

# Atypical Presentation of Anti-NMDAR encephalitis in a Male Patient – an Unfortunate Mimic

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## Abstract:

### Background

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a neuroinflammatory disorder with a predilection for females. Males present differently, with seizures rather than the better-recognized constellation of psychiatric and behavioral symptoms dominating the initial stages of the disease, providing a potential substrate for delayed recognition and treatment.

### Case Presentation

An 18-year-old man presented with fever and “seizures. When examined, he was febrile but alert and coherent. His neurologic, respiratory, cardiovascular, and abdominal examinations were unremarkable. Diagnosed with infective meningoencephalitis, he was started on intravenous ceftriaxone and acyclovir concurrently with anti-epileptic medications. However, he deteriorated into refractory status epilepticus.

Electroencephalograms showed left temporo-parietal seizures. Cerebrospinal fluid analysis revealed inflammatory features, but the virologic assays and bacterial cultures returned negative. Magnetic resonance imaging scans performed in the first and second week from symptom-onset demonstrated the interval development of widespread sulcal T2 hyperintensity, with florid and diffuse leptomeningeal enhancement. Anti-NMDAR antibodies were subsequently detected in his cerebrospinal fluid by indirect immunofluorescence. Diagnosed with anti-NMDAR encephalitis, he received plasmapheresis, methylprednisolone and immunoglobulin infusions.

### Conclusion

Anti-NMDAR encephalitis should be considered in patients, especially males, who are treated for suspected infectious meningoencephalitis, but continue to deteriorate, even in the absence of prominent psychiatric or behavioral symptoms, considering how the initial symptoms differ between the genders. The interval development of diffuse and florid leptomeningeal enhancement on sequential magnetic resonance imaging scans of our patient has not been described in prior reports, and may be reflective of the underlying inflammatory processes.

**Keywords:** anti-nmdar encephalitis; meningoencephalitis; status epilepticus; leptomeningeal enhancement

## Case Presentation

An 18-year-old man presented acutely with recurrent generalized tonic-clonic seizures. He had no prior medical history, and did well in school. He was without behavioural, psychiatric or neurologic symptoms prior to the seizures. On examination, he was febrile but remained lucid and coherent. His blood pressure and heart rate were within normal limits. Neurologic, respiratory, cardiovascular and abdominal examinations were unremarkable. Suspecting infectious encephalitis, he received intravenous ceftriaxone and acyclovir, concurrently with antiepileptic medications for the control of his seizures.

Despite these measures, his continued to experience recurrent seizures, finally deteriorating into refractory status epilepticus three days later. He

was transferred to the neurological intensive care unit (ICU) where he was put into a barbiturate-induced coma. His cerebrospinal fluid (CSF) showed a white cell count of 146 cells/mm<sup>3</sup> (predominantly lymphocytic) and 0.75g/L of protein. CSF glucose was normal, and the virologic assays, inclusive of enterovirus, cytomegalovirus, measles, mumps, herpes-simplex and varicella zoster viruses, returned negative. CSF bacteriologic assays and cultures were also unremarkable. However, anti-NMDAR antibodies were detected in his CSF on indirect immunofluorescence, and plasmapheresis plus intravenous methylprednisolone were concurrently and promptly administered.

His electroencephalograms showed left temporo-parietal seizures on multiple occasions. Brain magnetic resonance imaging (MRI) was

performed with gadolinium on the fourth day from symptom-onset, showing swelling of the left fronto-parietal cortex, but without FLAIR abnormalities or leptomeningeal enhancement. An interval MRI performed a week later revealed interval development of widespread sulcal FLAIR hyperintensity, with florid and diffuse leptomeningeal enhancement the hippocampi appeared normal on both MRIs.

Our patient received five cycles of plasmapheresis, five days of intravenous methylprednisolone, followed by intravenous immunoglobulin infusions at 2g/kg. At the time of writing, two months from the day of admission, improvement of his modified Rankin Scale scores from 5 to 4 was observed, with no further recurrence of his seizures. He was transferred out of the ICU to the high dependency unit, but continued to display generalized dyskinesia and catatonia.

## Discussion

Anti-NMDAR encephalitis is a neuroinflammatory disorder due to autoantibodies against the receptor's GluN1/NR1 subunit, resulting in a well-recognized constellation of neuropsychiatric symptoms, with ovarian teratomas and herpes simplex encephalitis identified as triggers. [1, 2] With a clear predilection for females (female to male ratio of 4:1), prominent psychiatric symptoms tend to predominate at the earlier stages of the disease, including visual or auditory hallucinations, acute schizoaffective episodes, and depression. [1]

Our patient's case raised two learning points. Firstly, anti-NMDAR encephalitis should be considered in patients, especially males, who continue to deteriorate despite being appropriately treated for infectious meningoencephalitis, even in the absence of prominent psychiatric or behavioral symptoms. [3,5] Its recognition is particularly vital in male patients in whom the disease is comparatively less frequent than in females, and that the psychiatric, behavioral and cognitive symptoms which are well-described in females, are relatively uncommon initial symptoms in males.[1] In Viacoz's study of 13 male diagnosed with anti-NMDAR encephalitis, only 4 (30.8%) presented with psychiatric, behavioral or cognitive dysfunction, while 8 (61.5%) had seizures as the sole initial symptom.[4] Prompt recognition of anti-NMDAR encephalitis can serve to facilitate earlier initiation of immunotherapy, thus reducing the risk of poor clinical outcome. [6]

Secondly, the interval development of diffuse and prominent leptomeningeal enhancement on sequential MRIs has not been described in earlier literature, and may reflect the progressive floridity of the underlying inflammatory processes. While MRI abnormalities are observed in about half of the patients, and are notoriously non-specific, enhancement of the leptomeninges were rare occurrences, and often described as mild. [1, 2, 7] The interval appearance of the prominent and extensive enhancement our patient's leptomeninges differed significantly from those described in earlier studies, with its appearance coinciding with the clinical deterioration of our patient. However, the mechanisms behind the extensive dysfunction of the blood-brain barrier observed in our patient, be it the consequence of oxidative stress from the highly-active inflammatory processes, or as an epiphenomenon of the persistent seizures, or both, cannot be answered at this point.[8] Moreover, its clinical and prognostic value in terms of treatment response remains unknown and awaits future elucidation.

## Conclusion

Anti-NMDAR encephalitis should be considered, especially male patients, in those who continue to deteriorate despite being appropriately treated for infectious meningoencephalitis, even in the absence of prominent psychiatric or behavioral symptoms. This is particularly vital to male patients, as the early manifestations of anti-NMDAR encephalitis in males differ significantly from females, in which psychiatric and behavioral symptoms tend to predominate in the latter.[1, 4] The interval development of diffusely florid leptomeningeal enhancement is an uncommon finding in anti-NMDAR encephalitis, and may be reflective of floridity of the underlying inflammatory processes. Its clinical and prognostic significance, however, remains unknown.

## Declarations

### Ethics approval

As this is a case report of a single patient, the need for approval by the Institutional Review Board was waived.

### Consent to publication

Signed consent cannot be obtained from the patient as he lacked mental capacity at the time of submission, and remains on paralytic and anaesthetic agents. Patient's identifiers have been duly anonymized in the manuscript and the attached figures and diagrams.

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