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Case Report

Seronegative Autoimmune Encephalitis- A Diagnostic Challenge

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ABSTRACT

Background: Seronegative autoimmune encephalitis (AE) is a diagnostic challenge due to the absence of detectable neuronal autoantibodies despite characteristic clinical features. Delayed recognition often results in postponed immunotherapy and poorer neurological outcomes. This case highlights the importance of a clinicoradiological approach to diagnosis and management.

Case Presentation: A 62-year-old woman presented with an 8-day history of progressive memory impairment, language comprehension difficulties, and a 1-day history of behavioral changes, including altered mental status and inappropriate laughter. She had experienced a self-limiting febrile respiratory illness two weeks before symptom onset. Neurological examination showed no focal deficits. Magnetic resonance imaging demonstrated left temporal lobe hyperintensities suggestive of limbic encephalitis, while electroencephalography revealed slow-wave epileptiform discharges. Cerebrospinal fluid analysis, multiplex meningitis PCR, serum autoimmune encephalitis antibody panel, and PET-CT for occult malignancy were all negative. Based on the clinical presentation, supportive radiological findings, exclusion of infectious and paraneoplastic causes, and established diagnostic criteria, a diagnosis of probable seronegative autoimmune encephalitis was made. The patient showed minimal response to high-dose intravenous methylprednisolone but experienced marked clinical improvement following intravenous immunoglobulin therapy, with recovery of cognition, behavior, and neurological function.

Conclusion: This case underscores that seronegative autoimmune encephalitis remains primarily a clinical and radiological diagnosis. Negative antibody testing should not delay immunotherapy when clinical suspicion is high. Early recognition and prompt treatment are essential to improve neurological outcomes, particularly in resource-limited settings where advanced antibody testing may be unavailable.

Keywords*: Seronegative autoimmune encephalitis, Autoimmune encephalitis, Limbic, Encephalitis, Antibody-negative encephalitis, Cognitive impairment.*

INTRODUCTION

Autoimmune encephalitis (AE) is a group of inflammatory brain disorders characterized by subacute onset of cognitive impairment, behavioral abnormalities, seizures, and altered sensorium. Over the past decade, increasing recognition of neuronal surface antibodies has significantly improved the diagnosis of AE. However, a substantial proportion of patients with clinical features suggestive of autoimmune encephalitis remain antibody-negative, posing a major diagnostic and therapeutic challenge.[1]

Antibody-negative autoimmune encephalitis, also referred to as seronegative autoimmune encephalitis, accounts for nearly one-third to half of all AE cases reported in recent literature. The absence of detectable antibodies often leads to diagnostic uncertainty, resulting in delayed or inappropriate treatment, frequently with prolonged empirical antiviral therapy under

suspicion of viral encephalitis. This delay is clinically significant, as early initiation of immunotherapy has been shown to markedly improve neurological outcomes and reduce long-term morbidity.[2]

The diagnosis of seronegative AE is therefore largely clinical, supported by a constellation of findings including subacute neuropsychiatric symptoms, characteristic magnetic resonance imaging (MRI) abnormalities—particularly involving the temporal lobes—cerebrospinal fluid (CSF) evidence of inflammation, exclusion of infectious etiologies, and a favorable response to immunotherapy. Despite these indicators, there remains a lack of clear, universally accepted diagnostic pathways for antibody-negative cases, especially in resource-limited settings.[3]

This study is undertaken to address this important gap by evaluating the clinical presentation, radiological features, laboratory parameters, and therapeutic response in patients with suspected antibody-negative autoimmune encephalitis. By emphasizing a practical, evidence-based approach to diagnosis, this study aims to facilitate early recognition and timely initiation of treatment, thereby improving patient outcomes.

CASE PRESENTATION

A 62-year-old female from Bhopal presented to Hospital on 27 October 2025 with complaints of progressive forgetfulness for 8 days and abnormal behavior for 1 day.

The patient was apparently well until 8 days before admission, when she developed intermittent episodes of forgetfulness. Initially, she experienced difficulty understanding spoken language and intermittently failed to comprehend conversations and verbal instructions. At this stage, she remained independent in performing her routine daily activities. Her family initially attributed these symptoms to age-related cognitive decline and did not seek medical attention.

Over the following 6–7 days, her cognitive symptoms progressively worsened. She developed significant impairment of both recent memory and short-term recall, frequently forgetting recently communicated information and recent daily activities. The forgetfulness gradually became persistent rather than episodic, leading to a noticeable decline in her daily functioning and social interactions, which prompted hospital evaluation.

One day prior to admission, the patient's relatives observed a change in her behavior characterized by altered mental status and abnormal behavior. She became disoriented to her usual activities and surroundings. During the same period, she developed recurrent episodes of inappropriate laughter and smiling that were incongruent with the surrounding circumstances and occurred without any identifiable emotional trigger. These behavioral abnormalities were of new onset and increased progressively in frequency.

Notably, approximately two weeks before the onset of neurological symptoms, the patient had experienced an episode of fever and cough, which was managed with symptomatic treatment and resolved completely within 3–4 days. There was no history suggestive of seizures, focal neurological deficits, head trauma, or loss of consciousness during this period.

Neurological examination revealed:

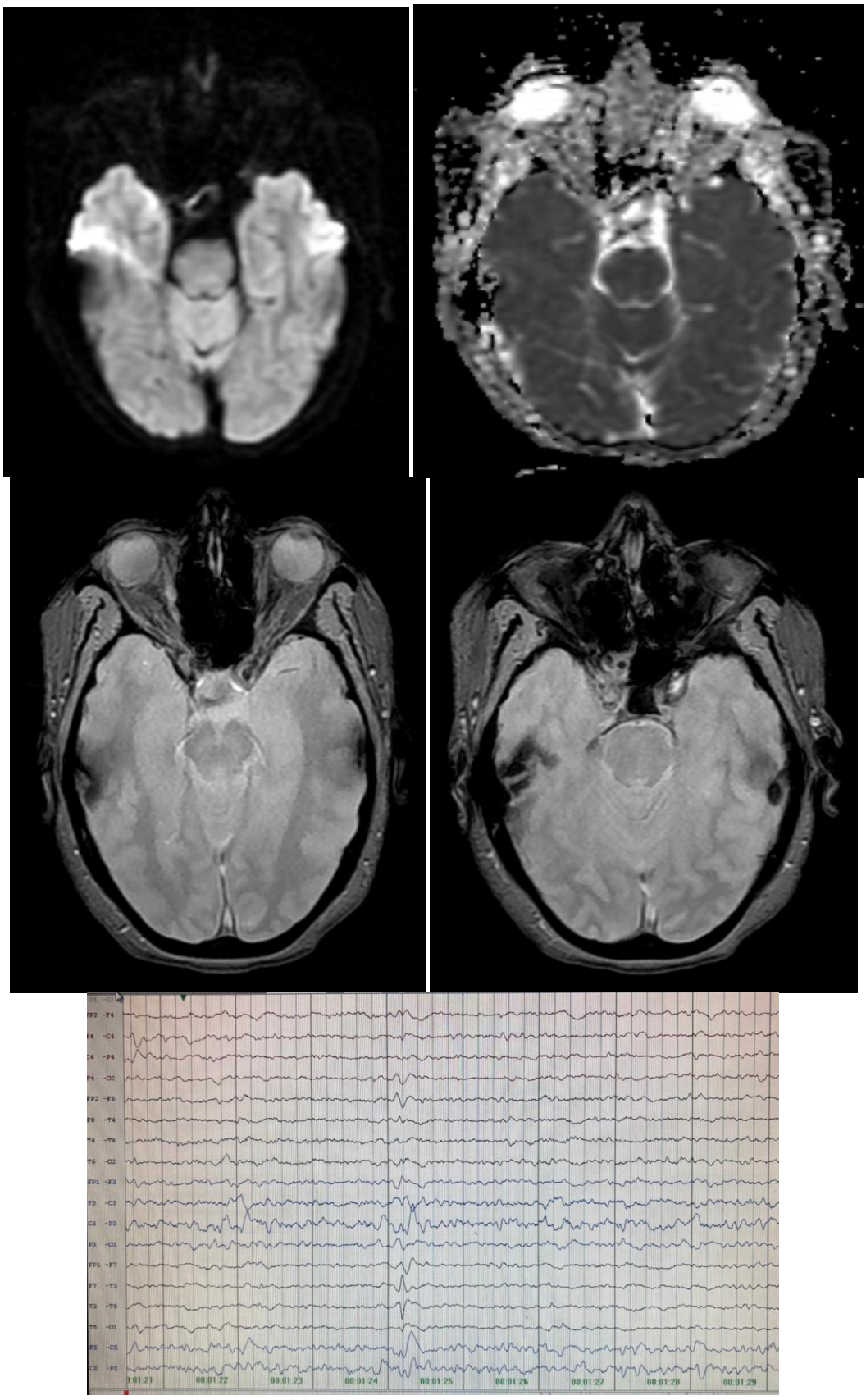
- HMF: Cannot be assessed as patient was altered and irritable
- CRANIAL NERVERS : INTACT
- MOTOR STSTEM: NO DEFICIT
- SENSORY DEFICIT: NO DEFICIT
- REFLEXES : A) SUPERFICIAL: INTACT

B) DEEP: INTACT
B\L PLANTARS: FLEXORS

- CEREBELLUM: INTACT
- GAIT: NO ABNORMAL GAIT
- SKULL AND SPINE: NORMAL

Investigations

* **CBC**: Hb 9.9 g/dL, WBC 8.13 × 10^3/mm^3, Platelets 180 × 10^3/mm^3
* **Renal and liver function tests**: Within normal limits
* **CSF**: Normal cell count, normal protein, no infection
* **MRI brain**: Hyperintensities noted in left temporal lobe region with suspicion of viral encephalitis.
* **EEG**: Slow wave epilepticform discharges with cerebral dysfunction.
***MENINGITIS PANEL** – Multiple real time PCR based Detection of 21 type of organisms- Negative
***SERUM AUTOIMMUNE ENCEPHALITIS PANEL (Cell based assay, IFA)**-Negative
***PET-CT SCAN-Negative for malignancy (done to rule out paraneoplastic etiology)**



Treatment

The patient was started on intravenous methylprednisolone (1 g/day for 5 days) along with multipleantiepileptic. She showed no significant clinical improvement after initiation of steroids.The patient was subsequently started on intravenous immunoglobulin (IVIG) (2gm/kg) for 5 days, following which she showed marked clinical improvement, with resolution of seizures, improvement in cognition and behavior, and overall neurological recovery.

DISCUSSION

Seronegative autoimmune encephalitis (AE) remains a significant diagnostic challenge because patients may present with typical clinical features despite negative neuronal antibody testing. This case highlights the importance of recognizing AE based on clinical presentation, supportive investigations, exclusion of infectious etiologies, and response to immunotherapy rather than antibody positivity alone.[4]

Our patient presented with a subacute onset of progressive memory impairment, language comprehension difficulties, behavioral disturbances, and altered mental status, consistent with the clinical spectrum of limbic encephalitis. A preceding febrile respiratory illness raised the possibility of infectious encephalitis; however, the absence of an identifiable infectious cause, together with supportive neuroimaging findings and subsequent clinical improvement following immunotherapy, favored a diagnosis of probable seronegative autoimmune encephalitis.[4] Similar post-infectious autoimmune mechanisms have been described, where systemic infections may trigger immune-mediated neuronal injury through molecular mimicry or immune dysregulation.

According to the diagnostic criteria proposed by Graus et al., autoimmune encephalitis can be diagnosed even in the absence of detectable neuronal antibodies when a compatible subacute clinical syndrome, supportive MRI or cerebrospinal fluid findings, and exclusion of alternative diagnoses are present.Approximately 30–50% of autoimmune encephalitis cases remain seronegative, reflecting the limitations of current antibody assays and the likelihood of unidentified antibodies or T-cell-mediated immune mechanisms.

The principal differential diagnosis is viral encephalitis, particularly herpes simplex virus encephalitis, because of overlapping clinical and radiological features. Consequently, empirical antiviral therapy is often initiated until infectious causes are excluded. However, delayed recognition of autoimmune encephalitis may postpone immunotherapy, resulting in poorer neurological outcomes. Early treatment with corticosteroids, intravenous immunoglobulin, or plasma exchange has consistently been associated with improved neurological recovery and reduced long-term disability.[5]
This case emphasizes that seronegative autoimmune encephalitis is primarily a clinicoradiological diagnosis. Clinicians should maintain a high index of suspicion in patients with rapidly progressive cognitive decline and behavioral abnormalities despite negative antibody testing. Early diagnosis and prompt immunotherapy remain essential for optimizing neurological recovery, particularly in resource-limited settings where comprehensive antibody testing may not be readily available.[6]

TABLE 5-6 **Response to Immunotherapy in Epilepsy Score[a]**

	Score
New-onset, rapidly progressive mental status changes that developed over 1-6 weeks or new-onset seizure activity (within 1 year of evaluation)	1
Neuropsychiatric changes: agitation, aggressiveness, emotional lability	1
Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension [≥20 mm Hg fall in systolic pressure or ≥10 mm Hg fall in diastolic pressure within 3 minutes of quiet standing], hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole, or gastrointestinal dysmotility)	1
Viral prodrome (rhinorrhea, sore throat, low-grade fever), only to be scored in the absence of underlying malignancy	2
Faciobrachial dystonic seizures	3
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	2
Seizure refractory to at least to two antiseizure medications	2
CSF findings consistent with inflammation (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/mm^3, if the total number of CSF red blood cells is <1000 cells/mm^3)	2
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both mesial temporal lobes, or multifocal in gray matter, white matter, or both compatible with demyelination or inflammation)	2
Systemic cancer diagnosed within 5 years of neurologic symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	2
Initiation of immunotherapy within 6 months of symptom onset	2
Neural plasma membrane autoantibody detected (*N*-methyl-D-aspartate [NMDA] receptor antibody, γ-aminobutyric acid A [$GABA_A$] receptor antibody, γ-aminobutyric acid B [$GABA_B$] receptor antibody, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA] receptor antibody, dipeptidyl-peptidase–like protein 6 [DPPX], metabotropic glutamate receptor 5 [mGlur1], mGluR2, mGluR5, leucine-rich glioma inactivated protein 1 [LGI1] antibody, IgLON5, contactin-associated proteinlike 2 [CASPR2] antibody or myelin oligodendrocyte glycoprotein [MOG])	2
Maximum score	**22**
Cutoff score predicting favorable seizure outcome	**≥7[b]**

CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging.
[a] Modified with permission from Dubey D, et al, Epilepsia.[85] © 2017 International League Against Epilepsy.
[b] Sensitivity = 87.5% and specificity = 83.8%.

Table 1 Proposed classification concepts in autoimmune encephalitis

Anatomical classification	Serological classification	Aetiological classification
1. Limbic	1. Antibodies to intracellular antigens (classical onconeuronal antibodies).*	1. Idiopathic
2. Cortical/subcortical	2. Antibodies to surface antigens and other antigens with high clinical relevance (eg, NMDAR, AMPAR, LGI1, CASPR2, GABAR A/B, DPPX, glycine receptor, AQP4, MOG, GFAP†).	2. Paraneoplastic
3. Striatal	3. Antibodies to surface antigens with low clinical relevance (eg, VGKC, VGCC).‡	3. Postinfectious
4. Diencephalic	4. Seronegative autoimmune encephalitis.	4. Iatrogenic (eg, in the setting of immune check point inhibitors or other immune-modulating agents).
5. Brainstem		
6. Cerebellar		
7. Encephalomyelitis		
8. Meningoencephalitis		
9. Combined		

*GAD65 antibody is directed against an intracellular antigen but in high titers, it mediates an autoimmune encephalitis phenotype similar to surface antibodies with high clinical relevance, and in low titers is usually clinically irrelevant to neurological symptoms.
†GFAP is a cytoplasmic antigen associated with intermediate filaments. Considered clinically relevant in patients presenting with typical radiological findings (perivascular radial enhancement).
‡Clinical relevance of these antibodies varies according to presentation. Although they may not be clinically relevant in certain patients with typical autoimmune encephalitis, some of these antibodies have higher clinical relevance to other neurological presentations (eg, VGCC is likely relevant in patients with Lambert-Eaton myasthenic syndrome and acquired autoimmune ataxia).
AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor ; AQP4, aquaporin-4; CASPR2, Contactin-associated protein-like 2 ; DPPX, Dipeptidyl-peptidase-like protein 6 ; GABAR, Gamma-Amino butyric acid Receptor ; GFAP, glial fibrillary acidic protein; LGI1, Leucine-rich glioma inactivated ; MOG, Myelin oligodendrocyte glycoprotein ; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel .

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CONCLUSION

This case highlights the importance of considering seronegative autoimmune encephalitis in patients presenting with rapidly progressive cognitive decline, behavioral disturbances, and altered mental status, even in the absence of detectable neuronal autoantibodies. Reliance solely on antibody testing may delay diagnosis and initiation of appropriate treatment. A comprehensive clinical assessment, supported by neuroimaging, cerebrospinal fluid analysis, exclusion of infectious etiologies, and application of established clinical diagnostic criteria, remains essential for timely diagnosis.[7]

Early recognition and prompt initiation of immunotherapy are critical for achieving favourable neurological outcomes and minimizing long-term cognitive impairment. This case emphasizes that autoimmune encephalitis is primarily a clinicoradiological diagnosis, and antibody negativity should not preclude treatment when clinical suspicion is high. Greater awareness of seronegative autoimmune encephalitis among clinicians, particularly in resource-limited settings, may facilitate earlier diagnosis, reduce unnecessary delays in therapy, and improve patient outcomes. Further research is warranted to identify novel biomarkers and develop standardized diagnostic and management strategies for antibody-negative autoimmune encephalitis.

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