MAJOR ARTICLE

# The Frequency of Autoimmune *N*-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project

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***Background.*** In 2007, the California Encephalitis Project (CEP), which was established to study the epidemiology of encephalitis, began identifying cases of anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Increasing numbers of anti-NMDAR encephalitis cases have been identified at the CEP, and this form rivals commonly known viral etiologies as a causal agent. We report here the relative frequency and differences among encephalitides caused by anti-NMDAR and viral etiologies within the CEP experience.

***Methods.*** Demographic, frequency, and clinical data from patients with anti-NMDAR encephalitis are compared with those with viral encephalitic agents: enterovirus, herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), and West Nile virus (WNV). All examined cases presented to the CEP between September 2007 and February 2011 and are limited to individuals aged ≤30 years because of the predominance of anti-NMDAR encephalitis in this group. The diagnostic costs incurred in a single case are also included.

***Results.*** Anti-NMDAR encephalitis was identified >4 times as frequently as HSV-1, WNV, or VZV and was the leading entity identified in our cohort. We found that 65% of anti-NMDAR encephalitis occurred in patients aged ≤18 years. This disorder demonstrated a predilection, which was not observed with viral etiologies, for females ($P < .01$). Seizures, language dysfunction, psychosis, and electroencephalographic abnormalities were significantly more frequent in patients with anti-NMDAR encephalitis ($P < .05$), and autonomic instability occurred exclusively in this group.

***Discussion.*** Anti-NMDAR encephalitis rivals viral etiologies as a cause of encephalitis within the CEP cohort. This entity deserves a prominent place on the encephalitic differential diagnosis to avoid unnecessary diagnostic and treatment costs, and to permit a more timely treatment.

The California Encephalitis Project (CEP) was established in 1998 to study the epidemiology of encephalitis and to identify its etiologies. In the fall of 2007, a novel form of autoimmune encephalitis was described with the name anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. That same year, this form of encephalitis was observed in 1 case referred to the CEP, leading to a collaboration with the University of Pennsylvania to facilitate the recognition of this entity. In 2009, the first 10 cases of anti-NMDAR encephalitis identified at CEP were reported and compared with encephalitis cases resulting from viral etiologies [1].

As increasing numbers of cases have presented to the CEP, the frequency of anti-NMDAR encephalitis has come to rival that of viral encephalitis, making it

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a significant cause of encephalitis in certain age groups. Although initially thought to affect primarily young adult females, often with associated teratomas, it was later described in men and children, frequently without any identifiable tumor [2]. Since the CEP's first publication on this topic in 2009, the frequency and importance of this entity have come to light [3], and we have a better understanding of how anti-NMDAR encephalitis compares with encephalitides of several viral etiologies. This report describes the relative frequency and essential differences between encephalitides caused by anti-NMDAR and viral etiologies within the CEP cohort.

## METHODS

Specimens from patients with suspected encephalitis are referred to the CEP by their treating physicians for diagnostic testing. The CEP case definition is as follows: immunocompetent, ≥6 months of age, and under hospitalization for encephalopathy (altered mental status) with at least 1 clinical or diagnostic finding of fever, seizure, focal neurologic finding, cerebrospinal fluid (CSF) pleocytosis, electroencephalographic alteration, or neuroimaging abnormality. A standardized case history form with information about patient demographics, exposures, clinical features, laboratory and neuroimaging results, and medication is submitted by the referring physician. Serum, CSF, and respiratory specimens are also submitted and tested for 15 potential agents including herpesviruses, arboviruses, respiratory viruses, and *Mycoplasma pneumonia* [4].

Since 2007 (when CEP became aware of this entity), if signs and symptoms suggestive of anti-NMDAR encephalitis—such as movement disorders, autonomic instability, or psychosis—are apparent, CEP staff contacts the referring physician and asks if he or she wants to pursue testing. After we obtain consent for testing, specimens are forwarded to 1 of the coauthors (JD) for examination using protocols previously described elsewhere [5].

Herein, demographic, frequency, and clinical data are compared with data from other etiologic agents associated with encephalitis: enteroviruses, herpes simplex virus 1 (HSV-1), varicella-zoster virus (VZV), and West Nile virus (WNV). All examined cases are limited to those that meet the CEP case definition and those ≤ 30 years of age given that anti-NMDAR encephalitis predominates in this age group. Cases presenting to the CEP between September 2007 and February 2011 are included. Categorical data were analyzed using a 2-tailed Fisher exact test, and continuous data were subjected to the Kruskal–Wallis test. Statistical significance was defined as $P < .05$.

The costs of infectious disease testing for 1 case, prior to CEP referral, are estimated by reviewing all tests performed, with projected costs determined by referencing costs of a commonly used commercial laboratory.

## RESULTS

### Frequency and Demographics

Between September 2007 and February 2011, 761 cases of encephalitis of uncertain etiology in individuals aged ≤30 years were referred to the CEP. Of these, enterovirus was identified in 30 patients, HSV-1 in 7 patients, and VZV and WNV in 5 patients each. Another 47 patients were suspected of having anti-NMDAR encephalitis and were tested; 32 of these cases tested positive for this form. Of the cases of identified etiology, anti-NMDAR encephalitis was the leading entity (32 of 79 cases) identified within our cohort of patients (Table 1).

In examining cases with anti-NMDAR, HSV-1, WNV, and enteroviral encephalitis, we found anti-NMDAR encephalitis to be significantly more frequent than HSV-1–caused encephalitis, occurring at about 4 times the frequency over the defined time period of September 2007 through February 2011 (41% for anti-NMDAR vs 9% for HSV-1; $P < .01$). Absolute rates of anti-NMDAR encephalitis also exceeded those of enteroviral encephalitis, at 41% as opposed to 38%. And this autoimmune etiology exceeded WNV and VZV, at about 6 times the frequency for those identified with these agents ($P < .01$).

The median ages among anti-NMDAR encephalitis cases and those of the studied viral etiologies were similar: Of anti-NMDAR encephalitis cases, 65% occurred in patients aged ≤18 years. With anti-NMDAR encephalitis, however, females were affected significantly more often than males, at nearly 3 times the rate ($P < 0.01$), whereas other causes did not demonstrate this predilection (Table 1).

### Physical Signs and Symptoms

Most general symptoms did not allow us to definitively distinguish between the different causes of encephalitis. However, fever was nearly omnipresent in VZV and WNV cases, whereas it was seen in only about half to two-thirds of cases resulting from other entities. Intensive care unit admission rates were highest for encephalitis cases caused by HSV-1 (86%) and lowest for cases caused by VZV (20%). Rash and severe headache were significantly more likely with VZV-caused encephalitis (60% and 80%, respectively; $P < .05$), but seizures were more common in anti-NMDAR cases (69% vs 20%, $P < .05$). Intubation rates, however, were significantly higher for anti-NMDAR cases (41%; $P < .05$) than for cases with other etiologies, with the exception of WNV. Fatality rates were similarly low for all entities, ranging from 0% for VZV-, WNV-, and HSV-1–caused encephalitis to 7% for enteroviral encephalitis.

Movement disorders were observed significantly more often in cases of anti-NMDAR encephalitis (63%; $P < .01$), with enteroviral and WNV cases demonstrating no such findings. Language dysfunction was significantly more likely to occur in

**Table 1. Etiologies of Cases ≤30 Years of Age Enrolled in the California Encephalitis Project September 2007–February 2011**

| | Anti-NMDAR (n = 32) | Enterovirus (n = 30) | HSV-1 (n = 7) | VZV (n = 5) | WNV (n = 5) |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age, median, years | 12.5 (range 2–28) | 8.5 (range 0–22) | 11 (range 1–25) | 11 (range 5–17) | 7 (range 4–20) |
| Gender | | | | | |
| Female, no. (%) | 24 (75%) | 11 (37%) | 4 (57%) | 3 (60%) | 1 (20%) |
| Ethnicity | | | | | |
| White, Hispanic, no. (%) | 15 (47%) | 16 (53%) | 1 (14%) | 1 (20%) | 1 (20%) |
| White, non-Hispanic, no. (%) | 2 (6%) | 4 (13%) | 1 (14%) | 2 (40%) | 1 (20%) |
| Black, no. (%) | 4 (13%) | 4 (13%) | 2 (29%) | 0 (0%) | 1 (20%) |
| Asian/Pacific Islander, no. (%) | 10 (31%) | 1 (3%) | 2 (29%) | 0 (0%) | 0 (0%) |
| Other/unknown, no. (%) | 1 (3%) | 5 (17%) | 1 (14%) | 2 (40%) | 2 (40%) |
| Clinical Findings | | | | | |
| Neurologic Symptoms | | | | | |
| Movement disorder, no. (%) | 20 (63%) | 2 (7%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Aphasia, no. (%) | 23 (72%) | 3 (10%) | 2 (29%) | 2 (40%) | 1 (20%) |
| Ataxia, no. (%) | 14 (44%) | 6 (20%) | 1 (14%) | 3 (60%) | 2 (40%) |
| Stiff neck, no. (%) | 2 (6%) | 8 (27%) | 2 (29%) | 0 (0%) | 3 (60%) |
| Autonomic instability, no. (%) | 15 (47%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Cranial nerve abnormality, no. (%) | 3 (9%) | 2 (7%) | 0 (0%) | 0 (0%) | 2 (40%) |
| Psychiatric Symptoms | | | | | |
| Hallucinations, no. (%) | 21 (66%) | 3 (10%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Psychosis, no. (%) | 19 (59%) | 1 (3%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Irritability, no. (%) | 24 (75%) | 6 (20%) | 2 (29%) | 2 (40%) | 2 (40%) |
| General Symptoms | | | | | |
| Fever, no. (%) | 18 (56%) | 18 (60%) | 4 (57%) | 4 (80%) | 5 (100%) |
| GI, no. (%) | 9 (28%) | 11 (37%) | 3 (43%) | 4 (80%) | 0 (0%) |
| URI, no. (%) | 6 (19%) | 8 (27%) | 1 (14%) | 1 (20%) | 0 (0%) |
| Rash, no. (%) | 7 (22%) | 2 (7%) | 1 (14%) | 3 (60%) | 0 (0%) |
| Severe headache, no. (%) | 12 (38%) | 15 (50%) | 2 (29%) | 4 (80%) | 3 (60%) |
| Intubation, no. (%) | 13 (41%) | 7 (23%) | 1 (14%) | 1 (20%) | 2 (40%) |
| ICU admission, no. (%) | 17 (53%) | 13 (43%) | 6 (86%) | 1 (20%) | 3 (60%) |
| Seizures, no. (%) | 22 (69%) | 14 (47%) | 2 (29%) | 1 (20%) | 1 (20%) |
| Coma, no. (%) | 4 (13%) | 3 (10%) | 0 (0%) | 0 (0%) | 1 (20%) |
| Died, no. (%) | 1 (3%) | 2 (7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Neuroimaging and EEG[a] | | | | | |
| MRI | | | | | |
| Abnormal, no. (%) | 13/28 (46%) | 8/20 (40%) | 6/6 (100%) | 3/3 (100%) | 3/5 (60%) |
| Temporal lobe, no. (%) | 4/28 (14%) | 1/20 (5%) | 6/6 (100%) | 0/3 (0%) | 0/5 (0%) |
| White matter involvement, no. (%) | 3/28 (11%) | 1/20 (5%) | 1/6 (17%) | 0/3 (0%) | 1/5 (20%) |
| EEG | | | | | |
| Abnormal, no. (%) | 21/24 (88%) | 6/11 (55%) | 3/4 (75%) | 0/0 (0%) | 3/4 (75%) |
| Slowing, no. (%) | 9/24 (38%) | 3/11 (27%) | 2/4 (50%) | 0/0 (0%) | 3/4 (75%) |
| Epileptiform activity, no. (%) | 6/24 (25%) | 1/11 (9%) | 1/4 (25%) | 0/0 (0%) | 0/4 (0%) |
| Laboratory | | | | | |
| CSF median values (range) | | | | | |
| WBC count, cells/mm$^3$ | 23 (0–252) | 70 (1–2655) | 78 (3–540) | 167 (43–705) | 189 (17–645) |
| Protein level, mg/dL | 24 (10–67) | 34 (10–131) | 52 (6–126) | 70 (30–119) | 65 (48–179) |
| Glucose level, mg/dL | 64 (35–92) | 64 (42–122) | 55 (34–79) | 56 (40–58) | 59 (39–63) |

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; GI, gastrointestinal; HSV-1, herpes simplex virus type 1; ICU, intensive care unite; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; URI, upper respiratory infection; VZV, varicella-zoster virus; WBC, white blood cell; WNV, West Nile virus.

[a]Neuroimaging data was not provided for some patients in the study. Notably, no EEG reports were provided for patients with VZV illness.

patients with anti-NMDAR encephalitis (72% vs ≤40% in other entities; $P < .05$), whereas, with the exception of those with WNV (60%), stiff neck was significantly less likely to occur in anti-NMDAR cases (6% vs ≥27% of those with other agents; $P < .01$). In fact, language dysfunction occurred at nearly twice the rate or greater, whereas stiff neck was observed about 80% less often. Notably, autonomic instability (47%) occurred exclusively in anti-NMDAR cases.

Psychiatric symptoms were another major point of divergence, with hallucinations, psychosis, and each seen in about two-thirds or more of anti-NMDAR cases compared with ≤20% cases associated with other etiologies ($P < .01$ for all comparisons). Psychosis (observed in 59% of anti-NMDAR cases) was not observed in any HSV-1 or WNV cases, and was uncommonly a symptom in enteroviral or VZV cases (3% and 20%, respectively).

### Laboratory and Imaging Findings

Most anti-NMDAR encephalitis cases demonstrated CSF pleocytosis during the illness, but with a significantly lower median value than cases of viral etiologies (23 white blood cells/mm$^3$ for anti-NMDAR encephalitis, in contrast to medians of 70 cells/mm$^3$ and 78 cells/mm$^3$ in enterovirus and HSV-1, respectively; $P < .05$). WNV and VZV cases demonstrated substantially higher white blood cell levels in CSF, with medians of 189 cells/mm$^3$ and 167 cells/mm$^3$, respectively ($P < .05$). CSF protein levels were also significantly lower in anti-NMDAR encephalitis cases, with a median of 24 mg/dL compared with 34 mg/dL, 52 mg/dL, and 69.5 mg/dL in enterovirus, HSV, and VZV encephalitis cases ($P < .05$). In the cases of enteroviral or anti-NMDAR encephalitis, CSF protein medians were within the normal range. Glucose values were within normal range and demonstrated no significant difference among groups.

Brain magnetic resonance imaging (MRI) abnormalities, most of which were nonspecific, were detected in 46% of patients with anti-NMDAR encephalitis in whom imaging results were available, but anomalies were substantially higher, at 100%, in HSV-1 cases ($P < .01$) in which the temporal lobe was often involved. VZV and WNV cases were also more likely to manifest MRI abnormalities (100% and 60%, respectively, of those whom data were available; $P < .05$), whereas enterovirus cases were somewhat less likely to exhibit irregularities (40% of those in whom results were reported; $P < .05$).

Electroencephalograms (EEGs) were reported as abnormal in most patients with anti-NMDAR encephalitis (88%), significantly more often ($P < .05$) than in enterovirus (55%) or VZ (0%), but were similarly common in patients with HSV-1 or VZV-caused encephalitis (75% for each). Slowing was the most prevalent abnormality in anti-NMDAR encephalitis patients, observed in 38% of those with EEG changes, but it was also the most frequent change seen in HSV-1 and WNV cases (50% and 75% of those with EEG abnormalities, respectively).

### Example of Workup Prior to Diagnosis of Anti-NMDAR Encephalitis

If the diagnosis of anti-NMDAR encephalitis is not considered, the workup often includes an extensive study for infectious diseases. A case recently referred to CEP serves to illustrate this point. A previously healthy 22-year-old Asian male demonstrated extremely aggressive behavior (eg, he had thrown someone through a glass door on the day of admission) and was initially admitted for psychosis. He rapidly decompensated over the first few days of his hospitalization and required ventilatory support. Prior to CEP referral, the diagnostic workup had been extensive, including testing for HSV-1, herpes simplex virus type 2, VZV, cytomegalovirus, Epstein–Barr virus, human herpes virus type 6, enteroviruses, parvovirus B19, rabies, West Nile virus, human immunodeficiency virus, *Bartonella* species, *Schistosoma* species, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, hepatitis viruses, mumps virus, typhus, Rocky Mountain spotted fever, *Ehrlicia chaffeensis*, *Anaplasma phagocytophilia*, Q fever, and *Mycoplasma pneumonia*. The estimated cost of infectious-disease testing was approximately $10 000. This estimate does not take into account the expense of either neuroimaging or the extended hospital stay resulting from delayed diagnosis. The noninfectious workup was also extensive, including heavy-metal screens and autoimmune and paraneoplastic testing. The CEP was ultimately contacted for assistance with diagnosis. Because of the patient's presentation, anti-NMDAR encephalitis was suspected, and antibody testing confirmed the diagnosis.

## DISCUSSION

Anti-NMDAR encephalitis results from a highly specific antibody-mediated immune response against extracellular epitopes of the NR1 subunit of the NMDA receptor. The associated syndrome is characterized by prevalent psychiatric symptoms and behavioral changes that are often accompanied by seizures, dyskinesias, language dysfunctions, and, in many cases, autonomic instability and hypoventilation [5, 6]. In 2 large series, anti-NMDAR encephalitis was more likely to affect women and impact younger individuals (median age of 19 y), approximately 40% of whom were children in these case sets [6–8]. Most patients have extensive EEG abnormalities characterized by generalized or focal slow activity in the delta–theta range, sometimes with superimposed epileptic activity. The MRI result is abnormal in approximately 50% of patients, with often mild or transient cortical and subcortical increased signal on fluid-attenuated inversion recovery sequences, and

less-frequent transient cortical-meningeal enhancement with gadolinium. The CSF shows moderate pleocytosis in most patients. The disorder may occur as a paraneoplastic manifestation of ovarian teratomas, but the presence of a tumor is uncommon among children and male patients. Despite its seemingly devastating course, death is uncommon, and approximately 75% of patients will respond completely to tumor removal and immunotherapy that may include a combination of corticosteroids, intravenous immunoglobulin, plasmapheresis, rituximab, or cyclophosphamide. About 25% may have residual cognitive and motor deficits [6].

Anti-NMDAR encephalitis takes its place among a variety of immune-mediated encephalitides. There are the classic paraneoplastic entities, which precede a diagnosis of cancer in about 4 out of 5 cases and are associated with antibodies such as anti-Ma, anti-Yo, and anti-Hu, all of which interact with intraneuronal targets, inciting a cytotoxic T-cell response that is believed to be responsible for the primary pathogenic effects. Affected individuals may present with cerebellar signs or symptoms associated with limbic, hypothalamic, or brain-stem involvement. With tumor treatment and immunotherapy, disease progression can be slowed or stopped, but neurologic deficits are not likely to be reversible. These entities can be contrasted with other autoimmune encephalitides in which the target epitopes are extracellular, occur with or without tumor association, and are more responsive to immunotherapy [9]. For example, LGI1 antibody–associated encephalitis (previously attributed to voltage-gated potassium-channel antibodies) associates with antibodies that likely result in a syndrome characterized by short-term memory loss, confusion, hyponatremia, and epileptic seizures, but symptoms of psychosis are absent. This condition infrequently associates with tumors (ie, thymomas or small-cell lung cancer), and it usually responds to immunotherapy [10]. In the case of encephalitis associated with antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazoleprpionic acid receptor, the resulting syndrome is a limbic encephalitis that may associate with lung, breast, or thymic tumors and respond to treatment but with a high likelihood of relapse [11]. In contrast, the encephalitis related to antibodies against the γ-amino butyric acid B receptor also results in limbic dysfunction but associates with early and severe seizures, and the tumor most frequently involved is a small-cell lung cancer [12].

The patients with anti-NMDAR encephalitis presented here demonstrate characteristics consistent with those as described in the aforementioned literature and in other smaller series [13–15]. However, what is most remarkable is the relative frequency of anti-NMDAR encephalitis in individuals ≤ 30 years of age when compared with the frequencies of the most common infectious etiologies for encephalitis, HSV-1 and enterovirus. In fact, anti-NMDAR cases occurred much more often than HSV-1 cases. In the CEP pediatric cohort, anti-NMDAR is the most common entity identified. Because the CEP is not a population-based study and is limited by its small sample size, it is not possible to estimate the true frequency of anti-NMDAR encephalitis. It is possible that its actual frequency in the CEP population is somewhat higher than that observed here. This is likely with possible formes frustes of the disease (ie, predominant psychiatric symptoms or dyskinesias), for which there is an evolving understanding, that have not been previously elucidated and are therefore less recognizable. However, HSV-1 may be underrepresented because it is relatively easy to diagnose with readily accessible assays, resulting in fewer CEP referrals. The CEP is biased toward cases that are diagnostically challenging. It is noteworthy that when an etiology is difficult to ascertain, as is the case with many patients referred to the CEP, anti-NMDAR encephalitis is the leading entity identified.

This finding suggests that this entity deserves a place near the top of the differential diagnosis for encephalitis not only to avoid unnecessary diagnostic and treatment costs, but to permit more timely treatment, and by extension, a more rapid recovery. This is also important because relapses occur in 25% of patients and predominantly affect those without tumors or who are suboptimally treated with immunotherapy [6, 7, 14].

This study, consistent with an earlier series described by the CEP in 2009 [1], suggests that anti-NMDAR can be distinguished from key viral entities. The preponderance of psychiatric symptoms, primarily psychosis with hallucinations and personality change, usually in combination with EEG or MRI abnormalities that do not converge on the temporal lobe, and lower levels of pleocytosis and protein content in the CSF serve to highlight this diagnosis.

There are numerous causes of encephalitis, and most patients undergo extensive, expensive testing. Yet in many instances, an etiology is not identified. Early testing for this entity could alleviate the need for additional testing and allow for a clear diagnosis. The aforementioned case underwent thousands of dollars of testing before an anti-NMDAR etiology was identified. More important, the costs of sequential treatment with unnecessary antibiotics were not even addressed, let alone the costs of prolonged hospitalizations. Additionally, there is evidence to suggest that those patients with anti-NMDAR encephalitis who are treated earlier may be more likely to make complete recoveries [16]. Because nearly all of our suspected cases included HSV-1 polymerase chain reaction (PCR) and, many, in children, underwent enteroviral PCR, anti-NMDAR testing might be an appropriate complement to these regularly ordered tests, to avoid additional, costly testing. Importantly, testing for anti-NMDAR is now available in several clinical laboratories.

Anti-NMDAR encephalitis is not uncommon, particularly among children and women who present with a characteristic set of signs and symptoms. Early consideration of this diagnosis could eliminate expensive testing and allow for prompt, effective treatment.

## Notes

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