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Approach to the Management of Pediatric-Onset Anti-*N*-Methyl-D-Aspartate (Anti-NMDA) Receptor Encephalitis: A Case Series

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Abstract

Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a treatable cause of autoimmune encephalitis. It remains unclear if the natural history of this disease is altered by choice of acute therapy or the employment of chronic immunotherapy. Chart review was undertaken for pediatric patients diagnosed with anti-NMDA receptor encephalitis. Data obtained included patient demographics, disease manifestations, treatment course, and clinical outcomes. Ten patients with anti-NMDA receptor encephalitis were identified. All patients were treated with immunotherapy in the acute period, and all patients experienced good recovery. Neurologic relapse did not occur in any patient. All patients received varied forms of chronic immunosuppression to prevent relapses. Complications of chronic immunotherapy occurred in 50% of patients. The benefits of chronic immunotherapy and the duration of use should be carefully weighed against the risks. Complications from immunotherapy are not uncommon and can be serious. Clinical trials assessing the benefit of long-term immunotherapy in this population are needed.

Keywords

autoimmune, encephalitis, pediatric, NMDA

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A constellation of neuropsychiatric symptoms, seizures, and central hypoventilation was initially reported in 4 young women with an ovarian teratoma in 2005.[1] This syndrome was ultimately found to be secondary to a pathologic autoantibody targeted against the brain's *N*-methyl-D-aspartate (NMDA) receptor NR1 subunit and has since been labeled as anti-NMDA receptor encephalitis.[2] Since that time, multiple cases have been reported in adults and children.[3] There are many distinct differences in the disease course that appear to be dependent on the age of presentation. In pediatric cases (particularly in those children who are prepubertal), there is a lower likelihood of tumor association.[4] Children are also more likely to have a neurologic-based presentation (movement disorders, seizures) when compared to adults, who tend to present with more prominent psychiatric features.[4]

Although this disease has become increasingly recognized by neurologists, the medical community continues to learn how truly varied presenting symptoms in a given individual can be. Furthermore, though acute treatment with immunologic agents (eg, corticosteroids, intravenous immunoglobulin, plasma exchange, rituximab, cyclophosphamide) has been well accepted, the chronic management of these patients (particularly those without an identified tumor) remains largely subject to expert opinion. Of paramount concern is the use of chronic immunosuppression in childhood and the effects of such therapy on a young patient's developing neuroimmunologic system.

To further characterize and classify the presentation and disease course in pediatric patients, we report 10 patients diagnosed with anti-NMDA receptor encephalitis and provide a brief review of the disease in children. In addition, this case series illustrates the varied approach to long-term management of these patients and provides a basis for discussion of the complications that may arise from utilization of long-term immunotherapies.

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Methods

This retrospective, descriptive case series was approved by the individual institutional review boards of both the University of Virginia and Inova Health System. Ten pediatric patients were seen and diagnosed at one of 2 individual medical centers in central and northern Virginia. These patients were aged less than 18 years at presentation and received their diagnosis of anti-NMDA receptor encephalitis with onset of symptoms between January 2010 and August 2013. As there are no current formal diagnostic criteria for the disease, all patients in this series were diagnosed based on characteristic clinical symptomatology in addition to cerebrospinal fluid and/or serum testing that was positive for the NMDA receptor antibody via commercially available testing.

A retrospective chart review was undertaken for each of the 10 patients. Data obtained and analyzed included subject demographics (age at symptom onset, gender), disease characteristics (presenting symptom, prodromal history, disease course, laboratory values, imaging results, presence of tumor, relapse history), treatment course (initial and subsequent therapies, duration of therapeutic approach, adverse events associated with treatment), and long-term outcomes. Inclusion criteria required a diagnosis of anti-NMDA receptor encephalitis made by a child neurologist based on clinical history and examination in addition to the presence of a positive NMDA receptor autoantibody in either serum or cerebrospinal fluid. Although a single patient was positive for both NMDA receptor and voltage-gated potassium channel complex autoantibodies, the remainder of the subjects were negative for alternative autoantibodies including: ANNA-1/2/3, AGNA-1, PCA-1, PCA-2, PCA-Tr, Amphiphysin, CRMP-5, striational antibody, calcium channel binding antibody (PQ and N type), acetylcholine receptor binding antibody, and acetylcholine receptor ganglionic neuronal antibody. Patients were excluded from analysis if they remained on chronic immunotherapy for their disease at the time of chart review.

Results

Clinical Characteristics

Ten pediatric patients were seen and diagnosed with anti-NMDA receptor encephalitis over a 2.5-year period. The major demographic data for each of these patients is summarized in Table 1. Eight of 10 (80%) patients were female, and the mean and median age at presentation was 13 years (range: 6-17 years). Prodromal symptoms including fever, headache, upper respiratory symptoms, vomiting, diarrhea, or urinary tract infection were noted in 70% of patients. Headache was the most common prodromal symptom (4 of 7 patients with a prodrome) in our cohort.

The primary presenting complaint(s) in the majority of patients were altered mental status (including encephalopathy, behavioral/personality change, and/or lethargy) in 80%, seizures (50%), and speech abnormalities (including aphasia and dysarthria) in 20% (Table 2). All 10 patients experienced alterations in mental status, including mood, behavior, or personality changes during the course of the disease, the most common symptom of which was emotional lability. More prominent psychiatric symptoms were noted in half of the cohort and included visual/auditory hallucinations, delusions, and paranoia. Seizures were a prominent feature in most pediatric patients, with 90% experiencing seizures during their hospitalization. Five of these 9 patients (56%) had seizure as the presenting concern. Of the 9 children with seizures, 8 had either clinical or electrographic evidence to suggest focal-onset seizures (typically either left or right temporal), as opposed to a generalized semiology.

Dysautonomia, characterized by symptoms of hyper- or hypotension, brady- or tachycardia, hypersalivation, or hyper- or hypothermia, was noted in 70% of patients. A single patient (case 7) had dysautonomia as a major presenting symptom at clinical onset of her disease. Orolingual-facial dyskinesias were the most common movement disorder and were noted in half of our cohort. Choreoathetosis, dystonia, and other dyskinesias were less common. During the time of admission, 80% of our pediatric cohort had ongoing speech dysfunction, including reduction of verbal output or mutism (70%), perseveration (20%), and aphasia (20%). A single patient (case 9) was diagnosed with optic neuritis during the course of her anti-NMDA receptor encephalitis.

Laboratory Values and Neuroimaging

Cerebrospinal fluid testing in cases typically revealed evidence of a mild lymphocytic pleocytosis (white blood cell count range: 7-142/μL) with normal protein and glucose. Oligoclonal bands and IgG index were measured in only 4 patients. Of these 4, 3 patients had evidence of oligoclonal banding and an elevated IgG index. All patients in this case series had antibodies in their cerebrospinal fluid and/or serum that reacted with extracellular epitopes of NR1. In conjunction with the clinical picture, these antibodies helped to confirm the diagnosis of anti-NMDA receptor encephalitis. In addition, all patients had autoantibody panels assessed, and a single patient (case 6) was found to be dually positive for NMDA receptor and voltage-gated potassium channel complex autoantibodies. Magnetic resonance imaging (MRI) of the brain was obtained in all patients; however, only 3 patients had abnormal findings (Table 1). Continuous video-electroencephalographic (EEG) monitoring most often demonstrated evidence of diffuse and/or focal background slowing. Three patients had interictal focal epileptiform discharges, and 1 patient was found to have an "extreme delta brush" pattern on EEG.[5]

Treatment and Long-term Outcomes

The acute and chronic management of all cases is presented in Table 3. In the acute phase of the disease, all patients were treated with corticosteroids (intravenous or oral). In more than half of cases, intravenous immunoglobulin was given in conjunction with corticosteroids. After administration of these therapies, a patient was observed for a median of 8 days (range: 2-18 days) before second-line therapies were employed. A single patient required only first-line corticosteroid treatment; the remaining 9 subjects received second-line treatments. The second-line therapies included rituximab alone (45%), plasma

Table 1. Demographic and Clinical Features of Children Diagnosed With Anti-*N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis.

Case number	Gender	Age of onset (y)	Presenting symptom(s)	Length of hospitalization (wk)	Prodromal illness	Seizures	MRI, brain	Tumor	Relapses	Antibody positivity (serum/CSF)
1	M	6	AMS, seizures	8	No	Yes	Frontal subcortical leukoencephalopathy	No	No	Positive/positive
2	F	12	AMS, psychosis	4	No	No	Normal	Yes—ovarian teratoma	No	Positive/not tested
3	M	14	AMS, headache	8	Yes—headache, GI illness	Yes	Normal	No	No	Positive/not tested
4	F	17	AMS, dysarthria	4	Yes—headache	Yes	Normal	No	No	Positive/not tested
5	F	13	AMS, headache	8	No	Yes	Normal	No	No	Positive/not tested
6	F	10	AMS, aphasia	4	Yes—headache	Yes	Normal	No	No	Positive/not tested
7	F	13	Seizures, dysautonomia	2	Yes—urinary tract infection	Yes	Normal	No	No	Negative/positive
8	F	15	AMS, seizures	10	Yes—headache	Yes	Diffuse enhancement within cerebral/ cerebellar sulci, with associated abnormal sulcal FLAIR signal	Yes— ovarian teratoma	No	Positive/positive
9	F	17	Seizures	3	Yes—respiratory illness	Yes	Signal hyperintensity in posterior left temporal cortex and underlying white matter	No	No	Positive/positive
10	F	17	AMS, seizures	10	Yes—GI illness	Yes	Normal	No	No	Positive/not tested

Abbreviations: AMS, altered mental status; CSF, cerebrospinal fluid; F, female; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; M, male; MRI, magnetic resonance imaging.

Table 2. Constellation of Symptoms in Pediatric Patients Diagnosed With Anti-NMDA receptor Encephalitis.

Symptomatology	n (%)
Altered mental status	10 (100)
Psychosis (hallucinations/delusions)	5 (50)
Seizures	9 (90)
Focal	8 (80)
Generalized	1 (10)
Movement Disorders	7 (70)
Orolinguofacial dyskinesias	5 (50)
Choreoathetoid	2 (20)
Dystonia	2 (20)
Autonomic instability	7 (70)
Cranial nerve abnormalities	1 (10)
Speech abnormalities	8 (80)

exchange (33%), or rituximab plus cyclophosphamide (22%). Two of 3 patients failed to adequately respond to second-line plasma exchange and thus received a third-line treatment: rituximab. The 2 patients that were found to have an ovarian teratoma underwent surgical excision within the acute period.

After acute treatment of the disease, chronic immunotherapy was employed in every patient within this cohort—even those patients who had had successful resection of their ovarian teratoma. The choice of chronic immunotherapy utilized was varied (Figure 1) and typically consisted of a combination of either (1) rituximab plus intravenous immunoglobulin or cyclophosphamide or (2) mycophenolate mofetil $\pm$ oral corticosteroid taper. The duration of chronic therapy was also varied, with a median of 12 months (range: 6-48 months) and an average of 16 months' treatment. Complications thought to arise directly from long-term immunosuppression occurred in half of the cohort. These complications occurred at least 4 months post hospitalization for anti-NMDA receptor encephalitis and ranged from severe headache to septic shock, with all subjects requiring further hospitalization for these concerns. In at least 2 cases (subjects 7 and 10), complications prompted removal of the chronic immunotherapy.

The vast majority of our cohort (60%) had full recovery from their initial disease. Only 1 patient continues to require antiseizure medications for persistent seizures. The remaining 40% continue to experience mild behavioral problems (depression, anxiety, and/or irritability) and memory difficulties despite being 1 to 2 years post disease onset.

Discussion

Since its initial description in 2007, anti-NMDA receptor encephalitis has become a well-recognized autoimmune, inflammatory syndrome.[6] Since this time, more than 400 cases have been described in children and adolescents, including those as young as 8 months of age.[7-15] Approximately 40% of all patients reported are younger than 18 years of age, and young females constitute 80% of pediatric cases.[8] Although the exact prevalence of this disease has yet to be determined, large-scale studies have shown anti-NMDA receptor encephalitis to be the most frequent identified cause of antibody-mediated autoimmune encephalitis.[7,16,17]

Although several aspects of anti-NMDA receptor encephalitis can be generalized from adults into children, the clinical presentation, impact of a chosen therapy, and ultimate outcome are often distinct in pediatric patients. In past studies, children have been shown to present with more of a neurologic-based presentation (movement abnormalities, seizures) than adults, who tend to present with more psychiatric features.[4] Beyond this, our appreciation for the phenotypic variability in this disease continues to grow as younger children are being diagnosed and described.[18]

Our case series details the clinical and treatment parameters for all cases seen at our institutions within a 2.5-year time span. The demographic data in our case series is in line with previous pediatric case series', in regards to age of onset, gender ratio, prodromal presence, prevalence of concomitant seizures, presence of imaging abnormalities, and presence of an underlying ovarian teratoma.[4,8] Interestingly, past studies have indicated a relapse rate of 25%,[19] regardless of age of onset; however, in our case series, no patient has experienced a neurologic relapse, despite all cohort patients having been free from immunotherapy for at least 12 months at the time of chart review.

Current knowledge would suggest that acute treatment with tumor removal (if one is present) and prompt immunotherapy improves patient outcomes.[4] Perhaps the greatest void within the current literature is the absence of objective data to define and support the use and duration of chronic immunotherapy in anti-NMDA receptor encephalitis. In children, it is very important to consider the potential impact of a given immunotherapy on the developing neuro-immunologic system. Although the benefit of first-line, acute immunotherapies to treat the disease is typically justified, the beneficial use of long-term, steroid-sparing immunotherapeutic agents must be weighed carefully with respect to the patient's age and risk of disease recurrence. Additionally, as many chronic immunotherapeutic agents may have an adverse impact upon fertility and increase risk of future malignancy, these issues must be carefully discussed prior to initiation of the given treatment.

To our knowledge, there have been no specific studies assessing the long-term benefit and risk of chronic immunosuppression in cases of anti-NMDA receptor encephalitis. Current treatment guidelines are primarily based on expert opinion and general consensus.[19] Our case series provides unique insight into the varied approach toward management of anti-NMDA receptor encephalitis. The acute management of this disease is fairly standard within our cohort, with one of 2 basic methods employed for first-line therapies (corticosteroids vs corticosteroids + intravenous immunoglobulin) and second-line therapies (plasma exchange vs rituximab $\pm$ cyclophosphamide). Although chronic treatment was employed in all cases for at least 6 months, the choice and duration of therapy was quite varied. In our series, the typical choice for chronic management was either rituximab $\pm$ intravenous immunoglobulin or cyclophosphamide versus mycophenolate mofetil $\pm$ steroid

Table 3. Treatment Utilization of Pediatric Patients With Anti-*N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis.

Case number	Acute treatment	Chronic treatment (duration or number of doses)[a]	Chronic treatment duration	Complications	Outcomes
1	IV Corticosteroids, IVIg, rituximab	Rituximab (2 doses); IVIg (8 mo)	<1 y	None	Complete recovery
2	IV corticosteroids, rituximab	Teratoma excision; rituximab (2 doses); IVIg (6 mo); oral steroid taper (6 mo)	<1 y	Headache	Complete recovery
3	IV corticosteroids, IVIg, rituximab	IVIg (6 mo); Oral steroid taper (6 mo)	<1 y	None	Complete recovery
4	IV corticosteroids, IVIg, rituximab	Rituximab (1 dose); IVIg (6 mo); oral steroid taper (1 mo)	<1 y	None	Persistent behavioral abnormalities
5	IV corticosteroids, IVIg, PLEX, rituximab	Teratoma excision; rituximab (6 doses)	1.5 y	Urinary tract infection	Persistent behavioral abnormalities
6	IV corticosteroids, PLEX	Oral steroid taper (6 mo); mycophenolate mofetil	1 y	None	Persistent behavioral abnormalities
7	IV corticosteroids	Oral steroid taper (4 mo); mycophenolate mofetil	1 y	CMV colitis	Complete recovery
8	IV corticosteroids, IVIg, rituximab, cyclophosphamide	Teratoma excision; mycophenolate mofetil	4 y	None	Complete recovery
9	IV corticosteroids, IVIg, rituximab, cyclophosphamide	Mycophenolate mofetil	1.5 y	Respiratory infection	Seizures, persistent behavioral abnormalities
10	Oral corticosteroids, PLEX, rituximab	Rituximab (4 doses) and cyclophosphamide	2 y	Septic shock	Complete recovery

CMV, cytomegalovirus; IV, intravenous; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.
[a]Chronic treatment with IVIg was monthly (2 g/kg divided over 2-4 d); rituximab was weekly in doses of 375 mg/m^2 (patients 5 and 10) or 500 mg/m^2 every other week (patients 1, 2, and 4); cyclophosphamide was monthly in doses of 750 mg/m^2; mycophenolate mofetil was dosed twice daily at a dose of 750 mg for body surface area of 1.25-1.5 m^2 and 1 g for body surface area >1.5 m^2.

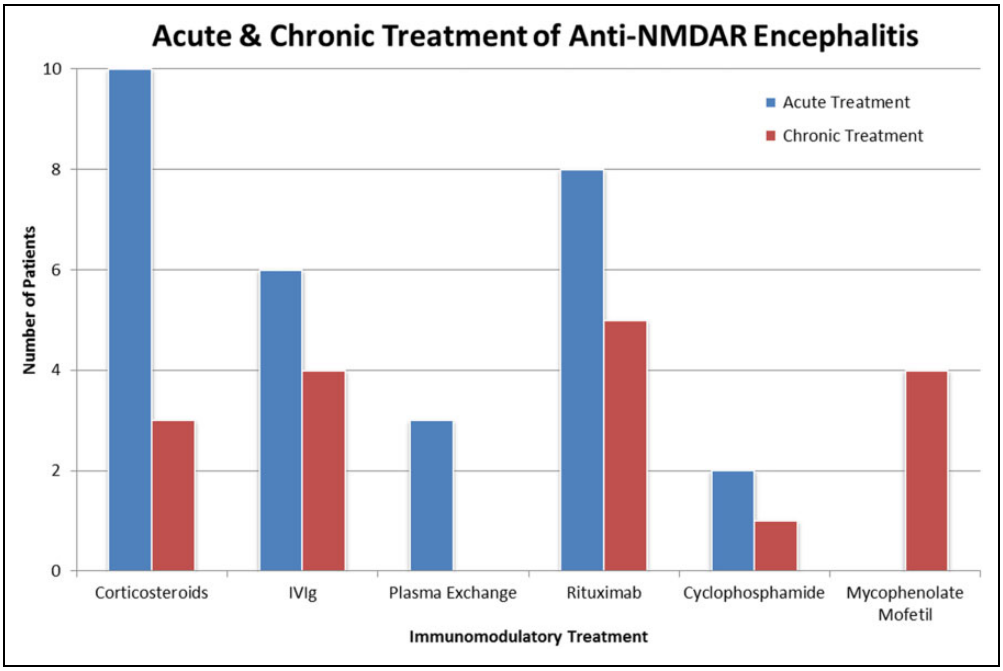

Figure 1. Acute and chronic treatment distribution in pediatric patients with anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis.

taper. Interestingly, 40% of our cohort received chronic immunotherapy for longer than 12 months, despite the lack of neurologic relapse within this time frame.

Of note, half of our cohort experienced adverse events considered to be secondary to chronic immunosuppression administered at conventional dosing. Although all patients

underwent hospitalization for these complications, the acuity was variable (from post–intravenous immunoglobulin headache to septic shock and cytomegalovirus colitis). Although complications of immunosuppression are well known to most prescribing providers, our data suggest that many providers consider the risk of potential anti-NMDA receptor relapse to outweigh the risk of medication-derived complications. In contrast, the majority of patients who suffer from a relapsing course of anti-NMDA receptor encephalitis experience a milder course than the initial attack.[4] This, taken collectively with the illustrated risk of iatrogenic adverse events and the estimated general risk of relapse ($\sim$25%), would suggest that abstaining from initiating chronic immunotherapy in an individual patient is a valid option for the clinician to consider. Robust, randomized placebo-controlled clinical trials assessing the need and benefit of long-term immunosuppression in a young, developing patient is of utmost importance.

Author Contributions

JNB provided cases for this case series, performed all data collection and analysis, wrote the initial draft of the manuscript, and provided revisions requested. JK assisted with data collection and analysis and provided critical revision of the initial draft. RHS provided cases for this case series, performed data collection, and provided critical revision of the initial draft.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the University of Virginia (IRB 18133) and Inova Fairfax (IRB 15-1803) institutional review board/ethics committee.

References

1. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol*. 2005;58:594-604.
2. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7:1091-1098.
3. Brenton JN, Schwartz RH, Madoo L. Anti-NMDA-receptor encephalitis: a review. *Contemp Pediatr*. 2015;32:14.
4. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *Lancet Neurol*. 2013;12:157-165.
5. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology*. 2012;79:1094-1100.
6. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25-36.
7. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. 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. *Clin Infect Dis*. 2012;54:899-904.
8. Florance NR, Davis RL, Lam C, et al. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol*. 2009;66:11-18.
9. Cantarin-Extremera V, Duat-Rodriguez A, Gonzalez-Gutierrez-Solana L, Lopez-Marin L, Armangue T. Clinical case of anti-*N*-methyl-D-aspartate receptor encephalitis in an 8-month-old patient with hyperkinetic movement disorder. *Pediatr Neurol*. 2013;48:400-402.
10. Goldberg EM, Titulaer M, de Blank PM, Sievert A, Ryan N. Anti-*N*-methyl-D-aspartate receptor-mediated encephalitis in infants and toddlers: case report and review of the literature. *Pediatr Neurol*. 2014;50:181-184.
11. Irani SR, Bera K, Waters P, et al. *N*-Methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain*. 2010;133(pt 6):1655-1667.
12. Kashyape P, Taylor E, Ng J, Krishnakumar D, Kirkham F, Whitney A. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. *Eur J Paediatr Neurol*. 2012;16:74-78.
13. Nunez-Enamorado N, Camacho-Salas A, Belda-Hofheinz S, et al. Fast and spectacular clinical response to plasmapheresis in a paediatric case of anti-NMDA encephalitis. *Rev Neurol*. 2012;54:420-424.
14. Wong-Kisiel LC, Ji T, Renaud DL, et al. Response to immunotherapy in a 20-month-old boy with anti-NMDA receptor encephalitis. *Neurology*. 2010;74:1550-1551.
15. Wright S, Hacohen Y, Jacobson L, et al. *N*-Methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. *Arch Dis Child*. 2015;100:521-526.
16. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10:835-844.
17. Pillai SC, Hacohen Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics*. 2015;135:e974-e984.
18. Scott O, Richer L, Forbes K, et al. Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis: an unusual cause of autistic regression in a toddler. *J Child Neurol*. 2014;29:691-694.
19. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63-74.