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Case Report

Cognitive Impairment in a Child With Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Case Report

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Correspondence to
Jiyong Kim
Department of Rehabilitation Medicine, Inje University Ilsan Paik Hospital, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea.
Email: halwayskim@gmail.com

HIGHLIGHTS

- This is a report of an anti-N-methyl-D-aspartate-receptor encephalitis case that occurred in a young female.
- There was minor improvement in cognitive function especially in working memory.
- This might be related to damage to the hippocampus and cingulum.

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Cognitive Impairment in a Child With Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Case Report

Seongsik Son [1], **Kil-Byung Lim** [1], **Jeehyun Yoo** [1], **Pamela Song** [2], **Jiyong Kim** [1]

[1]Department of Rehabilitation Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea
[2]Department of Neurology, Inje University Ilsan Paik Hospital, Goyang, Korea

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Department of Rehabilitation Medicine, Inje University Ilsan Paik Hospital, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea.
Email: halwayskim@gmail.com

ORCID iDs
Seongsik Son
https://orcid.org/0000-0002-1090-2759
Kil-Byung Lim
https://orcid.org/0000-0001-8971-7486
Jeehyun Yoo
https://orcid.org/0000-0002-1555-8029
Pamela Song
https://orcid.org/0000-0002-9750-5683
Jiyong Kim
https://orcid.org/0000-0003-4693-8400

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Anti-N-methyl-D-aspartate-receptor encephalitis is a complex autoimmune inflammatory neurological disorder that presents with epileptic seizures and rapid functional deterioration, including movement disorders and cognitive impairment, especially in young patients. Despite aggressive initial treatment with immune therapy, such as corticosteroids, intravenous immunoglobulin, and plasmapheresis, patients often need intensive rehabilitative therapies for their long-lasting deficits. We report a pediatric case of anti-N-methyl-D-aspartate receptor encephalitis in Korea that presented with symptoms of muscle weakness of the four extremities, dysarthria, dysphagia, and cognitive impairment in the acute phase. The patient underwent 4 weeks of comprehensive rehabilitative treatment, including physical therapy, occupational therapy, swallowing rehabilitation therapy, cognitive rehabilitation therapy, and speech therapy. At the follow-up evaluation after 4 weeks of treatment, she showed significant improvements in limb muscle strength, balance ability, swallowing, language function, and the ability to perform activities of daily living. However, when assessed using the Korean Wechsler Intelligence Scale for Children-IV, there was little improvement in cognitive function, particularly in working memory. While only a few cases have reported the progression of cognitive function using a standardized cognitive evaluation tool in patients with anti-N-methyl-D-aspartate receptor encephalitis, this present case report adds to the accumulation of evidence of neurocognitive deficits in these patients.

Keywords: Anti-N-Methyl-D-Aspartate Receptor Encephalitis; Cognitive Dysfunction; Executive Function

INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is an autoimmune inflammatory neurological disorder caused by autoantibodies to the GluN1 subunit of the N-methyl-D-aspartate (NMDA) receptor [1]. The NMDA receptor is a receptor for glutamic acid, a major excitatory neurotransmitter in the central nervous system, and as the brain ages, the NMDA receptor system gradually declines, and dysfunction of the NMDA receptor is associated with several neuropsychiatric disorders [2]. The symptoms of NMDARE typically start with mild general aches and then expand to various neurological symptoms, including

Author Contributions

Conceptualization: Lim KB, Yoo J, Kim J; Data curation: Son S, Song P; Formal analysis: Son S, Song P; Writing - original draft: Son S, Kim J; Writing - review & editing: Lim KB, Yoo J, Song P, Kim J.

movement disorders, epileptic seizures, cognitive impairment and loss of consciousness. In adolescents and adults, behavioral changes, psychosis, and catatonia are mainly observed, but in childhood, neurological abnormalities and movement disorders are more frequently present [3,4]. In some cases, mature ovarian teratomas were accompanied in NMDARE, and immunotherapy such as corticosteroids, immunoglobulin injection, and plasmapheresis, along with surgery to remove teratomas, can lead to improvement of the disease [1].

Since several problems, such as movement disorders and cognitive decline, appear in children with NMDARE, active rehabilitative management is thought to be important. However, in Korea, there have been no reports of cases about the effect of rehabilitation treatment in children with NMDARE and still underrecognized by clinicians; therefore, we would like to report a case of improvement in the clinical course after acute intensive rehabilitation treatment in a 16-year-old girl diagnosed with NMDARE. Written informed consent was obtained from the patient.

CASE DESCRIPTION

A healthy 16-year-old girl with no specific medical or drug history developed numbness and tremor in her right lower extremity 15 days before visiting our hospital. She was admitted to the Neurology Department of another hospital for evaluation, but no specific findings were observed in electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) (**Fig. 1**). At that time, it was recorded that the patient showed a different personality from her usual character, such as being annoyed, scared, crying, or suddenly unable to remember words. After being discharged from the hospital, she developed generalized tonic-clonic seizure that lasted for 1 minute and she visited the emergency room of our hospital right away. At the time of arrival at the emergency room, the patient's level of consciousness was drowsy and showed repeated meaningless behaviors, such as repeating only "yes" to questions or repeating the last word of the question and making repeated hand gestures in the air. Her initial vital signs were as follows: a blood pressure of 146/79 mmHg, a body temperature of 37.1°C, a pulse rate of 95 beats per minute, and a respiratory rate of 16 beats per minute.

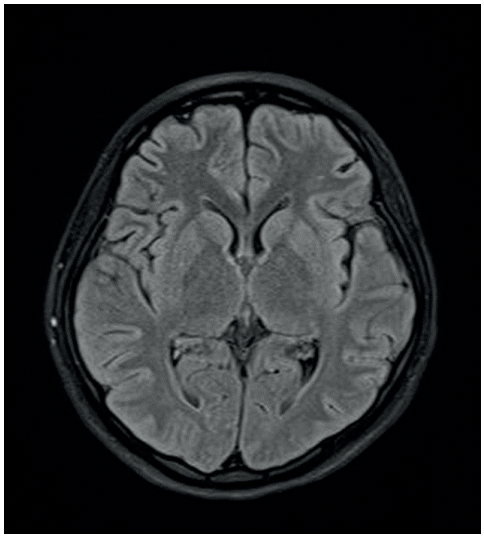

Fig. 1. Brain magnetic resonance imaging. Fluid-attenuated inversion recovery images showing no specific findings.

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In the neurological examination performed in the emergency room, there was no evidence of muscle weakness in the 4 extremities, and she expressed pain by twitching in response to the pain stimulus. Other detailed neurologic examinations, including cerebellar function tests, were limited due to poor cooperation. Laboratory tests did not show evidence of viral or bacterial meningitis on cerebrospinal fluid (CSF) analysis. CSF analysis showed clear appearance, pH 9.0, 20 white blood cells/μL (83% lymphocytes), 1,000 red blood cell/μL. The serum and CSF studies for possible autoimmune etiologies for encephalopathy, including antinuclear antibody and antineutrophil cytoplasmic antibodies, were unremarkable. Only nonspecific slow waves were observed on the EEG. For additional analysis, computed tomography of the abdomen and pelvis was performed, and a 3.8 × 3.0 cm mature ovarian teratoma was found in the right ovary (**Fig. 2**). An anti-NMDA receptor antibody test was performed under the suspicion of autoimmune encephalitis related to the teratoma, and right oophorosalpingectomy was performed after consultation with the Department of Obstetrics and Gynecology. The patient was treated with a course of intravenous immunoglobulin therapy (400 mg/kg/day for 5 days) and 2 cycles of methylprednisolone (1,000 mg/day for 5 days per cycle) and anticonvulsants were used to prevent the recurrence of epileptic seizures. At 10 days after the onset, presence of antibodies to NMDA receptor was confirmed in her serum and CSF study, and histopathologic findings after surgical management showed a mature cystic teratoma. Finally, she was diagnosed with NMDARE. During hospitalization, there were two events of epileptic seizure, so her anticonvulsants were adjusted accordingly, and her vital signs remained stable. However, several symptoms, such as functional impairment, dysarthria, dysphagia, and memory loss remained, and she was transferred to the Department of Rehabilitation Medicine for rehabilitation treatment.

At the time of transfer, the muscle strength of her bilateral upper and lower extremities was grade 4 by the Medical Research Council (MRC) scale. Her sensory function was normal and Korean Mini-Mental State Examination (K-MMSE) score was 20 out of 30 points. Her functional level was decreased compared to her muscle strength, so she needed a wheelchair for ambulation and needed maximum assistance in performing daily activities of living. She showed clinical dysphagia and took food through a nasogastric tube.

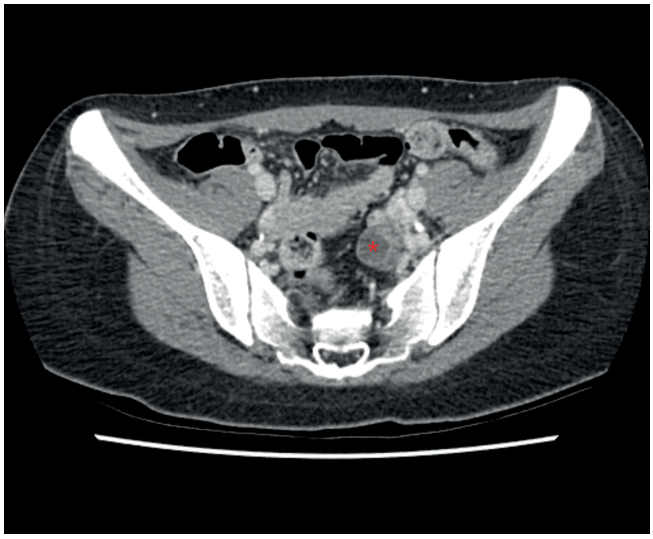

Fig. 2. Enhanced abdominopelvic computed tomography image. A 3.8 × 3.0 cm sized well-defined fat infiltrated, calcified lesion which was suspected as ovarian teratoma (asterisk).

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After transfer to the Department of Rehabilitation Medicine, comprehensive rehabilitation treatment, including physical therapy, occupational therapy, swallowing rehabilitation therapy, cognitive rehabilitation therapy, and speech therapy, was performed. Treatment was conducted 6 days a week, 3 hours a day during the weeks, and 1.5 hours on Saturday. Physical therapy consisted of muscle strengthening, dynamic balance training, and endurance training, and occupational therapy consisted of cognitive rehabilitation and swallowing rehabilitation along with fine motor exercise for improving hand function, grip strength training, and activities of daily living training. Speech therapy was also performed to address her deterioration of speech comprehension and expression, as well as decline in association ability and dysarthria.

Changes in the patient's function before and after 4 weeks of rehabilitation treatment were followed up through various assessments. Changes in muscle strength were measured on the MRC scale, balance ability on the Berg Balance Scale, activities of daily living performance on the modified Barthel Index, dysphagia on the penetration-aspiration scale through a video fluoroscopic swallowing study, language ability on the Korean version of the Western Aphasia Battery, and cognitive function on the K-MMSE and the Korean Wechsler Intelligence Scale for Children-IV (K-WISC-IV). In the follow-up evaluation after 4 weeks of treatment, the patient showed improvement in limb muscle strength and balance ability, ability to perform activities of daily living, language ability (**Table 1**). In addition, she was possible to eat general diet, drink liquids and take pills without symptoms of aspiration. However, regarding her cognitive function, the overall Full-Scale Intelligence Quotient (FSIQ) showed only a slight increase. When observing the subcategories of the test, it was found that the score slightly improved in verbal comprehension, perceptual reasoning, and processing speed, but her score decreased in the working memory subcategory (**Fig. 3**). In addition, despite receiving several sessions of cognitive rehabilitation treatment, attention declined after about 5 minutes from the start of each session and performance of the memory task deteriorated.

Table 1. Comparison of differences before and after 4 weeks of rehabilitation treatment

Variables	Initial	After 4 weeks of rehabilitation
Medical Research Council scale (Right/Left)		
Upper extremity	4/4	5/5
Lower extremity	4/4	5/5
Berg balance test	41	56
Modified Barthel Index	50	96
Korean version of the Western Aphasia Battery		
Aphasia Quotients	50	87
Spontaneous speech	9/20	16.5/20
Comprehension	100/200	174/200
Repetition	30/100	80/100
Naming	11/100	71/100
Korean Mini-Mental State Examination	20/30	30/30
Korean Wechsler Intelligence Scale for Children-IV		
Full-Scale IQ	51	62
Verbal Comprehension Index	52	67
Perceptual Reasoning Index	56	84
Working Memory Index	55	50
Processing Speed Index	62	74

IQ, intelligence quotient.

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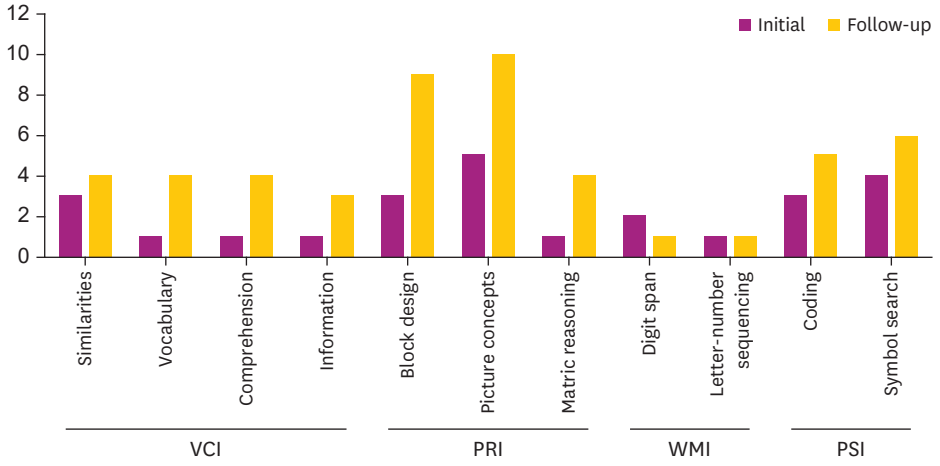

Fig. 3. Conversion score of subtests of Korean Wechsler Intelligence Scale for Children-IV.
VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index.

DISCUSSION

NMDARE is an autoimmune encephalitis first reported in 2007 by Dalmau et al. [5], which typically begins with nonspecific prodromal symptoms such as fever, diarrhea, and headache and then progresses to psychiatric and neurological symptoms and signs. In particular, because most patients are young women of Asian ethnicity, age, gender, and ethnicity are important factors related to disease [1,5,6]. Approximately 40% of reported NMDARE patients are younger than 18 years of age [7,8]. While psychiatric symptoms such as anxiety, paranoia, and hallucinations are common in adult patients, it has been reported that pediatric patients with NMDARE exhibit epileptic seizures or movement disorders more frequently than adult patients [9]. Decreased function of NMDA receptors is associated with cognitive impairment, and excessive stimulation of NMDA receptors causes excitotoxicity, which can lead to epileptic seizures and secondary neuronal degeneration and damage [10].

Since patients with NMDARE complain of several symptoms compared to their premorbid state, such as a decrease in their functional level and cognitive decline, early, appropriate, and active rehabilitative treatment is important for recovery. The patient in the present case was also transferred to the Department of Rehabilitation Medicine immediately after the acute medical treatment and underwent active and comprehensive rehabilitation treatment for 4 weeks. In the follow-up evaluation after treatment, there were marked improvements in balance ability, the ability to perform activities of daily living, and language ability. On the other hand, the FSIQ evaluated through K-WISC-IV showed no significant improvement from a score of 51 at her initial evaluation to a score of 62 at her re-evaluation after 4 weeks, and no improvement was shown in the working memory subcategory.

Yang et al. [11] reported a case of a 19-year-old female patient with ovarian teratoma, the authors stated that in patients with suspected NMDARE with teratomas, early surgery may help the better clinical outcome even before the diagnosis was confirmed. In the present case, surgical resection of teratoma was performed under NMDARE impression before antibodies to NMDA receptor was confirmed, and it is thought that early surgery had positive effect on the good prognosis. Kim et al. described that a 3-year-old girl diagnosed

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with NMDARE received intensive rehabilitation treatment and showed gradual motor and cognitive function improvement, but no detailed description of the rehabilitation treatment was provided [12]. Lim et al. [13] reported the clinical characteristics of adult NMDARE patients over 18 years of age. The authors classified favorable outcome and poor outcome based on the modified Rankin Scale, and mentioned decrease consciousness and dysautonomia as factors related to poor outcome. According to the authors' criteria, the present case belongs to a favorable outcome group even though she showed decrease consciousness initially, and although direct comparison with adult patients would be difficult, it is thought that the intensive rehabilitation treatment administered to the patient had a positive effect to her prognosis.

According to a previous study reviewing the progress of inpatient rehabilitation treatment for 26 pediatric NMDARE patients, approximately 65% of patients showed a favorable outcome when the effectiveness of rehabilitation treatment was evaluated with the Functional Independence Measure for children (WeeFIM) [14,15]. The authors reported that younger age and the presence of epileptic seizures were associated with unfavorable outcomes. However, even among patients with favorable outcomes, only a few cases reveal complete functional independence, and this trend was particularly prominent in the cognitive domain. However, since they did not use a detailed cognitive evaluation tool, they could not confirm the improvement pattern in the various domains of cognitive function. McKeon et al. [16] reported that episodic memory and executive functioning were most severely affected in children with NMDARE, but their profiles varied widely. Along with the present case, it can be seen that there is only a little improvement in cognitive function compared with that of other functional aspects, and the deterioration of working memory was notable on the K-WISC in particular. K-WISC-IV conducts 'digit span' and 'letter-number sequencing' tests to evaluate the subject's working memory. The digit span test measures the ability of temporary attention and continuous attention, and the letter-number sequencing test evaluates the ability of divided attention. The present patient showed marked impairment of working memory including global attention from the initial evaluation. The conversion score of digit span and letter-number sequencing tests were almost at the lowest level, and there was no significant improvement in the follow-up test.

NMDARE patients can cause wide-ranging cognitive declines, in particular prefrontal cortex dysfunction, especially in dorsolateral prefrontal cortex, leading to severe deficits in attention, working memory, and executive function [17]. In addition, there are some reports that memory function is degraded in patients with NMDARE, which may due to deterioration of attention and working memory during information encoding, an early stage of memory [18,19]. Finke et al. [20] reported that alterations in functional connectivity and widespread changes in white matter integrity might exist in patients with NMDARE even when routine clinical brain MRI shows normal findings. The authors reported that functional MRI showed decreased hippocampal connectivity, and diffusion tensor images showed white matter changes, which were particularly evident in the cingulum bundle. Damage to these lesions is associated with impairments in the patient's cognitive functions, particularly working memory and executive functions.

Considering that NMDARE is prevalent in childhood and adolescents, the recovery of cognitive function is a very important part of the patient's return to daily life. However, few studies have conducted detailed evaluations of cognitive functions, and in the cases reported to date, the recovery of cognitive function was slow and showed substantial improvement

rather than full recovery [1,4]. The present case report adds to the accumulation of evidence of neurocognitive deficits in patients with NMDARE. In the future, further research on cognitive function in NMDARE patients through various imaging techniques and detailed cognitive assessments are needed. In addition, attention and working memory may not be easily recovered within a short period. Therefore, when performing rehabilitation treatment for NMDARE patients, steady and long-term cognitive rehabilitation intervention for attention and working memory is needed.

In conclusion, this is a case report confirming the effect of early comprehensive rehabilitation treatment for children with NMDARE. Through active rehabilitative treatment, there was much improvement in balance ability, ability to perform daily activities, and language function. However, the recovery of cognitive function, especially working memory, appears to be slow. It is thought that steady treatment and further study for improving cognitive function in patients with NMDARE are needed.

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