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BRIEF COMMUNICATION

Pediatric anti-NMDA receptor encephalitis is seasonal

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Abstract

In the majority of pediatric anti-*N*-methyl-D-aspartate receptor encephalitis (NMDARe) cases, the underlying cause of antibody production and subsequent disease remains unknown. We aimed to characterize this poorly understood population, investigating epidemiological factors potentially related to disease etiology, particularly season of onset. In this retrospective case review study, we analyzed data from the 29 pediatric subjects with anti-NMDAR antibodies and found that symptoms were first reported in the warm months of April–September in 78% of non-tumor-related NMDARe (NT-NMDARe) cases. These findings support further investigation into a possible seasonal trigger of NT-NMDARe.

Introduction

Anti-NMDA receptor encephalitis is an autoimmune disorder characterized by the aberrant production of IgG antibodies targeting the NMDA receptor.[1] Although first described in adults, NMDARe is increasingly recognized as a cause of morbidity in children.[2] After acute demyelinating encephalomyelitis, NMDARe is the most common autoimmune encephalitis in children.[3] In adults, NMDARe is typically a paraneoplastic process, with a well-characterized association with ovarian teratomas. In children, however, the presence of tumors is inversely associated with age.[2] Recently, it was described that, in a subset of patients, herpes simplex virus (HSV) encephalitis precedes the development of NMDARe, and anti-HSV antibodies can be found during active NMDARe disease.[4] However, for the majority of NT-NMDARe patients, a cause has not been identified. Because of the severity of the disorder and the unclear provenance of autoantibody production, we were interested in characterizing the timing of symptom onset, as this could give insight into an environmental or pathogenic trigger. We hypothesized that if there is a seasonal trigger for NT-NMDARe autoantibody production, then symptom onset may also have a seasonal pattern.

Subjects and Methods

All cases of patients with NMDAR antibodies observed in the inpatient and outpatient facilities of the divisions of neurology and oncology at the Children's Hospital of Philadelphia within 13-year period (1/1/2001–8/1/2013), 21 years or younger were included in this study. Prior to 2012, all testing for NMDAR antibodies at our institution was completed by Josep Dalmau's laboratory. This testing registry and additional patients after 2012 were included from existing clinical registries. This study was approved by the institutional review boards of CHOP (study number 10416). The population of patients with opsoclonus-myoclonus-ataxia syndrome (OMAS) was similarly determined from existing databases. Attempts were made to include a complete patient cohort, and the comprehensiveness of our list was confirmed by physicians involved in NMDARe and OMAS care at our institution.

The month of symptom onset was determined from electronic records of neurology consult notes and admission

documentation. Due to our small population size, we classified the timing of symptom onset as warm weather (April–September) or cold weather (October–March), as defined Philadelphia region frost dates.[5] A two-tailed Fisher's exact test was used to determine the statistical significance.

NMDAR antibodies from the cerebrospinal fluid (CSF) or serum were determined to be present by commercial testing or previously published criteria.[2] Using electronic records, we collected demographic information and testing results, including electroencephalogram (EEG), magnetic resonance imaging (MRI), and lumbar puncture (LP). EEG results were classified as normal, focal or diffuse delta/theta wave or disorganized activity, or epileptiform as documented. MRI readings were classified as normal, atrophied, or otherwise abnormal. Active disease was noted by the presence of IgM antibodies, while prior infections were classified as $IgM^{-}IgG^{+}$. First-line immunotherapies (IV steroids, IVIG, plasmapheresis) were given to all but three patients of our cohort, one of which received chemotherapy (including cyclophosphamide) after tumor removal and two with delayed diagnoses. In addition, follow-up information and neurologic outcomes were divided into three categories: limited (unable to perform activities of daily living, ADLs), substantial (able to perform ADLs, but requires support at home or at school), and full (at prior baseline). A relapse of encephalitis was defined as the new onset or worsening of symptoms occurring after documented improvement or stabilization.

Table 1. Characteristic of NMDARe patients: demographics and initial evaluation.

Characteristic	Total	NT-NMDARe	T-NMDARe
Demographics (%)	29	23 (79)	6 (21)
Female, sex, *N* (%)	22 (76)	17 (74)	5 (83)
Age in years, range (median)	12 (1–19)	10 (1–18)	14 (7–19)
Onset of symptoms			
Cold months, *N* (%)	11 (36)	5 (22)	6 (100)
Warm months, *N* (%)	18 (64)	18 (78)	0 (0)
Seizures, *N* (%)	24 (83)	19 (83)	5 (83)
EEG, *N* (%)			
ND/Unknown	1 (3)	0 (0)	1 (17)
Total with abnormal findings	20 (69)	17 (74)	3 (50)
Focal or diffuse delta/theta wave or disorganized activity	12 (41)	10 (43)	2 (33)
Epileptic activity	8 (28)	7 (30)	1 (17)
MRI, *N* (%)			
ND/unknown	2 (7)	0 (0)	2 (33)
Normal	19 (66)	17 (74)	2 (33)
Atrophy	4 (14)	3 (13)	1 (17)
Other	4 (14)	3 (13)	1 (17)
LP, *N* (range)			
WBC	11 (0–107)	11 (0–107)	11 (2–45)

The table shows the demographic information and initial evaluation of the patients with NMDARe and compares the total NMDARe population with the non-tumor-related and tumor-related subsets. Percentages or ranges are shown in parentheses, as designated in the table. NMDARe, *N*-methyl-D-aspartate receptor encephalitis.

Results

Of the 29 NMDARe patients enrolled in this study, 23 (79%) were tumor free (NT-NMDARe; Table 1), similar to previous case series.[2] Within the NMDARe population, there were six tumors identified: five teratomas and one Ewing's sarcoma.

We were particularly interested in characterizing the timing of symptom onset, as this could give insight into a possible pathogenic trigger. Due to population size, we classified the timing of symptom onset as warm weather (April–September) or cold weather (October–March) (Fig. 1A, Table 1). NT-NMDARe was more common in warm months (18/23, 78%), whereas tumor-related cases (T-NMDARe) presented during cold months (6/6, 100%; Fisher's exact test comparing season and presence of tumor, $P = 0.0010$).

As several autoimmune diseases are known to have well-established seasonal variation, we sought to characterize the timing of onset for a control population of children with OMAS. Like NMDARe, OMAS is a presumed autoimmune neurologic disease that is paraneoplastic (neuroblastoma-associated) in a subset of patients, and without tumor association or known viral trigger in the remainder.[6] In contrast to NMDARe, there was no seasonal variation in OMAS onset, with 8/14 (57%) of non-tumor-associated and 9/16 (56%) tumor-associated cases beginning in the warm months of April–September ($P = 1.0000$).

Upon presentation to medical attention, the majority of NMDARe patients received a comprehensive evaluation including EEGs, lumbar punctures with CSF analysis, and brain MRIs (Table 1). CSF analysis revealed a mild pleocytosis ($N = 23$ for NT-NMDARe, $N = 3$ for T-NMDARe). Most initial EEGs were abnormal, and the majority of patients ultimately had a seizure during their disease course ($N = 17$ and 19 for NT-NMDARe, $N = 3$ and 5 for T-NMDARe for initial EEG abnormality and seizure prevalence, respectively).

Analysis of prior infectious exposure was limited by the heterogeneity of testing, but the rates of prior infectious exposure ($IgM^{-}IgG^{+}$) were within that previously described for the general pediatric population; three of the 13 tested (23%) had evidence of prior Epstein–Barr

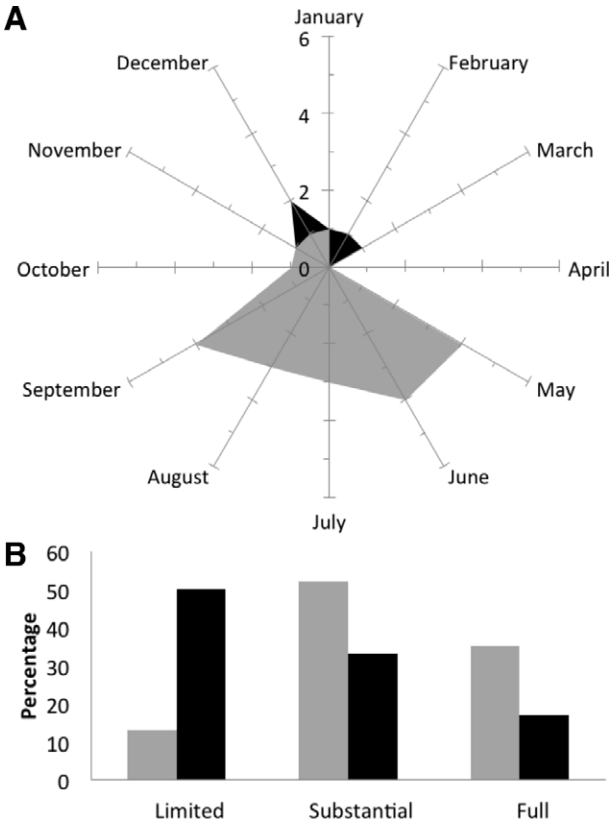

Figure 1. Seasonal onset of NMDARe and graded long-term recovery. (A) Patients without tumors (NT-NMDARe) were more likely to have symptom onset in the summer (gray) compared to T-NMDARe (black). (B) Outcome information was collected from the last follow-up encounter with neurology or oncology. Patients were stratified into three categories: limited recovery, substantial recovery, and full recovery. Patients without tumors (NT-NMDARe) (grey bars) and T-NMDARe (black bars) are shown. NMDARe, *N*-methyl-D-aspartate receptor encephalitis.

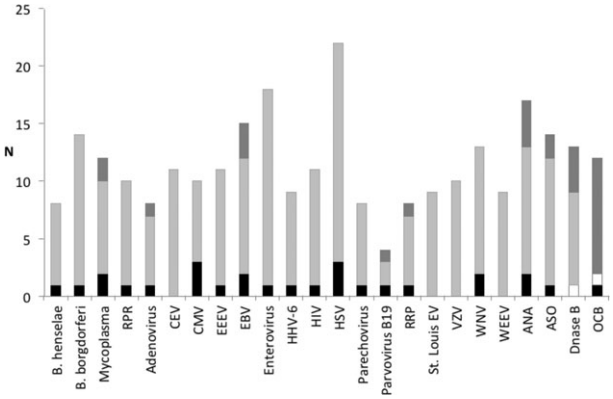

Figure 2. Laboratory testing of serum or CSF from patients with NMDARe upon presentation. Bars are divided as follows: dark grey bars = NT-NMDARe positive results, light grey = NT-NMDARe negative/normal results, white bars = T-NMDARe positive results, and black = T-NMDARe negative/normal results. Three of the 13 tested had evidence of prior EBV infection (IgM-IgG+), 2/10 mycoplasma IgM-IgG+ (PCR negative), 1/3 parvovirus B19 IgM-IgG+ (PCR negative), and 1/7 Adenovirus PCR+ of respiratory sample (negative CSF PCR). RPR, rapid plasma reagin (for syphilis); CEV, California encephalitis virus; CMV, cytomegalovirus; EEEV, Eastern equine encephalitis virus; EBV, Epstein–Barr virus; HHV-6, human herpesvirus-6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; St. Louis EV, St. Louis encephalitis virus; RRP, rapid respiratory panel (respiratory syncytial virus, influenza A and B, parainfluenza viruses 1, 2, and 3, adenovirus, rhinovirus, and human metapneumovirus by sputum sample PCR), VZV, varicella zoster virus; WNV, West Nile virus; WEEV, Western equine encephalitis virus; ANA, antinuclear antibody; ASO, antistreptolysin antibodies; OCB, oligoclonal bands. NMDARe, *N*-methyl-D-aspartate receptor encephalitis.

virus (EBV) infection, two of 10 (20%) were positive for mycoplasma IgG (PCR negative), one of three (33%) was positive for parvovirus B19 antibodies (PCR negative; IgG), and one of seven was positive for Adenovirus by PCR of respiratory sample (14%) (negative CSF PCR) (Fig. 2).[9–11] No patients within the T-NMDARe population were positive for infectious studies.

We also assessed the treatments administered to patients with NMDARe. Of the patients who received first-line therapy, second-line agents (rituximab or cyclophosphamide) were given to 30% of NT-NMDARe ($N = 6$) and 67% of T-NMDARe patients ($N = 3$) ($P = 0.1627$). The average length of follow-up was 27 months. Within the NT-NMDARe population, 87% had a substantial or full recovery at last encounter, while 50% of T-NMDARe patients had good outcomes ($P = 0.0828$), similar to previously published data (Fig. 1B).[12] While the difference in outcomes is limited by the small population of T-NMDARe cases, the three poor responders with tumors were followed up for a minimum 3 years each.

Discussion

In this single institution, retrospective study, we found that children with NT-NMDARe were more likely to have their symptoms begin during warm months, clustered between April and September (Fig. 1A). While determining the etiology of NMDARe is beyond the scope of our study, this strong seasonal variation provokes further questions into the pathogenesis of NMDARe. Infections can be seasonal; enterovirus, West Nile virus, and Lyme disease predominate in late spring–early summer. Also, several rheumatologic disorders have a seasonal onset without a clear infectious trigger. Systemic vasculitis and Wegener's granulomatosis typically present in the winter months, while giant cell arteritis varies by region.[7,8,13] The timing of pathogen

exposure to secondary autoimmune disease can be variable as well. For HSV encephalitis, the delay to development of secondary NMDRe has been reported to be weeks,[4] whereas in Sydenham's chorea, the delay can be months.[14] Also, as is the example with narcolepsy with cataplexy triggered by the influenza virus or vaccine, a systemic stimulus can result in Central Nervous System (CNS) autoantibodies.[15]

In recent studies on the role of HSV in NMDARe, only anti-HSV antibodies, not viral DNA, are present with NMDARe.[4] Our cohort would be insensitive to this switch from direct pathogen effect to postinfectious autoimmune phenomenon, as testing (PCR or antibody production) was variable. Of note, the strong summer predominance of NT-NMDARe argues against a role of vaccinations (measles-mumps-rubella, for example), which are given throughout the year, or winter pathogens, such as influenza.

Interestingly, we found that while NT-NMDARe was more common in warm months, T-NMDARe clustered in the wintertime. While we hypothesize that the winter prevalence is an artifact of small numbers, it is possible that a different seasonal variable is the part of the complex process of triggering an autoimmune disease in these patients. To address this issue, in future studies, we will characterize the seasonal variation of both NT-NMDARe and T-NMDARe in a larger cohort of patients across multiple institutions.

While this study demonstrates a strong seasonal bias in NMDARe onset, the underlying cause of this phenomenon remains still unknown. To address question, future studies could utilize patient sample banks and screen for common pathogens by both PCR and antibodies. Although molecular mimicry has been hypothesized as a possible trigger of autoimmunity in NMDARe, the epitope targeted by the autoantibodies appears to be a conformational epitope, making direct sequence comparisons to known pathogens difficult.[1] It is also possible that NMDAR antibodies are not a product of molecular mimicry, but rather result from autoantigen exposure in an inflammatory brain.

In summary, we present a retrospective case series of the 29 pediatric patients at our institution with anti-NMDA receptor antibodies. We found that the subset of patients without tumors had their onset of symptoms primarily in warm months. This study might provide insight into a possible trigger to this serious disorder.

Acknowledgments

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Conflict of Interest

D. R. L. received NIH grant support during the conduct of the study and has a patent testing for anti-NMDARe with royalties paid to Eurimmune. J. A. P. during the conduct of the study was (in part) supported by Award number T32NS007413 from the National Institute of Neurological Disorders and Stroke (NINDS). The content of this study is the sole responsibility of the authors and does not necessarily represent the official views of the NINDS of the National Institutes of Health. L. A. A. has no disclosures.

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