

# Anti-N-methyl-D-aspartate Receptor Encephalitis: Characteristics and Rapid Diagnostic Approach in the Emergency Department

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## Research Article

**Keywords:** Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Diagnostic Errors, Emergency Department, Oligoclonal Bands, Teratoma

**Posted Date:** April 15th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1535433/v1>

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# Abstract

## Background

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a common type of autoimmune encephalitis. Patients with this condition are frequently very ill but are often misdiagnosed in the Emergency Department (ED). The objective of this study was to analyze the clinical characteristics of anti-NMDAR patients in the ED and to identify any associations with a diagnosis of anti-NMDAR encephalitis.

## Methods

We performed a retrospective analysis of a prospectively obtained cohort of ED patients from May 2011 to December 2017. We identified patients diagnosed with anti-NMDAR encephalitis in this cohort and extracted key patient characteristics and clinical data, including patient gender, age, presentation, modified Rank Score (m-RS), laboratory test results, significant treatments, and mortality.

## Results

87 patients with anti-NMDAR encephalitis were identified. 54 (62.1%) were female, 23 (26.4%) were <18 years old, 14 (16.1%) had teratoma, and 45 (51.7%) had an m-RS  $\geq 4$ . Fever, altered mental status, and seizures were the most common symptoms, with a >50% incidence of each symptom in the cohort. The sensitivity of CSF oligoclonal band (OB) testing was 78.9%. 22 (25.3%) were admitted to the ICU, 20 (23.0%) patients were intubated, but only one patient died (1.1%). 47 (54.0%) were misdiagnosed prior to ED arrival. All patients underwent immunotherapy as first-line treatment for anti-NMDAR encephalitis.

## Conclusions

A majority of anti-NMDAR encephalitis patients presenting to the ED were female and were likely to be misdiagnosed prior to arrival. Patients with symptoms of fever, altered mental status, and seizures need a lumbar puncture, including CSF OB testing, for definitive diagnosis.

## Background

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a common type of autoimmune encephalitis, where pathogenic auto-antibodies are directed against the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are found in the hippocampus of the human brain, where they are involved in learning and memory<sup>1</sup>. Anti-NMDAR autoantibodies attack these receptors, leading to neuropsychiatric symptoms. Anti-NMDAR encephalitis predominantly affects children and young adults and surpasses the frequency of any individual virus encephalitis in young people<sup>2</sup>. Furthermore, 53%-77% of anti-NMDAR encephalitis patients are severely ill and require intensive care unit (ICU) admission<sup>3,4</sup>. In a retrospective study, anti-NMDAR encephalitis accounted for 1% of all admissions for young adults to ICUs<sup>5</sup>. However, prompt diagnosis and treatment lead to improvement or full recovery in most cases<sup>6</sup>. As some of these patients (especially those who are severely ill) present to Emergency Departments (EDs), many can be misdiagnosed as having purely psychiatric illnesses on first contact with ED physicians<sup>7</sup>. There may be room to improve on the ED diagnosis for this disease by examining a cohort of anti-NMDAR encephalitis patients.

## Methods

Our institution is a national referral center for complicated diseases, and many encephalitis cases are seen in our ED. Since we have seen many anti-NMDAR encephalitis patients in our ED, we sought to establish a prospective anti-NMDAR encephalitis cohort to learn more about this patient population.

321 patients were enrolled in a prospective anti-NMDAR encephalitis cohort between May 2011 and December 2017. We retrospectively analyzed all patients who were admitted through the ED in this cohort. Patient characteristics, including gender, age, presenting complaint(s), modified Rank Score (m-RS), ancillary test results, treatments, and follow up results were recorded for analysis. The m-RS is widely used in the neurology literature to measure functional independence as part of a severity assessment. We recorded m-RS in patients admitted to the ED resuscitation room for ECG/BP/SpO2 monitoring after initial clinical assessment by an ER physician.

Additional data collected included: (1) symptoms upon ED presentation, including: abnormal (psychiatric) behaviors or cognitive dysfunction, speech dysfunction (pressured speech, paucity of speech, or mutism), seizures, movement disorders (including dyskinesia or abnormal posturing), decreased level of consciousness, autonomic dysfunction or central hypoventilation, fevers, or headaches; (2) m-

RS; (3) ancillary tests, including: complete blood count (CBC), cerebrospinal fluid (CSF) results, anti-NMDAR serum antibody level, electroencephalogram (EEG), and magnetic resonance imaging (MRI); (4) time and date of anti-NMDAR diagnosis, including any possible misdiagnoses and relation to symptom onset; (5) patient monitoring; (6) ICU admission or airway intubation; (7) treatments, including corticosteroids or intravenous immunoglobulin (IVIG); (8) presence of a teratoma and timing of removal surgery; (9) survival and follow-up results.

Continuous variables were presented as medians with quartiles, and categorical variables as frequencies with percentages. Median m-RS's were compared using the Mann-Whitney rank sum test.

## Results

After review of the database, 87 ED patients with anti-NMDAR encephalitis were included in the analysis. Of these 87 patients, 54 (62.1%) were female, and 23 (26.4%) were < 18 years old (including three patients < 12). Fever and abnormal behavior were the two most frequent symptoms, while a decreased level of consciousness and seizures were the next two most frequent symptoms (see Table 1).

Table 1  
Anti-NMDAR encephalitis ED patient characteristics

Gender (Male: Female)	Age (Adult = ≥ 18 y/o; Pediatric < 18 y/o)	Fever	Abnormal Behavior	Decreased consciousness	Seizures	Headache	Speech Dysfunction.	Movement disorder	Autonomic Dysfunction
33:54	Adult: 64; Pediatric: 23	58 66.7%	53 60.9%	49 56.3%	44 50.6%	33 37.9%	19 21.8%	18 20.7%	6 6.9%

84 (96.6%) patients had complete m-RS records, and 45 (51.7%) had an m-RS ≥ 4, of which 36 patients were admitted into the ED resuscitation area and received Electrocardiography (ECG), Saturation of peripheral Oxygen (SpO<sub>2</sub>), and Blood Pressure (BP) monitoring. Of these 36 monitored patients, 20 were subsequently intubated, placed on mechanical ventilation, and admitted to an ICU. Out of 87 total patients, only one patient died (1.1%). Of the 45 patients with an m-RS ≥ 4, 11 patients had ovarian teratomas, with one case of relapse and no deaths. 37 patients had low m-RS scores (0–3), of which five patients were lost to follow-up, but no deaths were recorded otherwise (see Fig. 1).

Overall, 14 (16.1%) patients had teratomas, all of which had teratoma removal operations, with the earliest operation being carried out five days following the diagnosis of anti-NMDAR encephalitis, while the latest operation was 42 days after diagnosis (median 13.5 days) (see Fig. 2a). Of these 14 patients, 10 patients had an m-RS score of 5, with others having lower scores (see Fig. 2b). In the group of patients without a teratoma, the median m-RS score was 3 (3, 5),  $P = 0.002$ . After surgery, almost all anti-NMDAR patients with a teratoma were in remission (except for one, who had a presenting m-RS = 5) (see Fig. 2b).

44 (50.6%) patients were admitted to the ED resuscitation area and received ECG, SpO<sub>2</sub>, and BP monitoring after being assessed by an ED physician. Of these 44 patients, 21 presented to the ED due to epileptic seizures, five due to autonomic dysfunction or hypoventilation, five for a decreased level of consciousness, four after teratoma removal operations, and 10 patients did not have any reason listed on their emergency medical records. Of the 44 monitored patients, 20 patients were intubated, 22 were admitted to the ICU, and one patient died (see Table 2).

Table 2  
Reasons for starting ED monitoring

87 total anti-NMDAR patients	44 patients monitored	Due to epileptic seizure: 21 patients
		* Due to autonomic dysfunction/hypoventilation: 5 patients
		After operation: 4 patients
		Due to decreased level of consciousness: 5 patients
		Unknown reasons: 10 patients
43 patients were not monitored		
*: 1 patient had a contemporaneous epileptic seizure.		

In reviewing the diagnostic pathway of the 87 total patients, 47 (54.0%) patients had been misdiagnosed before being transferred to our ED. 21 patients were diagnosed as having a viral encephalitis, 17 were diagnosed with a psychiatric condition, including schizophrenia, depression, or anxiety, and 9 had another (not anti-NMDAR encephalitis) diagnosis. 34 patients were diagnosed with anti-NMDAR encephalitis in our ED, with a mean time of diagnosis of 20.5 days. In our study, the sensitivity of an abnormal EEG was 71.2% and CSF oligoclonal band testing (OB) was 78.9%. Notably, finding serum antibodies against the NMDA receptor had a sensitivity of only 66.3%. Additional test results are shown in Table 3.

Table 3  
Ancillary test results for anti-NMDAR encephalitis ED patients

	Lymp% in routine blood tests	ESR	CRP	CSF					CSF pressure		MRI	EEG	Serum anti- NMDAR antibody	
				Cell count	wbc	Pro	glu	Cyto. Exam	OB					
+	7	22	24	52	37	23	11	43	45	24	34	47	55	
-	78	44	39	33	48	64	72	36	12	44	36	19	28	
X	2	21	24	2	2	0	4	8	30	19	17	21	4	
+: Positive. -: Negative. X: data unavailable. wbc: white blood cell. Pro: protein. Glu: glucose														

## Discussion

The diagnosis of anti-NMDAR encephalitis is very difficult to make at the point of first medical contact in the ED. To confirm the diagnosis, a positive anti-NMDAR test result from a patient's CSF is needed, however this may not be available in many medical institutions. Fortunately, anti-NMDAR encephalitis presents with a constellation of characteristic symptoms. In this study, we found fever, abnormal (psychiatric) behaviors, a decreased level of consciousness, and seizures were the most common symptoms, all with an incidence above 50%. Unfortunately, the psychiatric symptoms associated with anti-NMDAR encephalitis can be so significant that many family or emergency physicians refer these patients to psychiatrists for consultation<sup>7,8</sup>. Our study found rates of misdiagnosis were relatively high with 47 (54.0%) patients experiencing a misdiagnosis. A key hallmark of anti-NMDAR encephalitis is that, unlike in cases of 'pure' psychosis, it is often associated with other symptoms such as fever, decreased level of consciousness, or seizures.

An important first step in the ED is to search for causes of fever, identify possible drug overdoses or other metabolic factors which may lead to decreased levels of consciousness and seizures, but anti-NMDA receptor encephalitis should be on the differential diagnosis for patients with a fever and psychiatric symptoms. Since many patients presenting to the ED with such symptoms will require a lumbar puncture for CSF testing as part of routine ED evaluation, we recommend considering testing for anti-NMDAR antibodies if a clinician suspects the diagnosis and if the medical institution can perform the necessary tests. Meanwhile, more ancillary tests are needed to support the diagnosis of anti-NMDAR encephalitis if antibody testing is unavailable.

In our study, we found the sensitivity of CSF oligoclonal band testing (OB) was 78.9%, and an abnormal EEG 71.2%, but serum antibody against NMDAR had a sensitivity of only 66.3%. Compared with EEG and serum antibody against NMDAR, CSF OB testing is more

sensitive and more widely available in many EDs. Graus et al. reported CSF OB sensitivity to be >60% and could be a useful ancillary test for the clinical diagnosis of anti-NMDAR encephalitis<sup>9</sup>.

Patients who presented to the ED were quite ill. According to the m-RS scores, more than half were  $\geq 4$ , and, of these, >80% received monitoring. Overall, in our study, more than half the patients needed to be monitored after being assessed by an ED physician, and half of those monitored patients were subsequently intubated and admitted to an ICU. We analyzed the reasons why patients were monitored, and we found that seizures, autonomic dysfunction, central hypoventilation, or a decreased level of consciousness were the top three reasons. As is common for many other serious ED conditions, airway and ventilation abnormalities or risks were of most concern in these patients. On a more positive note, only one out of 87 patients with anti-NMDAR encephalitis died.

Female patients suspected of anti-NMDAR encephalitis need tumor screening and teratoma removal operations. A majority of anti-NMDAR encephalitis patients in our study were female, and 14 had teratomas. In these 14 patients, 10 had an m-RS of 5, and one had a m-RS of 4, so 78.6% had an m-RS score  $\geq 4$ . Patients with teratomas in our study had higher m-RS scores compared to those without teratomas ( $p = 0.002$ ). Given this association, we reviewed the source database (ED and non-ED patients) and found that, out of 201 female patients, 39 had a teratoma (19.4%). Of those patients with a teratoma, 27 had an m-RS of 5, and patients with a mRS  $\geq 4$  take up 74.4% of all patients, like the results in this ED study. We strongly suggest that female patients diagnosed with anti-NMDAR encephalitis should receive tumor screening, especially for ovarian tumors such as teratomas. The most common method for this would be via abdominal or pelvic ultrasound, with computer tomography or MRI of the pelvis as possible options as well.

Immunotherapy is the first line treatment for the anti-NMDAR encephalitis: every patient received a combination of steroids and IVIG to treat anti-NMDAR encephalitis. 39 patients received steroid pulse therapy (methylprednisolone 500 ~ 1000mg daily). All steroid pulse therapy plans were decided after consultation with a neurologist. 84 (96.6%) patients received IVIG, which was sometimes ordered by ED physicians before consultation a neurologist.

## Limitations

This study had some limitations. First, anti-NMDAR encephalitis is just one of the autoimmune encephalitis types, which also includes  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA),  $\gamma$ -aminobutyric acid (GABA), and leucine-rich, glioma-inactivated 1 (LGI1) et.al, among others. Like these other types of autoimmune encephalitis, they all may have some overlap in symptoms and clinical characteristics. As anti-NMDAR was the most common type of autoimmune encephalitis we encountered in our institution, we limited this study to this sub-type. Second, although we suggest patients with common symptoms need a lumbar puncture for CSF testing, including OB testing, this suggestion needs further study to prove its effectiveness. Third, we used the mRS score as a proxy to assess for clinical severity in this study, but the decision to monitor depends on each patient's airway and ventilation condition. We believe future prospective studies will help clarify these limitations.

## Conclusions

Although anti-NMDAR encephalitis is hard to diagnose upon first medical contact in the ED, three common symptoms (fever, altered mental status, and seizures) should prompt emergency medicine physicians to perform a lumbar puncture. CSF testing should include testing for OB and anti-NMDAR antibodies. Like other encephalitis patients in the ED, we should pay attention to their mental status, airway protection and ventilation capabilities. As for female patients with diagnosed or suspected anti-NMDAR encephalitis, tumor screening (most often with ultrasound) is recommended. For patients of both genders, neurologist consultant and immunotherapy are the next steps, which can begin in the ED.

## List Of Abbreviations

anti-NMDAR encephalitis  
Anti-N-methyl-D-aspartate receptor encephalitis  
ED  
Emergency Department  
m-RS  
modified Rank Score  
ICU  
intensive care unit

CBC  
complete blood count  
CSF  
cerebrospinal fluid  
OB  
oligoclonal band testing  
EEG  
electroencephalogram  
MRI  
magnetic resonance imaging  
IVIg  
intravenous immunoglobulin  
ECG  
electrocardiography  
SpO<sub>2</sub>  
saturation of peripheral oxygen  
BP  
blood pressure

## Declarations

All methods were carried out in accordance with relevant guidelines and regulations.

### Ethics approval and consent to participate

This study was approved by The Institutional Review Board (IRB) of Peking Union Medical College Hospital on June 23, 2015 (JS-891), and informed consent was obtained from each patient or patient's next-of-kin.

### Consent for publication

Not applicable.

### Availability of data and materials

Anonymized data from this study is available from the corresponding author upon reasonable request from any qualified investigator.

### Competing interests

The authors declare that they have no competing interests.

### Funding

Not applicable.

### Authors' contributions

Jin Xu, Hongzhi Guan and Xuezhong Yu conceived and designed the study. Jin Xu and Na Zhao conducted the search of clinical parameters and data collection. Hongzhi Guan, Xuezhong Yu and Huadong Zhu provided professional advises on study design and data analysis. Jin Xu drafted the manuscript, Jin Xu, Na Zhao and Joseph Walline revised this article in English. Xuezhong Yu takes responsibility for the paper as a whole.

### Acknowledgements

This study has taken so many years, I will give my deepest thanks to all the colleges and students who support this program. And I will give thanks to my wife, my son and daughter that you are greatest support for my soul.

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## Figures

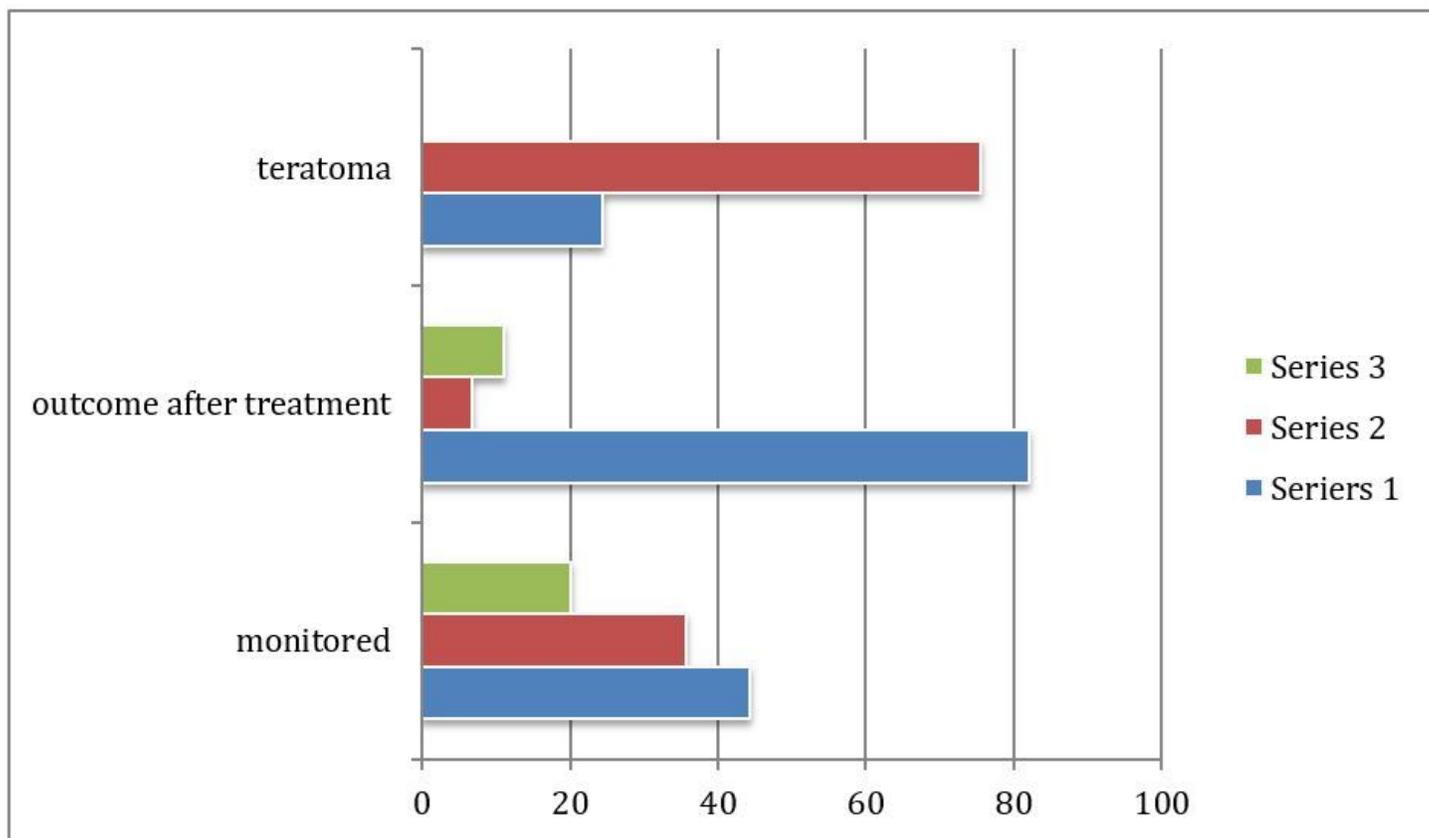


Figure 1

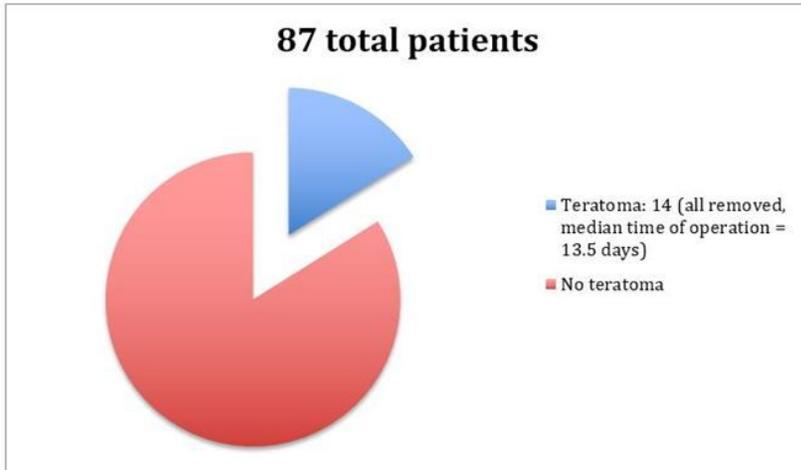
Patients with m-RS  $\geq 4$

\* Teratoma: 11 patients positive (blue) and 34 patients negative (red)

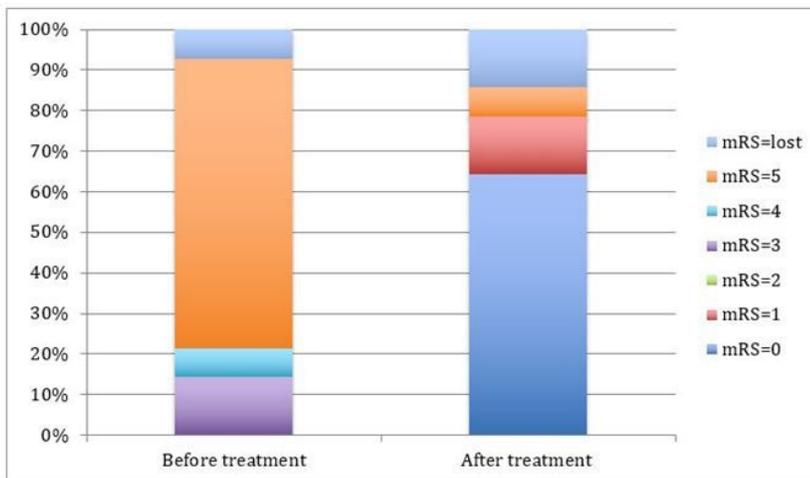
Outcome after treatment: 37 patients went into remission (blue), 3 patients had no response (red), and 5 patients' data were lost (green)

Monitored: 20 patients were monitored and intubated (blue), 16 patients were monitored only (red), and 9 patients had no monitoring (green).

**Figure 2a**



**Figure 2b: m-RS data**



**Figure 2**

Patients with teratomas