brain computed tomography was unremarkable. Magnetic resonance imaging demonstrated bilateral mesial temporal hyperintensity, more pronounced on the right side, consistent with limbic encephalitis. Electroencephalography showed diffuse slowing of background activity, indicative of moderate global cerebral dysfunction. After exclusion of infectious etiologies, cerebrospinal fluid analysis was performed and was within normal limits; however, anti-LGI1 antibodies were detected in both serum and cerebrospinal fluid, confirming the diagnosis of anti-LGI1 autoimmune encephalitis.

The patient was promptly treated with high-dose intravenous methylprednisolone followed by intravenous immunoglobulins, in combination with antiepileptic therapy, leading to progressive clinical and cognitive recovery and normalization of electroencephalographic abnormalities. At the 3-month follow-up, he had fully regained cognitive and functional independence.

This case highlights the critical importance of early recognition of autoimmune encephalitis in elderly patients presenting with rapidly progressive cognitive decline and seizures, even in internal medicine settings where these conditions are often overlooked. Timely diagnosis and immunotherapy can dramatically improve prognosis and prevent irreversible neurological damage.

Key words: encephalitis, dementia, autoimmune, elderly patient, anti-LGI1.

Correspondence to: Carmine Siniscalchi, Internal Medicine Ward, Parma University Hospital, Parma, Italy.
E-mail: csiniscalchi84@gmail.com

Introduction

Rapidly progressive cognitive decline in elderly individuals is most commonly attributed to neurodegenerative diseases, vascular dementia, metabolic disorders, or infectious encephalopathies. However, in recent years, autoimmune encephalitis has emerged as an increasingly recognized and potentially reversible group of disorders that can closely mimic these more common conditions.[1,2] Despite growing awareness of autoimmune encephalitis in neurology, these disorders remain frequently underrecognized in internal medicine wards, particularly when elderly patients present with predominant cognitive or behavioral symptoms rather than focal neurological deficits, leading to significant diagnostic delay.

Among the autoimmune encephalitis, anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis is one of the most characteristic and clinically important forms of autoimmune limbic encephalitis. This condition typically affects middle-aged to elderly individuals and is associated with a subacute onset of memory impairment, confusion, behavioral changes, and seizures, including the highly suggestive facio-brachial dystonic seizures.[3,4] Additionally, hyponatremia, often presumed to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), is a common accompanying laboratory finding in anti-LGI1 encephalitis and may provide an important diagnostic clue, even when other investigations remain inconclusive.[2,3]

Early recognition of anti-LGI1 encephalitis is crucial because this condition responds remarkably well to immunotherapy, and timely initiation of treatment can markedly improve outcomes, reducing the risk of persistent cognitive impairment or refractory epilepsy.[3]

However, the insidious onset and phenotypic overlap with more common causes of cognitive decline often lead to diagnostic delays, with many patients not receiving appropriate immunotherapy until well after symptom progression.[1-3]

Here, we report a paradigmatic case of anti-LGI1 encephalitis in an 80-year-old man who initially presented with progressive cognitive and behavioral changes that were misinterpreted as early dementia, before evolving into acute encephalopathy with seizures.

Case Report

An 80-year-old man with no history of hypertension, diabetes mellitus, dyslipidemia, smoking, or prior cerebrovascular events was brought to the emergency department for the acute onset of confusion and recurrent generalized tonic-clonic seizures. The patient had previously been fully independent in all activities of daily living and cognitively intact until approximately 2 months before admission, when he gradually developed subtle memory impairment, apathy, irritability, and personality changes. Over time, he became increasingly disoriented, showed difficulty performing complex tasks, and exhibited episodes of socially inappropriate behavior. These symptoms were initially interpreted as the early manifestation of a neurodegenerative dementia, and no targeted diagnostic investigations were undertaken at that stage. At that stage, no formal neurological or geriatric assessment was performed, and no standardized cognitive or functional scales were documented. Based on retrospective clinical reconstruction, the patient's functional status at symptom onset was estimated as modified Rankin Scale 1-2, while formal cognitive testing, such as the Mini-Mental State Examination (MMSE), was not performed at that time.

In the days preceding admission, the patient's mental status rapidly deteriorated, culminating in an acute confusional state and recurrent generalized convulsive seizures, which prompted urgent medical evaluation. On presentation, he was disoriented, inattentive, and agitated, with fluctuating levels of consciousness. No focal neurological deficits were evident in the interictal period. Vital signs were stable, and there were no clinical signs of systemic infection. No signs of meningism were observed on physical examination, and there were no identifiable infectious risk factors such as recent infections, immunosuppression, or relevant exposure history.

Routine laboratory investigations revealed severe hyponatremia (serum sodium 118 mmol/L), while hematological and other biochemical parameters were within normal limits. Serum osmolality was reduced, and urinary osmolality was inappropriately elevated, supporting the diagnosis of SIADH. In view of the acute neurological presentation, an urgent brain computed tomography (CT) scan was performed, which showed no evidence of acute ischemia, intracranial hemorrhage, mass effect, or hydrocephalus. CT angiography was performed and showed no evidence of large vessel occlusion, vascular stenosis, or other acute cerebrovascular abnormalities.

Despite partial correction of hyponatremia and the initiation of antiseizure medication, the patient remained confused and continued to experience seizures. A brain magnetic resonance imaging (MRI) study was therefore obtained. MRI revealed mild bilateral hyperintensity of the mesial temporal lobes on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences, more pronounced on the right side, associated with mild regional swelling and without contrast enhancement or diffusion restriction. No structural abnormalities were observed in the hypothalamic or pituitary regions. These findings were highly suggestive of limbic encephalitis (Figure 1).

Electroencephalography (EEG) demonstrated diffuse slowing of the background rhythm with intermittent bursts of frontal intermittent rhythmic delta activity, consistent with moderate global cerebral dysfunction, without definite epileptiform discharges (Figure 2).

In light of the subacute cognitive decline, recurrent seizures, severe hyponatremia, and characteristic MRI abnormalities, an autoimmune encephalitis was strongly suspected. Extensive microbiological investigations, including blood cultures and viral serologies, were negative. Lumbar puncture showed normal opening pressure and cerebrospinal fluid (CSF) analysis within normal limits, with no pleocytosis, normal protein concentration, and normal glucose levels; CSF bacterial and viral PCR panels were also negative.

Serum and CSF were subsequently tested for neuronal surface antibodies, revealing positivity for anti-LGI1 antibodies in both compartments, thereby confirming the diagnosis of anti-LGI1 autoimmune encephalitis. A CT scan of the chest, abdomen, and pelvis did not reveal any evidence of cancer. Although additional serological testing for systemic autoimmune disorders was not performed, the overall clinical picture did not suggest an underlying systemic autoimmune disease, and the diagnosis was supported by the detection of anti-LGI1 antibodies in both serum and CSF.

High-dose intravenous methylprednisolone (1 g/day for 5 consecutive days) was promptly initiated, followed by intravenous immunoglobulin therapy (0.4 g/kg/day for 5 days), in association with ongoing antiseizure treatment. Following intravenous methylprednisolone pulses, a gradual oral steroid tapering regimen was initiated. Intravenous immunoglobulin therapy was administered for 5 consecutive days, with no need for additional cycles during follow-up. Given the favorable clinical response, second-line immunosuppressive therapy was not required.

Over the subsequent 2 weeks, the patient showed progressive clinical improvement, with complete resolution of seizures, gradual normalization of serum sodium levels, and marked recovery of attention, orientation, and memory. Repeat EEG demonstrated significant electrophysiological improvement, with reduction of slow-

Figure 1. Brain magnetic resonance imaging. Axial and coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging of the brain showing bilateral mesial temporal and hippocampal hyperintensity, more pronounced on the right side, consistent with limbic system inflammation. These findings are characteristic of autoimmune limbic encephalitis and support the diagnosis of anti-LGI1 encephalitis in the appropriate clinical context.

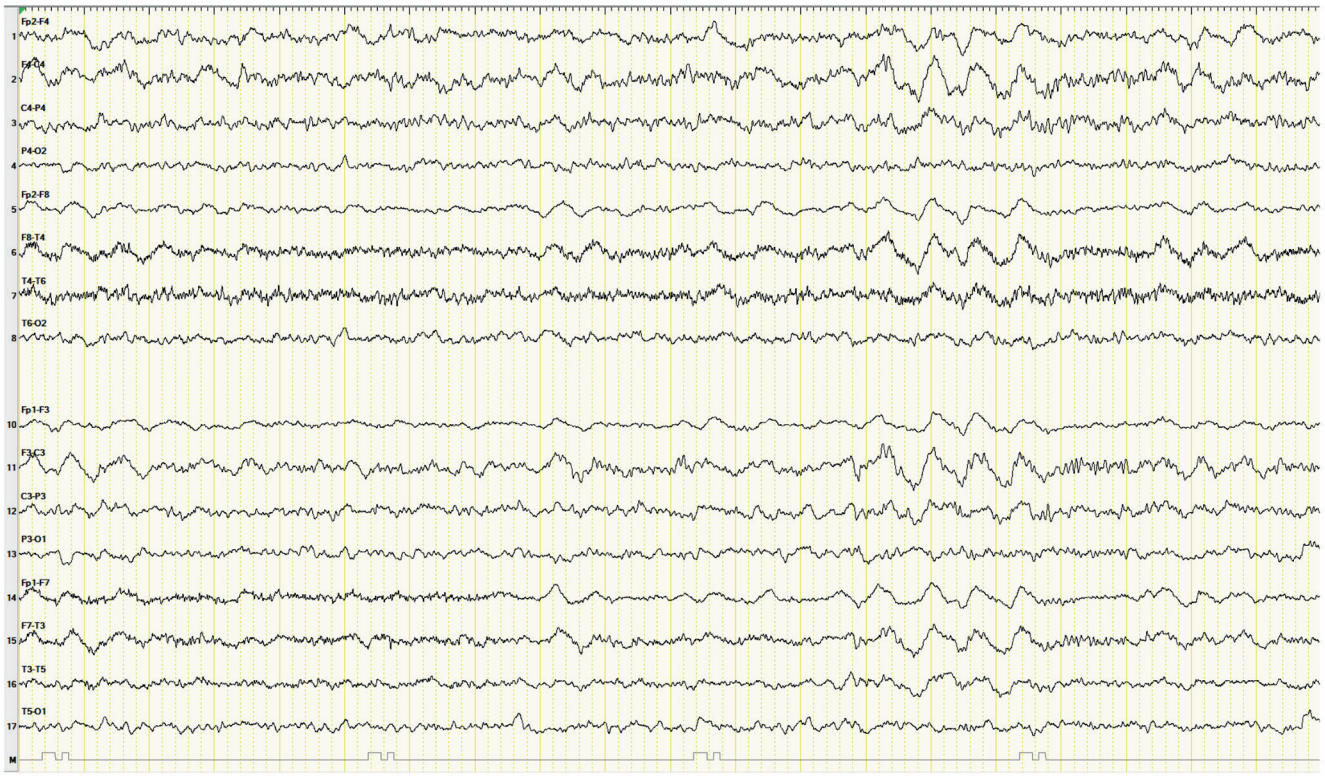

Figure 2. Electroencephalography before immunotherapy. Electroencephalogram obtained during the acute phase of the disease, demonstrating diffuse slowing of the background rhythm with bursts of rhythmic delta activity, frontally maximal (FIRDA). This pattern is consistent with moderate global cerebral dysfunction.

wave activity and restoration of a more organized background rhythm (Figure 3).

For further diagnostic work-up and specialized management, the patient was transferred to the Neurology Unit of Fidenza. At the 3-month follow-up, he had fully regained cognitive and functional autonomy, returning to his premorbid level of independence.

Follow-up and outcome

A structured follow-up was conducted at 3 and 6 months and at 1 year, including clinical evaluation, CT to exclude occult neoplasms, and brain MRI.

Following discharge from the neurology unit, the patient carried out a structured neuro-motor and cognitive rehabilitation program. At 3-month follow-up (August 2025), the patient underwent an outpatient neurological evaluation at the Epilepsy Center of the Neurology Unit of the Hospital of Fidenza. At that time, he had recovered to a near-baseline functional status. He was awake, fully alert, oriented to time and place, coherent, and cooperative. He was able to ambulate independently, use a mobile phone, and perform all activities of daily living without assistance. No further episodes of insomnia, confusion, or seizures were reported.

From a functional perspective, the patient had been completely autonomous prior to disease onset (modified Rankin Scale score 0-1), and this level of independence had essentially been restored. Formal cognitive assessment using MMSE yielded a score of 28.7, indicating preserved global cognitive functioning without clinically significant impairment.

A follow-up brain MRI study performed on 4 August 2025 was reported as substantially within normal limits, demonstrating resolution of the previously observed mesial temporal and hippocampal hyperintensities that had characterized the acute phase of limbic encephalitis. This radiological normalization closely paralleled the patient's clinical recovery.

Follow-up EEG confirmed a marked improvement in cerebral electrophysiological activity with a well-organized alpha background rhythm (8-9 Hz), bilaterally symmetric and of medium voltage, and only occasional theta waves were observed over the frontotemporal regions, with rare sharp transients, consistent with minimal residual cortical irritability.

These EEG findings were interpreted as a clear electrophysiological correlate of the patient's neurological recovery and were consistent with an excellent response to immunomodulatory therapy. In light of this improvement, progressive tapering of antiseizure medication was started.

Given that anti-LGI1 encephalitis is only rarely paraneoplastic but carries a small associated oncological risk, a long-term surveillance plan with clinical evaluation, EEG, brain MRI, and CT of chest and abdomen was established, including contrast-enhanced CT of the chest and abdomen at 6 months and repeat brain MRI at 1 year.

Overall, the first follow-up evaluation confirmed complete clinical, radiological, and electrophysiological remission, reinforcing the diagnosis of anti-LGI1 autoimmune encephalitis and underscoring the remarkable reversibility of this condition when timely immunotherapy is initiated.

These findings collectively illustrate the rapid reversibility of anti-LGI1 encephalitis when early immunotherapy is initiated.

Discussion

Anti-LGI1 autoimmune encephalitis is a distinct subtype of antibody-mediated limbic encephalitis that predominantly affects middle-aged and elderly individuals and represents one of the most fre-

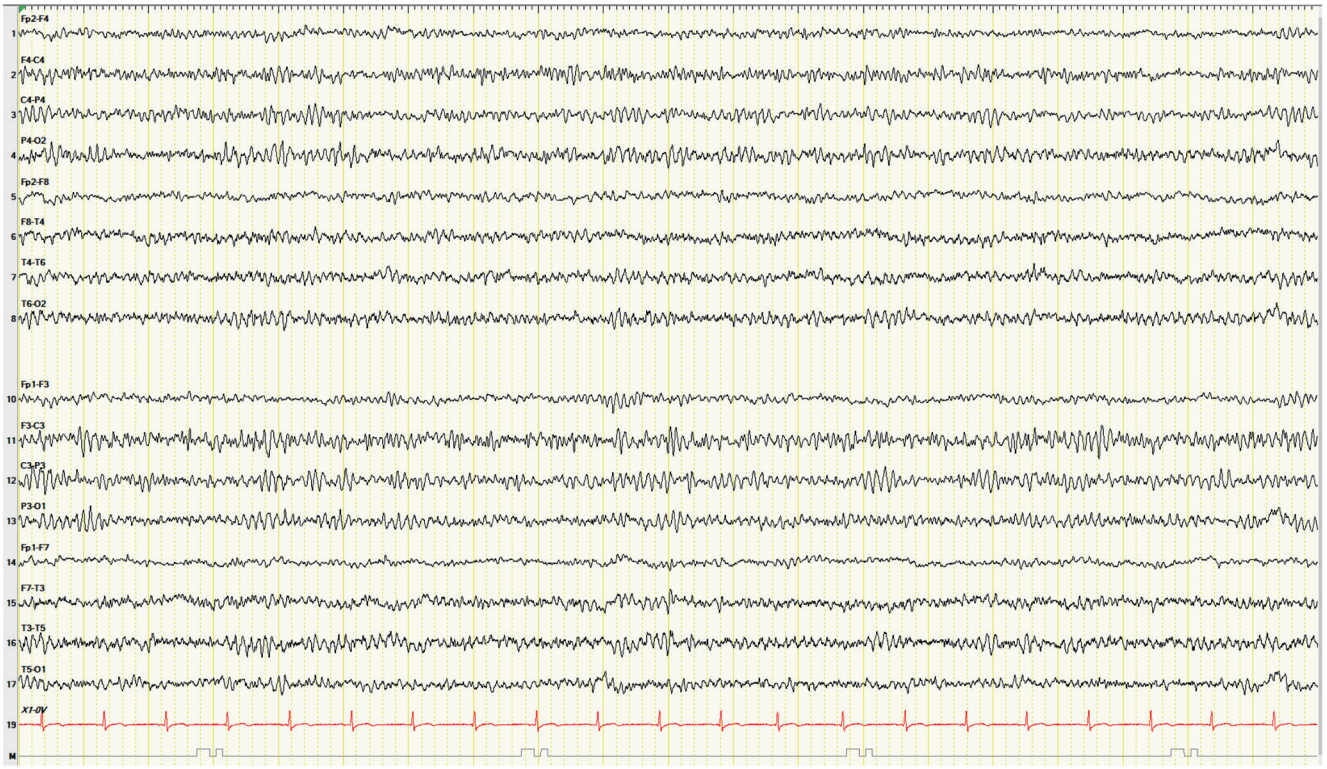

Figure 3. Electroencephalography after immunotherapy. Follow-up electroencephalogram after immunomodulatory treatment showing a marked improvement in electrocortical activity, with restoration of a more organized background rhythm and near-complete resolution of rhythmic delta activity, consistent with clinical and neurophysiological recovery.

quent forms of autoimmune encephalitis in this age group.[5] Since its initial characterization, increasing awareness has led to improved recognition; however, delayed diagnosis remains common, particularly in non-neurological settings where subacute cognitive decline is more readily attributed to neurodegenerative disease.[5]

Epidemiology and pathophysiology

Anti-LGI1 encephalitis is mediated by antibodies targeting the leucine-rich glioma-inactivated 1 protein, a secreted neuronal protein that interacts with *ADAM22* and *ADAM23* and plays a crucial role in synaptic stabilization and excitatory neurotransmission.[6,7] Disruption of this complex leads to neuronal hyperexcitability and limbic dysfunction. Unlike classical paraneoplastic limbic encephalitis associated with intracellular antigens, anti-LGI1 encephalitis is only rarely tumor-associated, with reported neoplastic associations in less than 10% of cases.[5,7]

The disease primarily affects older adults, often with male predominance.[5,8] Its incidence is estimated to be approximately 0.4-0.8 per million per year, although this is likely underestimated due to diagnostic delay and underrecognition.[8]

Clinical features

Clinically, anti-LGI1 encephalitis is characterized by subacute memory impairment, confusion, behavioral changes, and seizures.[5] Facio-brachial dystonic seizures are highly characteristic and may precede cognitive decline by weeks or months, representing an important early diagnostic clue.[9] However, in elderly patients, generalized tonic-clonic seizures or non-specific focal seizures may predominate.

Hyponatremia is reported in up to 60-70% of cases and is thought to result from SIADH mediated by hypothalamic involvement.[7,9] In some patients, hyponatremia precedes neurological manifestations and may be the first laboratory clue prompting further investigation.[9]

Rapidly progressive dementia is a recognized presentation, and several studies emphasize that anti-LGI1 encephalitis is among the most treatable causes of dementia mimic in memory clinics.[4] Delayed immunotherapy has been associated with persistent hippocampal atrophy and long-term cognitive impairment.[4,9]

Neuroimaging and electroencephalography findings

Brain MRI typically demonstrates bilateral mesial temporal hyperintensity on FLAIR and T2-weighted sequences, although imaging may initially be unilateral or even normal.[5,8] Chronic, untreated disease can lead to hippocampal sclerosis and permanent memory deficits.[4]

EEG findings are usually non-specific and include diffuse or temporal slowing; epileptiform discharges may be present but are not universal.[8,9] Importantly, EEG abnormalities often improve rapidly after immunotherapy, paralleling clinical recovery.[9]

CSF findings are frequently normal or only mildly abnormal, with pleocytosis being uncommon.[5,8] Therefore, normal CSF should not exclude autoimmune encephalitis when clinical suspicion is high. Serum antibody testing may even demonstrate higher sensitivity than CSF testing in LGI1-associated disease.[5]

Treatment and management

Early immunotherapy is the cornerstone of treatment and is associated with favorable outcomes.[6,9,10] First-line therapy generally includes high-dose intravenous corticosteroids, intravenous immunoglobulin, or plasma exchange. Among these, corticosteroids appear particularly effective in anti-LGI1 encephalitis.[9,10]

If first-line treatment fails or relapse occurs, second-line agents such as rituximab may be considered.[6,10] Early initiation of immunotherapy is associated with improved seizure control and better long-term cognitive recovery.[4,9,10]

Antiseizure medications are useful adjuncts but are rarely sufficient alone. Seizure control often improves dramatically following immunotherapy, underscoring the immune-mediated nature of the disorder.[9]

Prognosis and long-term outcomes

Overall prognosis is favorable when treatment is initiated early. Most patients experience substantial neurological improvement, although residual memory impairment may persist in a subset.[4,8] Relapse rates have been reported between 15% and 25%, supporting the need for structured follow-up.[4,8]

Given the low but non-negligible tumor association rate, oncological screening at diagnosis and periodic surveillance are recommended.[5,7]

Implications for internal medicine

This case underscores the need for heightened awareness of autoimmune encephalitis in internal medicine and geriatric settings. Rapidly progressive cognitive decline associated with seizures and unexplained hyponatremia should prompt consideration of anti-LGI1 encephalitis even in the absence of CSF abnormalities.[9] Early MRI and antibody testing are essential to avoid misdiagnosis as a primary neurodegenerative disease.

Timely immunotherapy can dramatically alter disease trajectory, transforming a seemingly irreversible dementia-like presentation into a fully reversible neurological disorder.[9]

Conclusions

Autoimmune encephalitis, and particularly anti-LGI1 encephalitis, should always be included in the differential diagnosis of acute or subacute cognitive deterioration in elderly patients, especially when the clinical course is rapidly progressive or atypical for neurodegenerative disease. Early recognition, supported by characteristic findings on neuroimaging, EEG abnormalities, and detection of neuronal surface antibodies, allows the prompt initiation of immunotherapy, which can dramatically improve neurological outcome and restore functional independence. This case exemplifies how timely diagnosis and treatment can convert a seemingly irreversible neurodegenerative presentation into a fully reversible neurological condition, underscoring the critical importance of maintaining a high index of suspicion for autoimmune etiologies in internal medicine and geriatric practice.

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