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Case Series

The many faces of autoimmune encephalitis: a case series of three distinct clinical and antibody phenotypes

Shashank M.*, Kalaiyarasi, Sugil E., Navin Raj R., Hemachandrika K., Namitha Narayanan, Vishaalpalaniswamy Ramaswamy, Abishekapriyan P.

Institute of Internal Medicine, Madras Medical College, Chennai, Tamil Nadu, India

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***Correspondence:**
Shashank M.,
E-mail: shashankshashank052@gmail.com

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ABSTRACT

Autoimmune encephalitis (AE) is an immune-mediated neurological disorder with diverse clinical presentations, often posing diagnostic challenges due to nonspecific clinical and radiological findings. We report three cases of AE with distinct clinical presentations and antibody profiles. The first involved a 24-year-old woman presenting with fever, seizures, behavioral abnormalities and altered sensorium, with cerebrospinal fluid positivity for anti-N-methyl-D-aspartate receptor (NMDAR) antibodies. The second, a 50-year-old man, presented with subacute memory impairment and behavioral changes, demonstrating dual positivity for contactin-associated protein-like 2 (CASPR2) and leucine-rich glioma-inactivated 1 (LGI1) antibodies. The third, a 44-year-old man, presented with tremulousness, hypertonia, slurred speech and stimulus-induced myokymia, with positive LGI1 antibodies. These cases highlight the heterogeneous manifestations of AE, limitations of routine investigations and the importance of neuronal antibody testing. Early recognition, appropriate immunotherapy and careful clinical correlation are essential for timely diagnosis and improved outcomes.

Keywords: Autoimmune encephalitis, Anti-NMDAR encephalitis, LGI1 antibodies, CASPR2 antibodies, Neuronal surface antibodies, Neuropsychiatric manifestations, Immunotherapy

INTRODUCTION

Autoimmune encephalitis (AE) encompasses a heterogeneous group of inflammatory disorders of the central nervous system characterized by immune-mediated responses against neuronal antigens. The identification of antibodies targeting neuronal surface antigens has broadened the clinical and immunological spectrum of these disorders and enhanced the understanding of encephalitic syndromes previously considered of unknown etiology.[1] Among these, antibodies against the N-methyl-D-aspartate receptor (NMDAR) are a well-established cause of AE and are associated with a broad range of neuropsychiatric and neurological manifestations.[2] Detection of relevant neuronal antibodies, particularly in cerebrospinal fluid (CSF), is an important component of the diagnostic evaluation and should be interpreted in the context of the patient's clinical features and other supportive investigations.[3] We report three cases of AE presenting with distinct clinical manifestations and antibody profiles, highlighting the heterogeneous clinical spectrum, diagnostic complexities and potential reversibility of this treatable neurological condition.

CASE SERIES

Case 1

A 24-year-old woman presented with fever, seizures, abnormal behavior and episodes of projectile vomiting. On examination, she was febrile and exhibited inappropriate, meaningless smiling and incoherent speech. She was

unable to obey verbal commands. Neurological examination revealed increased tone in all four limbs. No sensory loss or autonomic dysfunction noted. The combination of febrile illness, seizures, altered sensorium, prominent behavioral disturbances and abnormal limb tone raised suspicion of an underlying encephalitic process.

Initial neuroimaging with computed tomography (CT) of the brain was unremarkable. Cerebrospinal fluid (CSF) examination revealed an elevated protein concentration of 125 mg/dL, glucose of 67 mg/dL, and adenosine deaminase (ADA) level of 42 U/L; the CSF was acellular. CSF CBNAAT for *Mycobacterium tuberculosis* was negative. A viral panel, including polymerase chain reaction testing for herpes simplex virus, as well as testing for varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus, was negative. Contrast-enhanced magnetic resonance imaging (MRI) of the brain demonstrated mild bilateral temporal lobe hyperintensities. However, based on the initial clinical and investigative findings, she was started on antitubercular therapy and corticosteroids, but there was no appreciable clinical improvement. In view of the persistent encephalopathy and neuropsychiatric manifestations, CSF was subsequently evaluated for autoimmune encephalitis, which demonstrated strong positivity for anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, establishing the diagnosis of anti-NMDAR encephalitis.

The patient received intravenous methylprednisolone for five days. As there was no significant improvement in sensorium following corticosteroid therapy, therapeutic plasma exchange was initiated. After three cycles of plasma exchange, the patient demonstrated neurological improvement, notably regaining the ability to obey simple verbal commands.

Case 2

A 50-year-old man with systemic hypertension presented with progressive memory impairment of 20 days' duration, accompanied by altered speech and behavioral disturbances characterized by talking to himself. He also reported low-grade fever. There was no associated loss of weight or appetite and he had no history of smoking or alcohol consumption. On examination, the patient was conscious but intermittently confused. Neurological evaluation revealed impairment of short-term memory. Muscle tone and power were preserved. CT of the brain was unremarkable (as shown in Figure 1). CSF protein and glucose concentrations were within normal limits, and testing for viral markers was negative. MRI of the brain did not reveal any significant abnormality. In view of the subacute onset of cognitive and behavioral symptoms despite unrevealing conventional neuroimaging and CSF studies, an autoimmune encephalitis panel was performed. CSF testing was positive for CASPR2 and LGI1 antibodies, supporting a diagnosis of autoimmune encephalitis associated with neuronal surface antibodies. The patient was treated with intravenous immunoglobulin at a dose of 0.4 g/kg/day for five days. He was subsequently discharged on maintenance oral corticosteroid therapy.

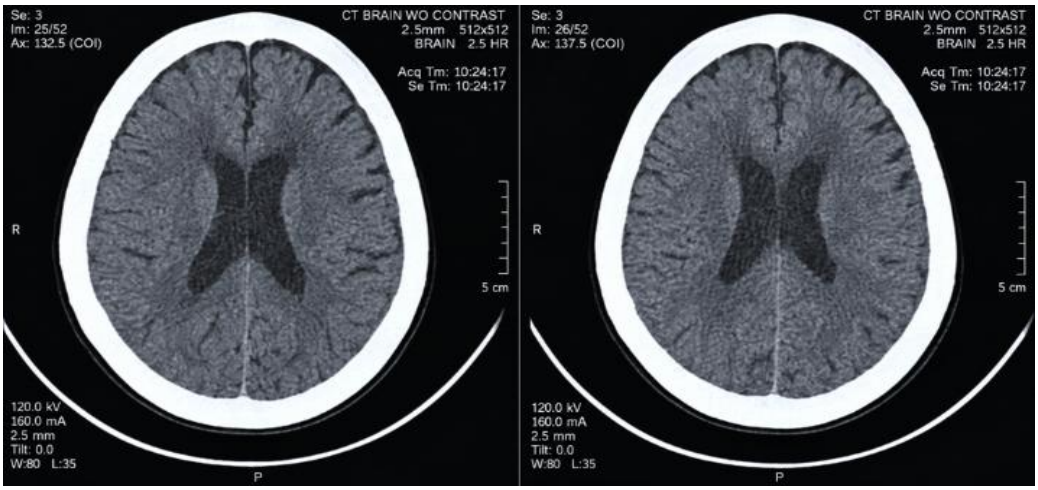


Figure 1: CT brain showing no acute intracranial abnormality or evidence of encephalitis.

Case 3

A 44-year-old man with type 2 diabetes mellitus presented with decreased responsiveness, slurring of speech, and tremulousness involving both upper and lower limbs. During the subsequent course of illness, he developed difficulty retaining his footwear while walking and difficulty rising from a squatting position, suggestive of evolving motor dysfunction. There was no history of seizures. On examination, he was conscious and oriented. His speech was slurred, with a possible spastic quality. Markedly increased muscle tone was documented. Cerebellar examination was unremarkable. Stimulus-induced myokymia was observed over both calves. Routine hematological investigations and renal and liver function tests were within normal limits. Serum creatine

kinase was 371 U/L and serum calcium was 8.2 mg/dL. Echocardiography demonstrated no regional wall-motion abnormality, with a left ventricular ejection fraction of 60%. CT imaging of the brain, chest, and abdomen was unremarkable. MRI of the brain demonstrated a hypoplastic left transverse sinus. Nerve conduction studies showed that the bilateral sural nerves were not stimulable. Given the neurological presentation and absence of a structural explanation on neuroimaging, an autoimmune antibody panel was performed and was positive for LGI1 antibodies. The patient was treated with intravenous immunoglobulin at a dose of 0.4 g/kg. He subsequently demonstrated symptomatic improvement and was discharged on oral corticosteroid therapy.

Table 1: Comparing investigation findings for the 3 individual cases.

Investigation parameters	Case 1	Case 2	Case 3
Cerebrospinal fluid (CSF)	Protein: 125 mg/dL; Glucose: 67 mg/dL; ADA: 42 U/L; Acellular; TB-CBNAAT & Viral PCR (HSV, VZV, CMV, EBV): Negative	Protein & Glucose: Normal limits; Viral panel: Negative	Not performed / Not reported
CT brain	Unremarkable	Unremarkable	Unremarkable
MRI Brain	Mild bilateral temporal lobe hyperintensities	No significant abnormality	Hypoplastic left transverse sinus
Electrophysiology and ancillary tests	Not performed	Not performed	NCS: Non-stimulable bilateral sural nerves; 2D-Echo: LVEF 60%
Autoimmune encephalitis panel	Positive for Anti-NMDAR antibodies (CSF)	Dual positive for CASPR2 and LGI1 antibodies (CSF)	Positive for LGI1 antibodies

Table 2: Comparative overview of case presentations, diagnostic findings and management of the 3 individual cases.

Clinical / Diagnostic Parameter	Case 1	Case 2	Case 3
Age / Sex	24 / Female	50 / Male	44 / Male
Comorbidities	None	Systemic hypertension	Type 2 diabetes mellitus
Primary clinical features	Fever, seizures, abnormal behavior, incoherent speech, hypertonia, projectile vomiting	Memory impairment (20 days), speech alterations, self-talking behavior, low-grade fever, confusion	Decreased responsiveness, slurred spastic speech, generalized hypertonia, calf myokymia, gait difficulty
Routine CSF pattern	Inflammatory (Elevated protein & ADA, acellular)	Normal	Not reported
Brain imaging features	Mild bilateral temporal hyperintensities (MRI)	Normal CT & MRI	Normal CT; Hypoplastic left transverse sinus (MRI)
Electrophysiological abnormalities	None reported	None reported	Bilateral sural sensory neuropathy on NCS
Antibody profile	Anti-NMDAR	Dual CASPR2 + LGI1	LGI1
Primary immunotherapy and outcome	IV Methylprednisolone (no improvement), then Plasma Exchange (3 cycles leading to Clinical recovery)	IVIG (0.4 g/kg/day for 5 days), then maintained on oral steroids	IVIG (0.4 g/kg) until symptomatic improvement, then maintained on oral steroids

DISCUSSION

AE encompasses a heterogeneous group of immune-mediated neurological disorders that may present with cognitive impairment, behavioral or psychiatric disturbances, seizures, abnormal movements, and altered levels of consciousness. Early recognition is essential, as timely diagnosis and initiation of immunotherapy may improve clinical outcomes. Graus et al proposed a syndrome-based diagnostic approach that integrates clinical features with magnetic resonance imaging (MRI), electroencephalography (EEG), CSF analysis and neuronal antibody testing, rather than relying exclusively on antibody detection.[1] The present case series highlights the diverse clinical manifestations of AE, the limitations of conventional investigations and the importance of

considering an autoimmune etiology in patients with otherwise unexplained neurological dysfunction. The three patients demonstrated distinct clinical phenotypes, including prominent neuropsychiatric manifestations, subacute cognitive impairment and motor hyperexcitability.

The first patient, a 24-year-old woman, presented with fever, seizures, behavioral abnormalities, incoherent speech and reduced responsiveness. This clinical presentation was suggestive of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, which frequently begins with behavioral or psychiatric manifestations and may subsequently progress to speech dysfunction, seizures, movement abnormalities, and impaired consciousness.[2] The second patient, a 50-year-old man, predominantly presented with subacute memory impairment, confusion, and behavioral disturbances. The third patient manifested increased muscle tone, tremulousness, slurred speech, and stimulus-induced myokymia. Collectively, these cases illustrate the broad clinical spectrum of AE, which may initially mimic psychiatric or cognitive disorders, whereas movement abnormalities and peripheral nerve hyperexcitability may predominate in other presentations. Diagnostic delays may occur when behavioral or cognitive symptoms precede more recognizable neurological manifestations.[1]

The first patient exhibited behavioral abnormalities, seizures, memory impairment, and reduced consciousness, features consistent with the clinical spectrum of anti-NMDAR encephalitis described by Dalmau et al.[2] The strongly positive CSF anti-NMDAR antibody result provided additional evidence supporting the diagnosis. MRI revealed mild bilateral temporal lobe hyperintensities, which were nonspecific and required interpretation in conjunction with the clinical presentation and laboratory findings. CSF antibody testing is particularly important in suspected anti-NMDAR encephalitis. Gresa-Arribas et al demonstrated the diagnostic value of examining both serum and CSF for anti-NMDAR antibodies, emphasizing the importance of selecting appropriate specimens for antibody detection.[3]

The second patient presented with memory impairment, speech disturbances, and behavioral changes, with CSF positivity for both leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) antibodies. These neuronal surface antibodies are associated with distinct clinical syndromes, although overlapping manifestations may occur. LGI1 antibody-associated encephalitis commonly presents with subacute memory impairment, confusion, behavioral changes and seizures. In contrast, CASPR2 antibody-associated disease may involve both the central and peripheral nervous systems, producing manifestations such as limbic encephalitis, peripheral nerve hyperexcitability, neuromyotonia and Morvan syndrome.[4] Although the patient's cognitive and behavioral manifestations were compatible with AE, the available clinical findings do not establish the relative contribution of either antibody to the observed phenotype. Therefore, dual antibody positivity warrants cautious interpretation. The original laboratory report should be reviewed to establish the assay methodology, specimen type, antibody titres or signal intensity and clinical relevance of both results. Neuronal antibody findings should be interpreted as supportive evidence within the overall clinical context rather than as independent determinants of diagnosis.[1]

The third patient was positive for LGI1 antibodies and presented with increased muscle tone, tremulousness, slurred speech, and stimulus-induced myokymia. LGI1 antibody-associated encephalitis is classically characterized by limbic dysfunction, memory impairment, and seizures, particularly faciobrachial dystonic seizures (FBDS). These typically manifest as brief, stereotyped dystonic episodes involving the face and ipsilateral arm and may precede the development of overt cognitive impairment.[5] However, the motor manifestations observed in the present patient should not be classified as FBDS without a sufficiently detailed description of their clinical semiology. Myokymia and peripheral nerve hyperexcitability are more characteristically associated with CASPR2 antibody-related disorders.[4] Consequently, the occurrence of myokymia in an LGI1 antibody-positive patient warrants careful clinical and electrophysiological evaluation. Detailed characterization of the abnormal movements, EEG, serum sodium assessment and nerve conduction studies with electromyography may help establish the underlying neurological syndrome.

Conventional investigations were either normal or nonspecific in several patients. Cranial computed tomography (CT) scans were unremarkable in all three cases, while MRI did not reveal significant abnormalities in the second patient. Similarly, the third patient had no major structural lesion that could account for the neurological manifestations. These findings emphasize the limitations of conventional neuroimaging in the evaluation of AE. Although MRI abnormalities may be observed in specific antibody-associated syndromes, normal or nonspecific neuroimaging findings do not exclude the diagnosis.[1] Routine CSF parameters may also be relatively unremarkable in some forms of neuronal surface antibody-associated encephalitis. Accordingly, diagnostic evaluation should integrate the clinical course with MRI, EEG, CSF findings, and appropriately selected neuronal antibody testing.[6]

The clinical course of the first patient also illustrates the diagnostic challenges involved in differentiating AE from infectious encephalitis. The presence of fever, seizures, behavioral abnormalities and temporal lobe hyperintensities initially raised suspicion of an infectious etiology, prompting treatment with antitubercular therapy and corticosteroids. CSF analysis revealed elevated protein levels and an adenosine deaminase (ADA) level of 42 U/L, despite the absence of pleocytosis. CSF testing for *Mycobacterium tuberculosis* using cartridge-based nucleic

acid amplification was negative, as were the reported viral investigations. However, an elevated CSF ADA level in isolation is insufficient to establish a diagnosis of tuberculous meningitis. The subsequent detection of strongly positive CSF anti-NMDAR antibodies provided substantial evidence in favor of an autoimmune etiology. This case highlights the importance of reassessing the initial diagnostic impression when the clinical course, investigation results, or response to treatment are inconsistent with the presumed diagnosis. Nevertheless, an appropriate evaluation for infectious causes remains essential before initiating immunosuppressive treatment, as unrecognized infections may worsen following immunotherapy.

Treatment in the present series was individualized according to the clinical presentation and available diagnostic findings. The first patient received intravenous methylprednisolone for five days, without substantial early clinical improvement, and subsequently underwent plasma exchange. Following three cycles of plasma exchange, she demonstrated clinical improvement, regaining the ability to follow simple commands. The second and third patients were treated with intravenous immunoglobulin (IVIG), followed by maintenance oral corticosteroid therapy. Corticosteroids, IVIG and plasma exchange are established first-line immunotherapeutic options for AE. Treatment selection depends on disease severity, the suspected antibody-associated syndrome, contraindications, and clinical response.[6]

Titulaer et al demonstrated the importance of immunotherapy in anti-NMDAR encephalitis and identified clinical factors associated with long-term outcomes.[7] Although the first patient improved following plasma exchange, this observation does not establish its superiority over other immunotherapeutic modalities. Furthermore, the available clinical information does not permit a direct comparison of treatment responses among the three patients. Documentation of the time to clinical improvement, functional status at discharge, residual neurological deficits and duration of follow-up would provide a more comprehensive assessment of treatment outcomes.

The present case series highlights several important clinical considerations. New-onset behavioral disturbances, subacute memory impairment, seizures, altered consciousness, and unexplained movement disorders should prompt consideration of AE in the differential diagnosis. Normal CT findings, unremarkable or nonspecific MRI findings, and relatively normal routine CSF parameters should not independently exclude the possibility of an autoimmune etiology. Neuronal antibody results must be interpreted in conjunction with the clinical phenotype and laboratory methodology, particularly when multiple antibodies are detected in the same patient. Early recognition, appropriate exclusion of relevant infectious etiologies, and timely initiation of immunotherapy are essential components of clinical management.[1]

Limitations

The small sample size and clinical heterogeneity limit the generalizability of these observations and prevent meaningful comparisons between antibody-associated syndromes or treatment strategies. Detailed long-term cognitive, functional, and relapse data were also unavailable.

CONCLUSION

Autoimmune encephalitis presents with a broad spectrum of neurological and neuropsychiatric manifestations, making early clinical recognition challenging. The present case series highlights the importance of considering AE in patients with unexplained behavioral changes, cognitive impairment, seizures, and abnormal movements. It also emphasizes the need for careful interpretation of neuronal antibody profiles in conjunction with clinical findings and supportive investigations. Early diagnosis and timely immunotherapy may contribute to favorable clinical outcomes and reduce the risk of long-term neurological disability.

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