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Comparative Outcomes in Children and Adults With Anti-*N*-Methyl-D-Aspartate (anti-NMDA) Receptor Encephalitis

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Abstract

This study compared neurologic disability and adaptive function in children and adults >1 year following anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis diagnosis. Retrospective record review identified 12 patients with anti-NMDAR encephalitis. At last follow-up, all surviving patients had "good" modified Rankin Score (0-2). Four children, 6 adults, and their families participated in a telephone interview. Median duration since diagnosis was similar for children (2.42 years, interquartile range 2.12-3.32) and adults (3.55 years, interquartile range 2.08-5.50 years). 3/4 (75%) pediatric and 3/5 (60%) adult patients reported neuropsychiatric symptoms (fatigue, emotional lability, short-term memory deficits or concentration deficits). On the Adaptive Behavior Assessment System (ABAS-3), although overall adaptive function was intact for adults (general adaptive composite standard score: median 104.5, interquartile range 98.8-112.5), the median for children was below average (General Adaptive Composite Standard Score: median 82.0, interquartile range 79.0-89.0). Children with anti-NDMAR encephalitis may have long-term effects impacting daily life while adults regain normal function.

Keywords

encephalitis, NMDA, autoimmune, outcome, adaptive

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Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was originally described in a series of young women with psychiatric symptoms, encephalopathy, seizures, movement disorder and autonomic instability found to have autoantibodies against the NR1 subunit of the NMDA receptor.[1,2] Since that time, anti-NMDAR encephalitis has become an increasingly recognized neurologic disorder in both children and adults.[3] In fact, anti-NMDAR encephalitis is one of the most common causes of encephalitis in children, more common than many viral encephalitides,[4,5] and the second most common autoimmune cause after acute disseminated encephalomyelitis (ADEM).[6]

The constellation of symptoms noted in children with anti-NMDAR encephalitis differs from that seen in adults.[7,8] Children may present with tantrums, aggression, or language regression rather than frank psychosis and are less likely to have autonomic instability or associated tumors.[8] Still, it remains unclear whether children with anti-NMDAR encephalitis have different long-term clinical outcomes than adults. Patients with anti-NMDAR encephalitis are typically thought to respond favorably to therapy despite their dramatic presentation, with 80% reported to have a "good" outcome.[9] However, existing outcomes studies have predominantly utilized stroke disability scales (the modified Rankin Scale) as the primary assessor of outcome,[10-12] which may not adequately capture neuropsychiatric or cognitive symptoms.

Preliminary evidence exists from small case series that adults with anti-NMDAR encephalitis may have cognitive deficits that persist years after diagnosis.[13] However, cognitive outcomes in children have yet to be studied. In other mechanisms of diffuse central nervous system injury, such as trauma,

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insults during critical periods of development are associated with poorer outcomes.[14,15] Therefore, NMDAR encephalitis may impact a developing brain differently than a mature brain, leading to differences in long-term cognitive and adaptive function.

Our objective in this study was to evaluate long-term adaptive behavior outcomes in children and adults with anti-NMDAR encephalitis at least 1 year following initial diagnosis. Adaptive behavior is an aspect of cognition that encompasses a repertoire of conceptual, social, and practical skills, which enable a person to function in everyday life. Limitations in adaptive behavior affect an individual's ability to respond appropriately to demands in their environment and to changes in daily life. We hypothesized that children with anti-NMDAR encephalitis would have poorer long-term adaptive behavior outcomes and different persistent neuropsychiatric symptoms.

Design/Methods

This study was approved by the Johns Hopkins Hospital Institutional Review Board.

Participants

Medical records of children (<18 years of age) and adults (≥18 years of age) treated at the Johns Hopkins Hospital in Baltimore from July 1, 2005, until June 30, 2015, with a billing diagnosis of encephalitis were reviewed. Cases were included if they met clinical criteria for definite autoimmune encephalitis per recent consensus criteria,[16] and had documentation of anti-NMDAR antibodies in the serum and/or cerebrospinal fluid.

Eligible adults and parent/caregiver of children were contacted by telephone and asked to consent to participate in a research survey. When oral telephone consent was provided, patients or their primary caregiver were asked questions from a structured survey and were administered a validated questionnaire.

Patients were excluded if limited chart review demonstrated a diagnosis other than anti-NMDAR encephalitis. If chart review indicated death of the patient, families were not contacted.

Clinical Data

Additional information was obtained from patients' medical records, including demographic information, presenting symptoms and signs, laboratory examinations, and clinical findings. Regarding treatment, subjects were classified into 2 categories: "first-line treatment only" if they received tumor removal, intravenous steroids, intravenous immunoglobulin, and/or plasmapheresis and "first and second-line treatment" if they received both first-line treatment and rituximab or cyclophosphamide.

Modified Rankin Scale

A modified Rankin Scale (mRS) score, with pediatric adaptation as appropriate, was assigned by 2 raters (E.G.L. and A.Y.) based on medical record review.[10,17-20] This scale has been used as an outcome measure of neurologic disability in prior studies of autoimmune encephalitis.[8-11] Scores range from 0 for no symptoms to 6 for death. Each subject was assigned a modified Rankin Scale score for hospital admission, hospital discharge, last neurology clinic follow-up, and study enrollment. A "good outcome" by modified Rankin Scale score was considered a score from 0 to 2.[9] Improvement in modified Rankin Scale score was defined as a subsequent score at discharge or at follow-up that was lower in value (indicating less disability) than initial modified Rankin Scale score on admission.

Assessments of Neuropsychiatric Symptoms and Adaptive Behavior

Structured Telephone Survey

A structured survey (available in supplementary materials) was administered to collect basic information about the subject's premorbid education status, initial presentation of autoimmune encephalitis, current medical status, services received, general function, and education status. The patient or caregiver was also asked if the patient currently experiences the following symptoms: fatigue, emotional lability, short-term memory deficits, and difficulty with concentration.

Adaptive Behavior Assessment System, Third Edition (ABAS-3)

Following the structured telephone survey, the Adaptive Behavior Assessment System, Third Edition, was completed by the parent or primary caregiver for pediatric participants and by adult participants or their primary caregiver. The Adaptive Behavior Assessment System, Third Edition,[21] is a validated neurobehavioral questionnaire that assesses adaptive skills and can be administered for individuals from early infancy through adulthood. It assesses 11 skill domains and generates norm-referenced scores for general adaptive function, or General Adaptive Composite (GAC), and 3 major adaptive domains (conceptual, social, practical). Age-normed standard scores[21] (mean of 100 with standard deviation of 15) were used for analysis in this study. A standard score less than 85 (>1 standard deviation below the mean) is considered below average. Three Adaptive Behavior Assessment System, Third Edition, forms were used for this study based on subject age: 0-5 years; 5-21 years; 16-89 years. For subjects 5 years of age or younger, the child form for ages 0 to 5 years was administered. For subjects between 6 and 17 years of age, the child form for ages 5 to 21 years was administered. For subjects greater than or equal to 18 years of age, the adult form was administered.

Results

Patients

Twelve patients with anti-NMDAR encephalitis were identified for record review, including 5 children and 7 adults. Demographics and clinical characteristics of each group are presented in Table 1; the adult group was female

Table 1. Clinical Characteristics of Subjects With Anti-*N*-Methyl-D-Aspartate Receptor (Anti-NMDAR) Encephalitis.

	Pediatric (n = 5)	Adult (n = 7)
Age onset, y, median (IQR)	2.4 (2.1-3.0)	24.7 (22.0-40.8)
Age enrollment, y, median (IQR)	4.8 (4.3-5.4)	26.4 (24.6-48.0)
Time symptoms to treatment initiation, d, median (IQR)	28.0 (27.0-48.0)	22.0 (15.5-66.5)
Female, n (%)	2 (40)	7 (100)
Tumor, n (%)	0 (0)	4 (57)
Seizures, n (%)	2 (40)	7 (100)
Intensive care unit, n (%)	2 (40)	5 (71)
Death, n (%)	0 (0)	1 (14)
First- and second-line treatment, n (%)	1 (20)	6 (86)

Abbreviations: ABAS-3, Adaptive Behavior Assessment System, Third Edition; IQR, interquartile range.

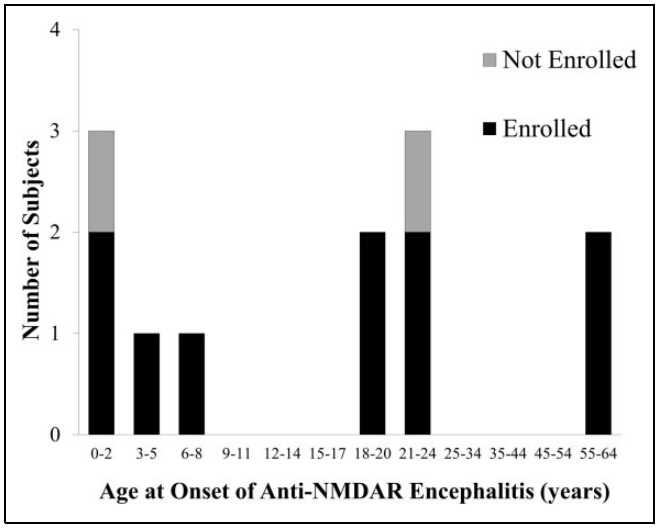

Figure 1. Age distribution of subjects with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in years.

predominant (100% vs 40%), had higher incidence of tumor (57% vs 0%), higher incidence of seizures (100% vs 40%), and more frequently received both first- and second-line treatment (86% vs 20%). The age distribution at presentation of the entire cohort is depicted in Figure 1. The median time from diagnosis to most recent follow-up in the pediatric group was 2.3 years (interquartile range 1.8-2.6 years), whereas the median time in the adult group was 3.6 years (interquartile range 2.1-5.5 years).

Neurologic Disability

Improvement in neurologic disability as measured by modified Rankin Scale from hospital admission to discharge was observed in 1/5 (20%) children and 2/7 (29%) adults (Figure 2). One adult patient died during admission. All surviving subjects had improved neurologic disability score by modified Rankin Scale from hospital discharge to most recent neurologic follow-up. At latest documented follow-up, all surviving subjects had a good modified Rankin Scale score. However, 4/5 (80%) of children and 3/6 (50%) of surviving adults had some degree of persistent disability (modified Rankin Scale score $\geq$ 1).

Neuropsychiatric Symptoms and Adaptive Behavior

Ten patients and their families consented to participation in the structured interview, including 4 children and 6 adults. Two subjects were not enrolled: 1 pediatric subject did not have a working telephone number and 1 adult subject died of complications from anti-NMDAR encephalitis.

Both children and adults had persistent, perceived neuropsychiatric symptoms (Table 2). Only 1/4 (25%) pediatric and 2/5 (40%) of adult patients were symptom free at follow-up.

Comparative adaptive behavior outcomes as measured by Adaptive Behavior Assessment System, Third Edition, General Adaptive Composite standard scores are depicted in Figure 3. Median standard scores of General Adaptive Composite and subdomains on the Adaptive Behavior Assessment System, Third Edition, for each group are presented in Table 2. The median standard score for the children was below average for General Adaptive Composite and the practical subdomain. In contrast, the median standard score for the adults was in the average range. There was no single subdomain in which all individual subjects had preferentially higher or lower scores.

Of note, in the pediatric group, the one subject who received second-line treatment was not the same subject whose standard score was >100 on the Adaptive Behavior Assessment System, Third Edition,.

Discussion

In this small study, adults with anti-NMDAR encephalitis had better adaptive behavior outcomes than children, despite no differences in modified Rankin Scale score or frequency of reported symptoms at last follow-up. Because of the small number of subjects and retrospective study recruitment, it is possible that our observations of the differences or lack of differences in outcome between children and adults were influenced by other variables not accounted for in this study.

When examined using the modified Rankin Scale disability scale alone, children and adults demonstrated similar good outcomes. However, when outcomes are examined using a measure of adaptive behavior, adults performed, on average, within normal range whereas children performed below expected norms. These findings suggest that pediatric patients have changes in adaptive behavior and everyday function that have not been captured previously when focusing on neurologic disability using the modified Rankin Scale. Although the

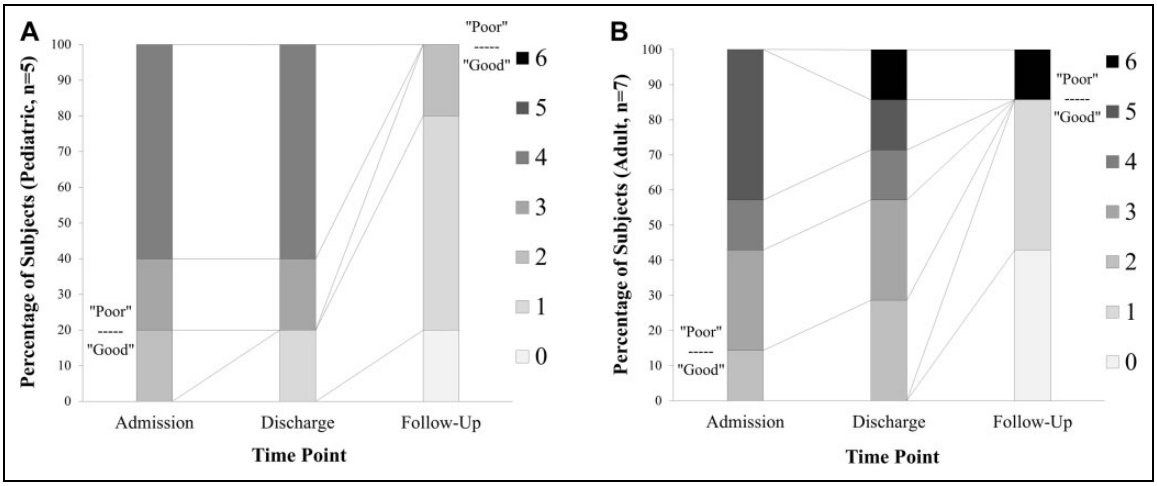

Figure 2. Neurologic disability, as measured by mRS at admission, discharge, and follow-up are depicted for pediatric (A) and adult (B) subjects. There was no difference between pediatric and adults groups in good vs poor mRS score at any of 3 time points. mRS, modified Rankin Scale.

Table 2. Clinical Characteristics, Neuropsychiatric Symptoms, and Adaptive Behavior in Enrolled Subjects.

	Pediatric (n = 4)	Adult (n = 6)
Clinical characteristics, median (IQR)		
Age onset, y	2.6 (1.9-4.2)	24.8 (21.1-48.8)
Age enrollment, y	5.1 (4.3-7.4)	31.9 (26.2-53.3)
Time symptoms to treatment initiation, d	27.5 (23.0-34.8)	26.0 (17.5-84.8)
Time diagnosis to enrollment, y	2.4 (2.1-3.3)	3.6 (2.1-5.5)
Neuropsychiatric symptoms, n (%)		
Any symptom	3 (75)	3 (60)
Fatigue	0 (0)	2 (33)
Emotional lability	0 (0)	3 (50)
Short-term memory	1 (25)	3 (50)
Concentration	2 (50)	1 (17)
ABAS-3 standard scores, median (IQR)		
General Adaptive Composite	82.0 (79.0-89.0)	104.5 (98.8-112.5)
Conceptual	87.0 (81.3-94.3)	103.5 (94.8-106.3)
Social	87.5 (84.8-94.0)	104.0 (103.0-109.5)
Practical	84.0 (80.8-88.8)	103.5 (100.0-113.0)

Abbreviations: ABAS-3, Adaptive Behavior Assessment System, Third Edition; IQR, interquartile range.

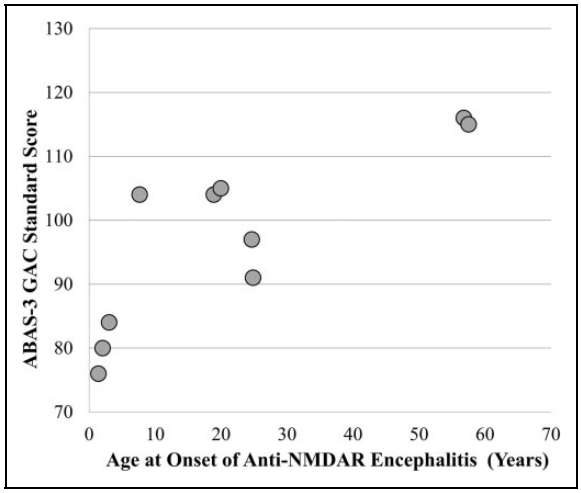

Figure 3. Age of encephalitis onset and long-term adaptive behavior outcomes as measured by ABAS-3 General Adaptive Composite (GAC) Standard Scores in anti-NMDAR encephalitis. Per the ABAS-3 normative data, the average standard score is 100 with a standard deviation of 15. Dots represent individual scores of individuals in this study. ABAS-3, Adaptive Behavior Assessment System, Third Edition; anti-NMDAR, anti-*N*-methyl-D-aspartate receptor.

modified Rankin Scale is a widely used clinical outcome measure for stroke clinical trials, it primarily reflects motor disability and does not reflect practical, everyday activities required to function independently and meet environmental demands, which are measured on the Adaptive Behavior Assessment System, Third Edition,.[21] Adaptive behavior may be affected by various types of disability, including neurocognitive disability. Why adaptive behavior in the practical domain may be affected more than conceptual or social domains warrants further study. One other study has also found subtle long-term changes in this disease that were not captured by the neurologic disability score. In a small series of adults, long-term cognitive deficits in executive function and memory were identified several years after anti-NMDAR encephalitis, despite improvement in neurologic disability.[13]

Although prior studies have observed differences in clinical presentation of this disorder between children and adults,[7,8] the role of age in long-term outcomes remains unclear. The differences in adaptive behavior observed in this study suggest that children may be left with long-term impairment following anti-NMDAR encephalitis, whereas adults appear to regain normal function. This has long-term implications for children and their families affected by the disorder, as these children may be more likely to require supports at home or in school and

to have less independence than typical children. However, further research is needed to distinguish whether children may continue to improve over a longer period of time or whether these deficits will be permanent, affecting adaptive function in their adult lives. The role of age as a continuum also warrants exploration to distinguish whether there is a threshold at which outcomes change, for example, pre- versus post-puberty or in the elderly.

When considering the reason for these differences in outcomes based on age, we put forth 2 hypotheses. First, we postulate that an inflammatory disease process may have more detrimental effects when it occurs in a developing brain, leading to more severe cognitive and functional deficits, than when it occurs in a mature brain. Evidence from traumatic brain injury studies similarly suggests that diffuse central nervous system insults during critical periods of brain development may portend poorer outcomes.[14,15] Further, not only is anti-NMDAR encephalitis associated with neuroinflammation but the associated antibodies target the NMDAR, which has critical roles in learning and memory. On the synaptic level, activity at the NMDAR contributes to the formation and maturation of glutamatergic synapses, refining the axonal and dendritic arborization of a developing neuron, defining its functional role within the neuronal circuit, and thereby shaping brain development.[22] It follows that the prolonged inhibitory effects of anti-NMDAR antibodies on a child may disrupt critical processes in learning and development as that child is laying a foundation of neuronal pathways.

Second, we hypothesize that clinical treatment factors may play a role in outcomes in this disorder. There is evidence that the type of treatment and the time from symptom onset to treatment may influence long-term outcome in anti-NMDAR encephalitis.[9] Because children may have different presenting features,[7,8] they may be more likely to have delayed diagnosis and treatment, leading to poorer outcomes. In this cohort, however, time from symptom onset to treatment was similar between groups, making delay of treatment unlikely to alone explain the poorer outcomes seen in these children, unless the required treatment initiation window is shorter in the pediatric, developing brain. Also of note in this study, fewer subjects in the pediatric cohort received second-line treatment than the adult cohort. This may reflect physician discomfort with the use of these medications in children (despite several studies indicating safety and efficacy in the pediatric population), as they are not approved by the FDA for pediatric use.[23] Prior studies have shown that second-line treatment may be associated with better long-term modified Rankin Scale scores.[10] Although we did not see differences in outcome modified Rankin Scale scores in these groups, this factor may have contributed to the difference in adaptive behavioral outcomes.

Regarding neuropsychiatric symptoms, many patients with anti-NMDAR encephalitis reported persistent fatigue, emotional lability, short-term memory deficits, and concentration deficits, several years following diagnosis. In the adults, these complaints did not seem to impact adaptive function, implying that they can sufficiently compensate in activities of daily life. However, these symptoms may be more impairing or more severe in children and thereby impact adaptive function. Severity of symptoms was not addressed in this study. Children may also underreport symptoms, not because they do not experience them but rather because they lack the language skills or the emotional/cognitive insight to report them. Further studies with larger cohorts examining neuropsychiatric symptoms with specific neuropsychological tools to quantify fatigue, mood, memory, processing speed, and quality of life in children and adults following anti-NMDAR encephalitis are warranted.

Limitations. Again, the greatest limitation of this study is its very small enrollment size. Other limitations of this study include a cross-sectional, retrospectively identified cohort at a tertiary center. We also acknowledge that as a patient- or caregiver-reported outcome, the Adaptive Behavior Assessment System, Third Edition, is a subjective outcome measure and may be discrepant from other performance-based measures of cognition. Further, given that adults in this study primarily self-reported on the Adaptive Behavior Assessment System, Third Edition, whereas children were rated by parent report, it is possible that a caregiver is more likely to report problems in the patient that they do not report in themselves. Therefore, some differences in outcomes could be impacted by differences in self versus caregiver reporting.

Finally, because of the retrospective nature of this study, we were not able to obtain baseline adaptive behavior measures on these individuals prior to the onset of illness and therefore cannot assess to what degree these outcomes are a change from baseline.

Conclusions

Children, more than adults, affected with anti-NMDAR encephalitis may have long-term changes in adaptive function. Measures of functional neurologic disability, such as the modified Rankin Scale, may be inadequate to measure long-term outcomes in this disorder, as they do not consistently or comprehensively capture deficits in neuropsychiatric symptoms and adaptive behavior. Understanding the differences in long-term disability profiles of children and adults with anti-NMDAR encephalitis may have implications for the clinical management, anticipatory guidance, and therapy needs of this patient population.

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Author Contributions

EGL, AKY, AA, and JCP contributed to conception and design. EGL and AKY acquired the data. EGL, AKY, and DS carried out the data analysis. All authors contributed to data interpretation. EGL drafted the manuscript and all authors critically revised and approved the final version for publication.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. JCP discloses receiving personal compensation as Editor-in-Chief of *NEJM Journal Watch Neurology*. The remaining authors have nothing to disclose.

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Ethical Approval

This study was approved by the Johns Hopkins University Institutional Review Board (IRB00082781).

Supplementary Material

Supplementary material is available for this article online.

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