Pediatric Neurology 50 (2014) 507–510

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Pediatric Anti-NMDA (*N*-methyl D-Aspartate) Receptor Encephalitis

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ABSTRACT

BACKGROUND: We report the clinical features and course of pediatric patients presenting with anti-*N*-methyl D-aspartate receptor (NMDA-R) encephalitis. **METHODS:** Single-center 4-year observational study of pediatric encephalitis associated with NMDA-R antibodies in the serum and/or the cerebrospinal fluid. **RESULTS:** Three girls with anti-NMDA-R encephalitis were identified. All presented with an acute hyperkinetic movement disorder and seizures, expressive aphasia, and emotional lability requiring inpatient treatment for 1-3 months. Imaging and electroencephalogram findings were nondiagnostic. None had an underlying tumor or ovarian teratoma. All received immune-modulatory therapy, including one or more of the following: high-dose methyl-prednisolone, plasma exchange, intravenous immunoglobulin or mycophenolate mofetil. Two of the three patients relapsed within 6 months of presentation and required retreatment with plasma exchange. All have remained in subsequent remission, with two of the three requiring second-line immunotherapy with rituximab. **CONCLUSIONS:** Hyperkinetic movements in pediatric patients presenting with acute encephalopathy and prominent psychiatric symptoms should elicit a search for NMDA-R antibodies early in the evaluation. Relapses require aggressive immunomodulatory treatment for remission. This series highlights a unique positron emission tomography scan finding of hypermetabolism in one of the patients that correlated with her clinical symptoms. Recovery and rehabilitation can be prolonged, often taking years after the initial diagnosis. Early identification and treatment is likely to reduce relapses and limit morbidity associated with this potentially devastating but treatable encephalitis.

Keywords: anti-NMDA-R, pediatric, encephalitis, aphasia, dyskinesia, neuropsychiatric, autoimmune

Pediatr Neurol 2014; 50: 507-510

Introduction

Anti-*N*-methyl D-aspartate receptor (anti-NMDA-R) encephalitis is an acute autoimmune neurological disorder first described in adults by Dalmau et al.[1] in 2007. Presentation is with a prodrome of flu-like symptoms that progress to psychiatric symptoms, dyskinesias, seizures, and cognitive decline. The diagnosis is confirmed by detection of autoantibodies against the NMDA-type glutamate receptors in the serum and cerebrospinal fluid. The majority of patients with anti-NMDA-R encephalitis are women with ovarian teratomas.[2] Children are increasingly being described with this condition,[3] but its natural history for pediatric patients remains not well defined. We describe the clinical syndrome, therapeutic interventions and clinical outcome of three consecutive children with confirmed anti-NMDA-R encephalitis from a single institution.

Case Series

Patient 1

A previously healthy 7-year-old Hispanic girl presented with a history of fever, inconsolable crying, and reversal of her sleep wake cycle,

Article History:
Received October 29, 2013; Accepted in final form January 1, 2014

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0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.01.012

with increased somnolence during the day and insomnia at night. Over the next week, she complained of abdominal pain and headaches and was diagnosed with a urinary tract infection.

Several days afterward, she became aphasic, catatonic, and had two complex partial seizures. She was admitted to an outside hospital for 31 days with progressive encephalopathy, orobuccal dyskinesias, and dystonia. She was diagnosed with presumed Epstein-Barr virus encephalitis. She was treated with 20 mg/kg intravenous methylprednisolone (IVMP) for 3 days, 2 g/kg of intravenous immunoglobulin (IVIG) administered over 4 days, as well as acyclovir, with minimal transient improvement.

She was transferred to our facility on day 47 of illness, at which time she was obtunded, nonambulatory, gastrostomy-tube dependent, and in a near-continuous hyperkinetic state characterized by choreodystonic movements with episodes of tachycardia and hypertension. On day 50, she received another course of IVMP for 5 days, followed by a 7-day course of plasma exchange (PLEX). The patient had transient improvement in her mental status, and she was able to make eye contact and pantomime. A week later, her mental status deteriorated and she had a seizure.

On day 87 of illness, NMDA receptor antibody was reported as positive in the patient's cerebrospinal fluid (CSF). She received 5 days of PLEX as well as 20 mg/kg IVMP. On day 99 of illness, she started cyclophosphamide followed by rituximab dosed at 375 mg/m^2. Cyclophosphamide was given monthly for 4 months, and rituximab was administered weekly for 4 weeks. In addition, she took 4 mg/kg/day of prednisone for 6 months. While on immunotherapy, she began to smile and was able to ambulate independently. She continued to be nonverbal, had unexplained behavioral outbursts, and preferred to play with children younger than her peers. She had one relapse with symptoms of insomnia, perseveration, emotional lability, and decline in cognitive functioning, which lasted approximately 4 weeks. Serum NMDA receptor antibody was positive, and she was again treated with PLEX. She was subsequently started on azathioprine 50 mg orally daily, which she took for 2 years. Over the next 2 years, she made gradual and steady improvement in her language and cognitive skills. Her emotional lability and immature behavior were the final symptoms to resolve.

Approximately 3 years from time of disease onset, she was back to her clinical baseline and had neuropsychological testing with a verbal intelligence quotient of 85 and full-scale intelligence quotient of 93. She is enrolled in regular academic classes, achieving As and Bs.

Patient 2

A previously healthy 8-year-old African-American girl presented with four generalized tonic clonic seizures in the setting of recent upper respiratory infection symptoms. Following the seizure activity, she developed a flat affect, psychomotor slowing, memory difficulties, and mild dysarthria. Two weeks after, she developed right upper extremity myorhythmia, orobuccal dyskinesia, and aphasia with echolalia.

On day 15 of illness, the patient was admitted to our facility with progressive encephalopathy with periods of extreme agitation. On day 21 of illness, she was treated with a 5-day course of 20 mg/kg IVMP with no clinical improvement. On day 30 of illness, a positron emission tomography (PET) scan showed an increased area of hypermetabolism in the left lentiform nuclei (*see* Fig). At the time, she had right arm myorhythmia. On day 34 of illness, a brain biopsy was performed, which demonstrated nonspecific lymphocytic proliferation. NMDA-R antibodies were absent in the serum but present in CSF. These results were reported on day 63 of illness. She subsequently received a 5-day course of IVIG, starting on day 82 of illness, which was followed by 4 months of prednisone. She became more verbal and started to consistently follow commands but continued to have emotional lability.

Over the course of 2 years, she continues to make cognitive and emotional progress but has persistent difficulties with social behavior and executive function. She is not yet back to her baseline and is in special education classes. She has a paucity of speech, her cognitive processing speed is slow, and she has difficulty maintaining attention and focus. She has been seizure free for more than a year and is maintained on oxcarbazepine.

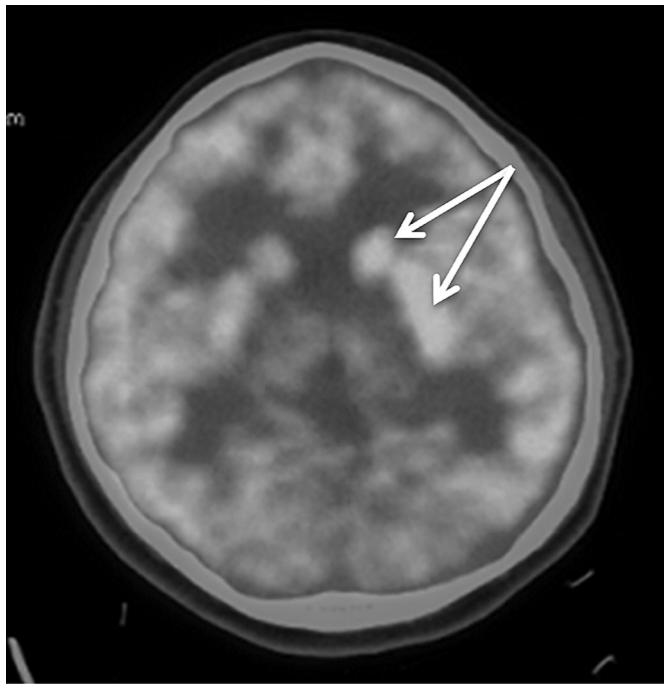

FIGURE.
Findings of patient 2's fludeoxyglucose positron emission tomography scan during the acute stage of disease showing acute hypermetabolism in basal ganglia (*arrows*) contralateral to extremity myorhythmia.

Patient 3

A previously healthy 14-year-old African-American girl presented with an unwitnessed seizure, a 4-day history of word-finding difficulties, and an 8-day history of increased fatigue and intermittent headaches. On day 8 of illness, she presented to our institution with right-sided orobuccal dyskinesias and expressive aphasia, along with a generalized tonic clonic seizure. The working diagnosis of anti-NMDAR encephalitis was made, and she was treated with concurrent IVMP and IVIG for 5 days. Her aphasia fluctuated over the course of 2 weeks. After treatment, she developed autoimmune hemolytic anemia for which she required red blood cell transfusion. She was started on prednisone 80 mg by mouth three times daily, and her anemia slowly resolved. The etiology of the autoimmune hemolytic anemia was presumed to be IVIG administration. Her expressive aphasia continued to improve. After her 18-day hospitalization, she was able to speak in full sentences with occasional slight hesitancy and was otherwise symptom free. CSF studies were reported positive for NMDA-R antibodies at a titer of 1:5 on day 16 of hospitalization. The patient remained on oral prednisone for 1 month after the autoimmune hemolytic anemia. She was started on mycophenolate mofetil 2 months after initial presentation in an attempt to prevent relapse.

Subsequently, 6 months after initial presentation, she presented with left-sided dystonia. CSF was again obtained and revealed NMDA-R antibodies at an increased titer of 1:10. Mycophenolate mofetil was increased, and she was placed on prednisone 40 mg by mouth twice daily. She was discharged home, but returned 9 days later with choreiform movements in her left arm, oromandibular dyskinesia, left arm tremor, psychosis with visual hallucinations, flat affect, and depressed mood. She received IVMP for 5 days with mild improvement. However, on day 5 of IVMP, she developed episodes of opisthotonus followed a few days later by nonepileptic episodes of uprolling of her eyes, generalized stiffening, and clonic activity. With the guidance of hematology, she received 5 days of IVIG and again developed hemolytic anemia requiring red blood cell transfusion, for which her oral steroids were increased. Her immunosuppressive regimen was modified given the relapse even on increased doses of mycophenolate mofetil. She was discharged to a rehabilitation facility with a plan for monthly cyclophosphamide

infusions and bimonthly rituximab infusions, with the long-term plan being to transition her to back to mycophenolate mofetil once the IV infusions are complete.

Findings of a neuropsychologic evaluation performed during a relapse in the hospital demonstrated frontal lobe disinhibition, left-sided coordination difficulties, dysarthria, decreased spontaneous oral output, impaired calculations, and verbal and visual memory deficits. At 6-month follow-up, she was at baseline physical and at near-baseline cognitive functioning. Repeat neuropsychologic testing is in process.

Discussion

We summarize three pediatric patients with anti-NMDA-R encephalitis (see Table). Early detection and aggressive treatment limit morbidity. Relapses should be proactively surveyed with the use of serum markers that guide immune-modulating therapy.

The patients initially presented with prominent neuropsychiatric deficits followed by aphasia and movement disorder. The movement disorder was characterized by orobuccal dyskinesia, choreodystonic, movements and myorhythmia.[4] Myorhythmia is a resting 1-3 Hertz tremor with an irregular frequency.[4] Although seizures were a presenting feature, all patients responded to initial antiepileptic therapy. The literature suggests that symptom presentation varies between children and adults, with symptoms more often neurological in children and more often psychiatric in adults.[5] However, as illustrated by a larger case series in the pediatric literature,[6] our pediatric patients presented with prominent psychiatric symptoms.

Delay in diagnosis is a common feature. Anti-NMDA-R encephalitis is often mistaken for psychosis or viral encephalitis. There are many causes for this delay, including nonspecific positivity of serum Epstein-Barr virus and Mycoplasma immunoglobulin M titer. However, the California Encephalitis Project found that anti-NMDA-R encephalitis was a more prevalent etiology of encephalitis than any individual virus in children.[7]

Imaging, EEG and brain biopsy are typically nondiagnostic,[5] although, PET may be useful in children. In patient 2, cerebral PET imaging demonstrated hypermetabolism in the basal ganglia that was contralateral to the extremity with hyperkinetic movements. The characteristic electroencephalographic pattern, extreme delta brush, was not observed in our patients, but has been demonstrated in the literature.[8] Ovarian teratoma and other neoplasms were not present in our patients, unlike the typical adult patient with anti-NMDA-R encephalitis. This finding is in keeping with other small case series which report lower incidence of tumor than the adult population.[9]

Recovery from anti-NMDA-R encephalitis is a prolonged and multiphase process.[10,11] Autonomic instability and abnormal movements were the first features to resolve in our patients, whereas behavioral and cognitive recovery was last. Acute immunotherapy is first-line treatment for anti-NMDA-R encephalitis with a combination of high-dose IVMP and IVIG. Prevention of relapse is possible with ongoing therapy with rituximab, mycophenolate mofetil, and/or cyclophosphamide.

In conclusion, pediatric anti-NMDA-R encephalitis should be suspected early in the course of encephalitis when the initial work-up is nondiagnostic. Hyperkinetic movement disorder (oromotor dyskinesia, choreodystonia, and myorhythmia[4]) or psychiatric symptoms should raise suspicion of anti-NMDA-R encephalitis. Cerebral PET imaging appears superior to magnetic resonance imaging and electroencephalography and may be useful to follow clinical course.[12-14] Although none of these tests are disease specific, PET would allow for a noninvasive method of monitoring clinical course, with the drawback, of course, being repeated exposure to radiation. This will require

TABLE.
Clinical features, evaluation, and management of pediatric anti-NMDA-R encephalitis

	Patient 1	Patient 2	Patient 3
Age (yrs); Ethnicity	8; Hispanic	7; African American	14; African American
Presenting feature			
Movement disorder	Catatonia, choreodystonia, OD	Right facial OD, right upper-extremity myorhythmia	OD, dystonic posturing, myorhythmia, opisthotonus
Psychiatric symptoms	Emotional lability	Flat affect, depressed mood	Emotional lability, depressed mood, psychosis
Autonomic instability	Fever, tachycardia	None	Fever, tachycardia, autoimmune hemolytic anemia
Evaluation			
EEG	Background disorganization	Background disorganization	Background disorganization
Brain MRI	Normal	Normal	Normal
Tumor screening	Negative	Negative	Negative
Treatment			
Methyl-prednisolone and IVIG	Yes	Yes	Yes
PLEX	Yes	No	No
Rituximab	Yes	No	Yes
Cyclophosphamide	Yes	No	Yes
Mycophenolate mofetil or azathioprine	Yes	No	Yes

Abbreviations:
anti-NMDA-R = Anti-*N*-methyl D-aspartate receptor
EEG = Electroencephalogram
IVIG = Intravenous immunoglobulin
MRI = Magnetic resonance imaging
OD = Orobuccal dyskinesia
PLEX = Plasma exchange

further investigation before a strong recommendation can be made. Optimized immunomodulatory treatment can result in dramatic recovery and may prevent relapses.

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