Published in final edited form as:
Am J Phys Med Rehabil. 2012 May ; 91(5): 435–441. doi:10.1097/PHM.0b013e3182465da6.

The Rehabilitation of Children with Anti-NMDA-Receptor Encephalitis: A Case Series

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Abstract

Anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis is a serious, complex, and potentially fatal disease in children. Children with this condition frequently present with altered mental status, rapid functional deterioration, and seizures. Despite aggressive treatment with immune therapy such as corticosteroids, intravenous immunoglobin (IVIG), and plasmapheresis, children often need extensive rehabilitative services and can be left with lasting deficits. In this case series we report on six known consecutive pediatric cases of NMDA-receptor antibody encephalitis in Northern California requiring comprehensive inpatient rehabilitation. The children presented with a variety of symptoms and had waxing and waning clinical courses. All children progressed well through their rehabilitation programs, but were discharged home with persistent functional deficits. At follow-up, all but one child had lasting deficits. Because of the complicated management and extensive rehabilitation needs of children with anti-NMDA-receptor encephalitis, physiatrists and other rehabilitation providers should be knowledgeable about this complex condition.

Keywords

Anti-NMDA-receptor Encephalitis; Rehabilitation; Function; Children

Anti-N-methyl-D-aspartate (NMDA) –receptor encephalitis is a disorder that was first described as a paraneoplastic syndrome in young women with ovarian teratomas.[1-3] The clinical presentation of anti-NMDA-receptor encephalitis frequently includes mood and behavior changes, seizures, altered levels of consciousness, dyskinesia, and functional deterioration.[1-7] Treatment includes tumor resection, if a tumor is identified, and immune therapies such as corticosteroids, intravenous immunoglobulins (IVIG), plasmapheresis, rituximab, and cyclophoshamide.[4-8] In addition, supportive management, including treatment with anti-epileptics and anti-psychotics, is often necessary.[1-7]

Because the clinical presentation of pediatric anti-NMDA-receptor encephalitis frequently includes functional decline in motor skills, self-care, and cognition, rehabilitation

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Disclosures:
Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.
The authors have nothing to disclose. None of the authors have any financial interest.

professionals are often involved in its ongoing management. Because anti-NMDA receptor encephalitis is a newly described condition, rehabilitation practitioners may be unfamiliar with its clinical course and management. Florance et al. identified the need for multidisciplinary team management with physical medicine and rehabilitation and psychiatry involvement for children with protracted symptoms.[4] Despite the obvious need for rehabilitation services for patients with anti-NMDA-receptor encephalitis, no case studies have described the rehabilitation needs and rehabilitation treatment of children with anti-NMDA-receptor encephalitis. This case series attempts to fill the gap in the medical rehabilitation literature by describing six cases of children with anti-NMDA-receptor encephalitis treated in three comprehensive inpatient rehabilitation programs in Northern California.

CASE DESCRIPTIONS

All consecutive children with anti-NMDA-receptor encephalitis who required comprehensive inpatient rehabilitation at three pediatric rehabilitation centers in Northern California from 2008-2009 are included in this case series. A total of six patients were positively diagnosed based on the presence of anti-NMDA-receptor antibodies and were reported to the California Encephalitis Project. One case, Patient 4, has been previously described in the medical literature in a case series describing findings of patients with anti-NMDA-receptor antibody positive encephalitis versus cases of patients with other types of encephalitis.[9]

Table 1 details demographic and clinical information for the six patients. Level of functioning was recorded using a seven-point scale as described in Table 2. Two of the three centers used the WeeFIM to capture functional data, while the third center extracted functional data from the FRESNO and therapy reports of functional levels consistent with the WeeFIM. Both the WeeFIM and FRESNO are validated rehabilitation outcome assessment tools for pediatric rehabilitation.[10,11] Table 3 quantitatively displays the functional status of the patients during rehabilitation, which were recorded at the time of admission to rehabilitation and disposition from rehabilitation (values correspond to the descriptions provided in Table 2). For self-care, the patient's lowest level of function was recorded.

Comprehensive Rehabilitation

At all three centers, comprehensive rehabilitation included at least three hours of therapy, six days a week. The therapeutic modalities were physical therapy, occupational therapy, speech therapy, and dysphagia therapy. Patients also received services from child life and, if school-aged, services from special education. Families were supported by social work and case management. At each of the three centers, the comprehensive rehabilitation team was led by a pediatric physiatrist. Admission to comprehensive rehabilitation was considered appropriate when the child was able to tolerate an intense therapy schedule and was deemed to be able to benefit from comprehensive services. Admission to rehabilitation did not require cessation of immunosuppressive therapy. In fact, all patients continued on their immunosuppressive regimens while participating in comprehensive rehabilitation. In all cases, the medical teams remained actively engaged in the patients' care. At the time of admission to comprehensive rehabilitation, team goals for functional outcomes were set and reviewed with each of the families. In general, the rehabilitation teams had the following goals: maximization of safe functioning, symptom management, accommodations for functional deficits, and family training. Weekly monitoring of progress was captured by WeeFIM or FRESNO data, as were qualitative descriptions of functional skills. Team meetings were held weekly to discuss progress, develop short-term goals, and identify barriers to success. Disposition planning for each patient occurred actively throughout their

rehabilitation stays and included input from the families, the rehabilitation team, and other medical providers. In general, disposition was deemed appropriate when the children were medically stable, functional goals were met, and family training had been completed.

This study falls under the University of California's (UC) Exempt category for human research. The Institutional Review Board at Children's Hospital and Research Center Oakland (CHRCO) approved this study as not involving human subjects. All patient related data was de-identified at the three collection sites (CHRCO, UC San Francisco, and UC Davis) in accordance with patient privacy protection, and were coordinated at CHRCO.

Case 1

This previously healthy two year-old Filipino girl had a three month clinical course prior to initiation of comprehensive inpatient rehabilitation. After treatment with methylprednisolone, IVIG, plasmapheresis, and rituximab, the patient showed clinical improvement and became more aware of her surroundings. Based on her extensive rehabilitation needs, she was deemed appropriate for a comprehensive rehabilitation program. At the time of presentation, she had aphasia, dysphagia with oral motor dyskinesis, hyperkinetic and choreoathetoid movements, and required total assistance for all functional tasks. After three weeks of ongoing immunosuppressive therapy, comprehensive inpatient rehabilitation, and family training, she was discharged home with her parents. At the time of disposition, she had improved cognition with sustained visual tracking, muted choreoathetoid movements, and improved head and trunk control. At follow-up at sixteen months post onset of symptoms and nearly one year after comprehensive rehabilitation, she had nearly full resolution of her symptoms and was developmentally on target. The only remaining deficit noted was mild impulsivity.

Case 2

This six year-old Asian girl with a past medical history significant for a seizure disorder had a two week clinical course prior to initiation of comprehensive inpatient rehabilitation. She improved after treatment with azithromycin and IVIG and was deemed appropriate for comprehensive rehabilitation due to receptive and expressive aphasia, agitation, and inability to maintain safety or perform any daily tasks. After two weeks of rehabilitation, the patient had markedly improved. At the time of disposition home with her family she was able to eat, speak in full sentences, follow commands, ambulate safely with supervision, and participate in activities of daily living (ADLs). She did not require any assistive devices or equipment for disposition home. She continued to have substantial deficits in communication and cognition and required an Individualized Education Program (IEP) for school reentry, as well as outpatient therapy services. She was discharged on valproic acid and melatonin. At the time of follow-up three months later (four months after symptom onset), this patient required assistance for communication and cognition. At the time of this submission, the patient still requires an IEP to address her slow processing speed, difficulty with new concepts, and limited ability to attend to details.

Case 3

This nine year-old Caucasian boy with a past medical history significant for attention deficit hyperactivity disorder (ADHD) had a four month clinical course prior to the initiation of comprehensive inpatient rehabilitation. With IVIG, plasmapheresis, valproic acid, clonidine, risperidone, propranolol, and levetiracetam, the patient's condition improved. He was managed with splints to address his rigidity. At the time of admission to the comprehensive inpatient rehabilitation program, he was alert with spontaneous, purposeful movements and was dependent for all care. After six weeks of comprehensive inpatient rehabilitation, this patient was discharged home with this mother on risperidone and melatonin. His physical

functioning had markedly improved, but he continued to have significant cognitive deficits, emotional lability, and behavioral outbursts. He was discharged with a rental wheelchair for long-distance mobility in the community when needed. He was reintegrated into the classroom with adaptations to his IEP and attended outpatient therapies. Because of the distance between the patient's home and the hospital, this patient received his follow-up locally. Telephone reports from the mother nearly two years after symptom onset indicate that he has had ongoing cognitive recovery but persistent deficits, especially with attention.

Case 4

This previously healthy nine year-old Caucasian girl had a five week clinical course prior to the initiation of comprehensive inpatient rehabilitation. After treatment with plasmapheresis and cyclophosphamide she was deemed appropriate for comprehensive inpatient rehabilitation to address her functional deficits. At the time of presentation to comprehensive inpatient rehabilitation, she had bouts of aggressive behavior, was nonverbal, and had variable arousal affecting her function. Her strength was noted to be normal, but she was unable to participate with functional testing and required total assistance in all domains. After one month, she was discharged home with ongoing cyclophosphamide treatments. At the time of disposition, she was ambulating with supervision and participating in self-care activities with minimal assistance, but she continued to have substantial deficits in communication and cognition. Based on her ongoing deficits, she required outpatient therapy services. At follow-up fourteen months after initial presentation, she had improved speech and cognition but did not regain her premorbid levels of functioning and had persistent language dysfunction.

Case 5

This previously healthy eleven year-old Filipino girl had a one month clinical course prior to the initiation of comprehensive inpatient rehabilitation. At the time of admission to comprehensive inpatient rehabilitation she had a movement disorder, agitation, impaired cognition, dysarthria, motor apraxia, and was non-ambulatory. She was discharged home after three weeks of comprehensive inpatient rehabilitation with marked motoric improvements. She was independent with self-care and ambulating short distances independently, but using a wheelchair for long distances. Because of her persistent deficits with short-term memory, new learning, auditory processing, and attention, her community reentry program included the recommendation for an IEP and outpatient therapy. Upon follow-up approximately four months after presentation and six weeks post discharge, the patient was functionally independent with mobility, ADLs, communication, and cognition, with the exception of short-term memory.

Case 6

This previously healthy fifteen year-old Hispanic young woman had a three month clinical course prior to the initiation of comprehensive inpatient rehabilitation. She was treated with methylprednisolone, IVIG, and plasmapheresis, and underwent operative intervention to remove a right periovarian calcification. Her post-operative course was complicated by pulmonary failure requiring extracorporeal membrane oxygenation (ECMO) and tracheostomy, renal failure requiring hemodialysis, and colonic obstruction requiring hemicolectomy and ileostomy. She also required bilateral salpingo-oophorectomies. At the time of admission to comprehensive inpatient rehabilitation, this patient was deconditioned, dependent for all care, and required maximal assistance for verbal expression. Her rehabilitation course was complicated by medical deterioration, requiring a three day stay in intensive care. Despite her complicated clinical course, this patient progressed well while on the rehabilitation program. Her cognition and language skills were nearly back to baseline at the time of disposition nine weeks after admission. She was discharged home with

supervision, a manual wheelchair for long distances, and a handrail for showering because she continued to have challenges with endurance and memory. At the time of follow-up thirteen months later (eighteen months after initial symptom presentation), she had full resolution of symptoms with no obvious deficits.

DISCUSSION

This case series highlights the presentation, general management, rehabilitation, and initial sequelae among children with anti-NMDA-receptor encephalitis who received comprehensive inpatient rehabilitation services. Consistent with the literature, there seems to be a female predominance for this condition.[1,4] In our series, only one child was male. Also consistent with recent reports,[4,6] but different than the original case reports, which were in adults,[1,2] only a third of our cases involved an identified tumor. Four of the six patients presented with psychiatric symptoms but only one had frank psychosis, a presenting finding in many adult cases.[1,4] In addition, two of our patients had hypoventilation, a clinical problem frequently seen in adults with anti-NMDA-receptor encephalitis as described in the original case reports.[1,2,4]

The children in this series were treated with a variety of immune therapies and all displayed clinical improvements upon treatment. Other cohort and case studies have also noted success in treatment with immune therapies.[1-8,12] Recent literature supports aggressive treatment with immunotherapies, including rituximab and cyclophosphamide,[13] which may or may not be possible on comprehensive rehabilitation units. While many case reports and series detail improvements past the initial hospitalization,[1,4,5] ours is the only case series to describe the changes in function during comprehensive inpatient rehabilitation. Upon presentation to comprehensive inpatient rehabilitation the patients in this series had an array of impairments, including movement disorders, behavioral issues, dysphagia, and language and cognitive deficits. The severity of these patients' impairments may have been a reflection of the underlying severity of their encephalitis, the timing of rehabilitation in relation to medical management, and/or the intensity of immunosuppressive therapy and supportive management. All of the patients in this series were either dependent or required maximal assistance for their mobility and self-care, and four of the six were dependent for communication and cognition. While all patients had clinical improvements and made functional gains during rehabilitation, their progress did not consistently correspond to the MRI findings. For example, both Patients 4 and 6 had normal MRIs, but Patient 4 had substantial cognitive deficits after disposition from rehabilitation, while Patient 6 had nearly normal cognitive skills at disposition. The lack of correlation between clinical presentation and MRI findings is well described in the medical literature.[13] The EEG finding of slowing was identified in all cases and is consistent with other reports.[9]

The presence of multiple impairments and the inconsistent relationship between MRI findings and outcomes can pose considerable challenges to rehabilitation teams. Estimating length of stay and anticipating functional outcomes is therefore difficult for patients with anti-NMDA-receptor encephalitis. Targeting medical interventions to address the movement disorders and psychiatric symptoms, in collaboration with the treating neurologist and other subspecialists, can help to set the stage for more productive interventions with physical, occupational, and speech therapies, which should help improve functional outcomes and decrease the time needed in a comprehensive rehabilitation setting. Similarly, providing a robust set of family-centered services to children and their families should help with rehabilitation goal setting, adjustment, and disposition planning.[14] This is especially true in the series of children herein described, as all continued to have functional deficits after comprehensive inpatient rehabilitation, primarily in the cognitive domains. Follow-up for these patients occurred between six weeks and over one year after disposition from

rehabilitation. This limits our ability to quantify long-term impacts for this group of patients. However, we note that only one of our patients had full resolution of symptoms and another had nearly full resolution of symptoms but continued to have cognitive deficits. Other studies have also found long-term persistence of symptoms.[1,4] The fact that many children have persistent deficits indicates the need for ongoing rehabilitative services to maximize functional skills, make adaptations for functional deficits, and assist with community integration.

CONCLUSION

This case series is the first to describe the rehabilitation of children with anti-NMDA-receptor encephalitis. The children in this series presented acutely with a variety of symptoms consistent with the neurological findings of children with anti-NMDA-receptor encephalitis. All of the children responded to immune therapy, but had significant functional deficits requiring intervention by pediatric rehabilitation teams. All of the children in the series had functional improvements while receiving comprehensive rehabilitation, but also had deficits at the time of disposition. A majority of them had lasting deficits in the cognitive domains. Because of the rehabilitation needs of children with anti-NMDA-receptor encephalitis in the hospital and outpatient settings, physiatrists and other rehabilitation professionals should be knowledgeable about the condition, the typical clinical course, and the management and treatment of this disease.

Acknowledgments

Manjit Bhandal and Napala Pratini received funding from The Short Term Research Education Program to Increase Diversity in Health Related Research from the National Institutes of Health (National Heart, Lung, and Blood Institute) 1 R25 HL096365. This work has not been presented previously.

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Abbreviations

NMDA	N-methyl-D-aspartate
IVIG	intravenous immunoglobulins
EEG	electroencephalogram
MRI	magnetic resonance imaging
ADLs	activities of daily living
UC	University of California
CHRCO	Children’s Hospital and Research Center Oakland
IEP	Individualized Education Program
ADHD	Attention Deficit Hyperactivity Disorder
D/C	discharge
FRESNO	Functional Rehabilitation Evaluation of Sensori-Neurologic Outcomes
WeeFIM	Functional Independence Measure for Children

Glossary

Drug names (Generic = Trade)

Acyclovir	Zovirax
Azithromycin	Zithromax
Benztropine	Cogentin
Clonidine	Caatapres
Cyclophosophamide	Cytoxan
Haloperidol	Haldol
IVIG	Carimune, Gamimune
Levetiracetam	Keppra
Melatonin	Circadin
Methylprednisolone	Solumedrol

Olanzapine	Zyprexa
Propranolol	Inderal
Quetiapine	Seroquel
Risperidone	Risperdal
Rituximab	Rituxan
Valproic acid	Depakote

Table 1

Demographic and Clinical Characteristics

Patient	1	2	3	4	5	6
Age (years)	2	6	9	9	11	15
Ethnicity	Pacific Islander	Asian	White	White	Pacific Islander	Hispanic
Medical history	Previously healthy	Seizure disorder	ADHD	Previously healthy	Previously healthy	Previously healthy
Initial Presentation to medical care	Seizure	Withdrawn behavior, followed by status epilectus	Aggressive behavior	Found limp and crying at home	Headache, vertigo and abnormal movements	Seizures, psychosis
Clinical Findings	Persistent seizures, behavioral problems, altered gait, abnormal movements and neurological decline to unresponsiveness	Rapid progression to an unresponsive state with GCS of 3 which followed by recovery with catatonic state. Motoric return occurred rapidly with cognitive return lagging behind	Aggression, ataxia, confusion, loss of verbal and ambulation skills followed by. extensive autonomic instability with minimally conscious state associated with dystonic posturing and rigidity	Seizure activity noted in the emergency department, she also developed choreathetoid movements, behavioral outbursts, echolalia, and waxing and waning arousal	Disorientation, agitation, left facial and thumb twitching seizures, and deterioration to a coma with respiratory instability	Psychosis, somnolence, hallucinations, agitation, seizure and deterioration to a comatose state.
EEG	Right frontal delta slowing, no true epileptiform activity.	Diffuse slowing, right-sided attenuation, right hemispheric sharp waves.	Diffuse slowing and disorganization	Slowing over left hemisphere and asymmetric mu rhythm.	Right frontal, temporal, and parietal diffuse slowing.	Diffuse delta slowing.
Brain MRI	Initially normal, global atrophy at 2 weeks post admission to the University Hospital.	Bilateral areas of cortical, basal ganglia, and white matter T2; flair signal intensity.	Diffuse volume loss	Normal	Right parietal flare hyper- intensity. Repeat imaging showed resolution of signal intensity.	Normal
Identification of malignancy	Workup negative	Workup negative	Workup Negative	Workup negative	Pelvic ultrasound and CT identified right ovarian teratoma.	Pelvic CT and MRI revealed right ovarian teratoma.
Medical treatment	Anti-epileptics, methyl-prednisone, IVIG, plasmapheresis, rituximab.	Valproic acid, azythromycin, IVIG.	IVIG, plasmapheresis, cyclophosphamide, clonidine, levetiracetam, valproic acid, risperidone, propranolol	Anti-epileptics, IVIG, methyl-prednisone, plasmapheresis.	haloperidol, acyclovir, IVIG, methyl-prednisone. Surgical resection.	Anti-psychotics (quetiapine, olanzapine, and benztropine), anti-epileptics, methyl-prednisone, IVIG, plasmapheresis. Surgical resection.

Table 2

Measurement of Function

Level of Function	Amount of Assistance Needed
1	Total assistance, dependent (patient performs less than 25% of activity)
2	Maximal assistance (patient performs between 25-49% of activity)
3	Moderate assistance (patient performs at least 50% of activity)
4	Minimal assistance (patient performs at least 75% of activity)
5	Supervision (patient can perform, but not independently)
6	Modified Independent (patient performs independently with an assistive device)
7	Independent (patient performs in timely and safe manner)

Table 3

Functional Scores for Functional Activities at Admission and Discharge from Comprehensive Inpatient Rehabilitation

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	Admit	D/C	Admit	D/C	Admit	D/C	Admit	D/C	Admit	D/C	Admit	D/C
Dynamic standing balance	1	1	2	5	1	7	1	5	1	6	1	7
Gait	1	1	2	5	1	5	1	5	1	6	1	6
Self care/ADLs	1	1	2	4	1	4	1	4	1	7	1	6
Swallowing	1	1	1	5	1	5	1	7	2	7	1	7
Attention	1	2	1	4	1	3	1	1	2	4	5	7
Memory	1	1	1	3	1	3	1	1	3	3	4	5
Comprehension	1	2	1	4	1	3	1	2	2	5	6	6
Expression	1	1	1	3	1	3	1	1	2	5	7	7

D/C =discharge, ADL =activities of daily living