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Anti-*N*-Methyl-D-Aspartate (Anti-NMDA) Receptor Encephalitis: Rapid and Sustained Clinical Improvement With Steroid Therapy Starting in the Late Phase

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Abstract

Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis is an autoimmune/paraneoplastic encephalitis, with neurologic and psychiatric symptoms. Early and aggressive therapy has been shown to improve prognosis although problems with executive functions and memory have continued for several years. A 15-year-old girl had a history of initial symptoms including behavioral difficulties, poor attention, and frequent seizures progressing to a catatonia-like state, 2.5 months after onset of initial symptoms. Anti–NMDA receptor antibodies were detected in serum and cerebrospinal fluid. Subsequent to treatment with methylprednisolone starting 3 months after onset, motor skills, responsiveness, self-care, and speech improved rapidly. Her neuropsychologica profile assessed after 2 months showed global difficulties predominantly in attention, executive functions, memory, and visual perception, which moderately recovered in the 7th and 24th months, respectively. Contrary to current literature supporting the positive impact of early immunomodulatory therapy, a dramatic resolution of major neurologic and psychiatric symptoms was detected with steroid treatment given in the late phase.

Keywords
autoimmune encephalitis, steroid treatment, cortical atrophy

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Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis has been recently reported as an autoimmune/paraneoplastic encephalitis, mostly affecting young females.[1-3] It is characterized by prodromal symptoms of a flulike disease followed by a combination of severe neurologic (seizures, abnormal movements and posture, loss of memory, decreased consciousness, and autonomic instability) and psychiatric symptoms (behavioral alterations, catatonia, and psychosis). The disorder is often misdiagnosed as viral or idiopathic encephalitis, neuroleptic malignant syndrome, and psychosis, and initially patients are frequently evaluated by a psychiatrist with the suspicion of drug abuse or an acute psychotic break. Enhanced awareness of the typical presentation can increase the index of suspicion and facilitate initiation of appropriate treatment. Previous data demonstrate that in the early phase (first 40 days), immunomodulatory therapy improves prognosis although problems with executive functions and memory have sustained for several months.[4,5]

We report herein the remarkable neurologic and psychiatric recovery of a female adolescent with anti–NMDA receptor encephalitis that occurred following the first weeks of the first-line therapy starting 3 months after onset and also neurocognitive improvement assessed sequentially in a follow-up period of 2 years.

Case Summary

A 15-year-old girl with no previous medical and psychiatric history had hypersomnia, attention problems, nervousness, and childlike behavior. After about 1 month, she had pain in her left arm and chest, orofacial twitching followed frequently by generalized tonic clonic seizures. The patient's status worsened to behavioral regression, disorientation, memory deficits, delirium, and visual hallucinations during the second month.

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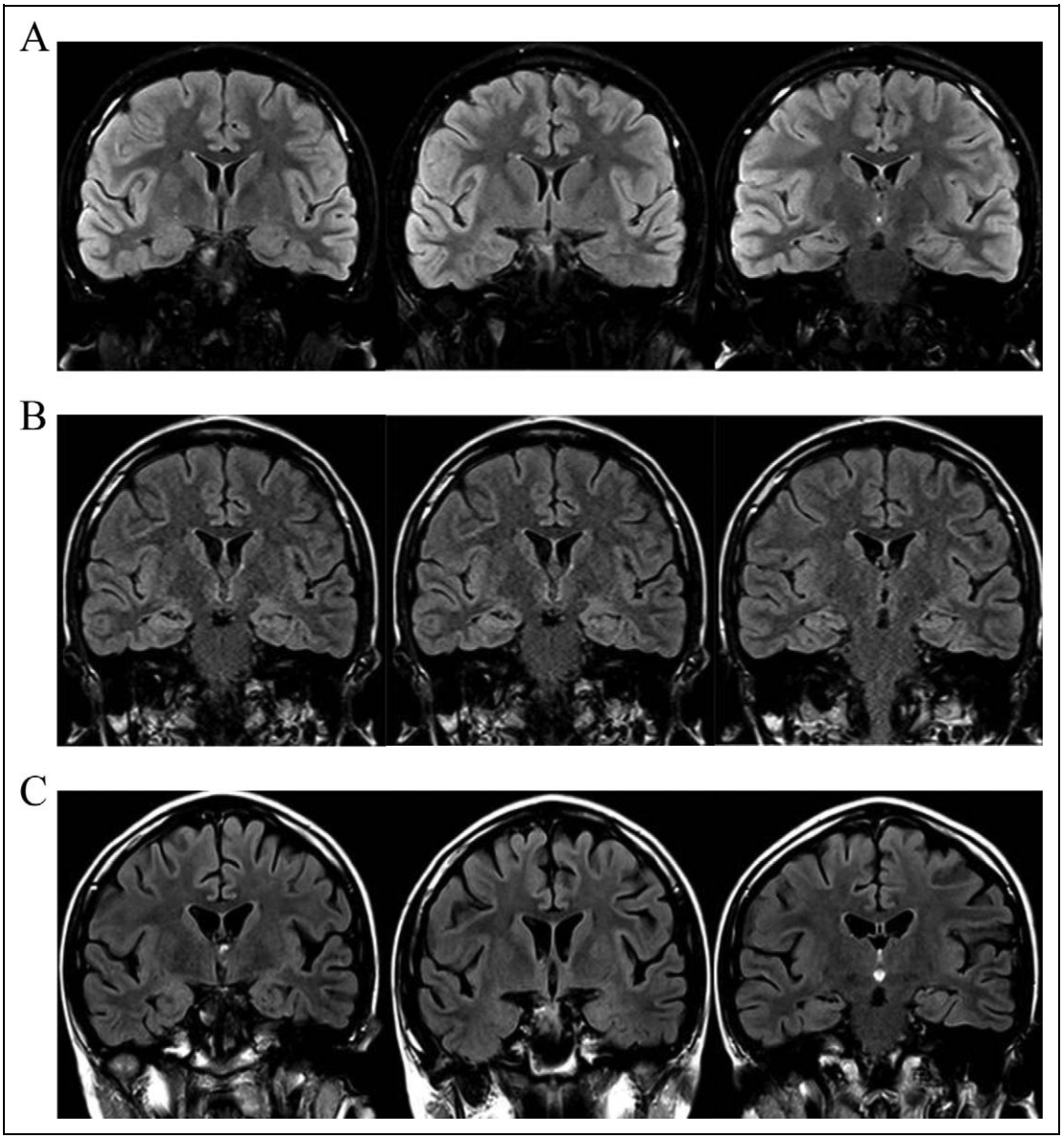

Figure 1. (A) Baseline coronal fluid-attenuated inversion recovery magnetic resonance images (MRIs) taken at the initial phase of the disease demonstrating normal size of hemispheric sulci and lateral ventricles. (B) Coronal fluid-attenuated inversion recovery MRIs show mild dilation of hemispheric sulci and lateral ventricles. (C) Coronal fluid-attenuated inversion recovery MRIs show increased dilation of hemispheric sulci and lateral ventricles compared to previous images.

The patient was referred to our clinic in a catatonia-like state (unresponsive to verbal and visual stimuli, making unintelligible sounds with agitation and crying episodes) about 2.5 months after onset of initial symptoms. She was bedridden and fed by nasogastric tube. Evaluation for etiology of encephalitis and encephalopathy (endocrine, metabolic, toxic, and rheumatologic) revealed no abnormality. Repeated cranial magnetic resonance (MR) examinations were normal (Figure 1A). Disorganized background with intermittent generalized rhythmic delta activity and frequent frontal epileptiform discharges were the main findings of electroencephalography (EEG). Routine cerebrospinal fluid examinations were normal except positive oligoclonal bands and increased IgG index. Autoantibody screening of serum and cerebrospinal fluid was negative except for positive anti-NMDA receptor antibody titers (2 positive in serum and 1 positive in cerebrospinal fluid). Extensive tumor screening was inconclusive.

Intravenous immunoglobulin (1 g/kg/d, for 5 days) and subsequently methylprednisolone 1 g/d intravenous pulse was started about 3 months after initial onset of symptoms. Following 5 days of pulse therapy, oral prednisolone therapy was planned in a dosage of 1 mg/kg/d during the first month and very slow tapering until the end of third year of therapy.

There was a slight and temporary clinical improvement with intravenous immunoglobulin treatment. Subsequent to treatment with methylprednisolone therapy, responsiveness, social

communication, and speech improved rapidly in 2 weeks. In the second day of steroid treatment, she had less confusion and became aware of her surroundings. In the fifth day, she was more alert, was repeating some words, and followed some simple commands. Within 15 days, she began to walk and eat independently, regained her urine control, and made short conversations. Seizures were controlled with levetiracetam and valproate.

The patient underwent comprehensive neuropsychological testing including general intelligence quotient (IQ) (Wechsler Intelligence Scale for Children–Revised), attention and executive functions (Wisconsin Card Sorting Test; Visual Memory Span, subtest of Wechsler Memory Scale–Revised; Stroop Task; Category Fluency), verbal learning and memory function (California Verbal Learning Test), naming (Boston Naming Test), and visual perception (Visual Perception Test) in the 2nd, 7th, and 24th months of treatment. At the initial assessment, verbal, performance, and total IQ scores were 46, not measurable, and 40, respectively. Attention and executive functions and immediate free recall were severely affected. Visual and auditory immediate and working memory and naming were moderately affected. She had psychomotor slowing and was anxious about her performance. In the 7th month follow-up assessment, IQ scores prominently improved (verbal IQ = 85, performance IQ = 74, and total IQ = 78). Attention and executive functions, verbal learning memory skills, and visual perception demonstrated moderate improvement. The final evaluation 2 years after onset did not demonstrate a significant change compared to the improvements detected during the first 6 months of recovery phase.

Anti–NMDA receptor antibodies were negative in cerebrospinal fluid and 1 positive in serum 1 month after treatment started. Serum titer of antibodies became negative 1 year later.

EEG recorded at the end of the third week showed normalization of background activity with less amount of frontal epileptiform activity, which completely resolved in the second month.

Cranial MR examinations done in the 10th and 18th months demonstrated progressing cerebral atrophy (Figure 1B and C). Tumor screening done every 6 months was negative.

Discussion

The wide spectrum of neurologic, cognitive, and psychiatric symptoms in anti–NMDA receptor encephalitis, especially in the early phase, presents a diagnostic challenge to pediatric neurologist and child psychiatrists. The initial symptoms of our patient were mainly neurobehavioral and were followed by seizures progressing to catatonia-like symptoms during about 2.5 months. During this period, the patient did not receive any definite diagnosis.

Previous studies reported that early (less than 40 days) first-line immunomodulatory treatment (mostly intravenous immunoglobulin and glucocorticosteroid) leads to a more rapid recovery and decreased morbidity or relapse.[1,5,6] A recently published long-term follow-up (median 24 months) study with a large cohort (211 pediatric cases) demonstrated that early initiation of immunotherapy (mean 21 days in pediatric cases) and lower severity of symptoms are 2 independent predictors of good outcome.[4] In patients with delayed diagnosis or insufficient response to first-line treatment, a second-line immunotherapy offers a better outcome.[3,4,7] Contrary to those data, we observed a dramatic recovery in our patient in both clinical and laboratory settings, despite the presence of severe and long-lasting clinical symptoms and late onset of immunomodulatory therapy. For that reason, instead of adding one other immunomodulatory agent as a second-line treatment, we preferred long-term treatment of oral prednisolone with decreasing doses to prevent relapses. The presence of initial dramatic and sustained clinical response to glucocorticosteroids, resolution of anti–NMDA receptor titers of cerebrospinal fluid, and recovery of background activity of EEG in the first month of the treatment and lack of deterioration of clinical or laboratory findings at the end of 2 years are in the favor of that treatment. However, we could have assessed the patient's probable recovery potential if she had received early treatment.

Recovery from anti–NMDA receptor encephalitis occurs as a multistage process that happens in the opposite direction of symptom presentation. Patients slowly wake from coma as they are able to follow simple commands and can have appropriate interactions before they recover verbal functions. In a large series of pediatric cases, improvement in almost half of patients did not occur in the first month of the treatment, but recovery occurred within 24 months of treatment in 81% of patients.[4] Dramatic clinical recovery in our case occurred shortly after treatment in terms of consciousness, responsiveness, self-care, speech, and motor abilities, which can be related to disappearance of cerebrospinal fluid antibodies. Positive NMDA receptor antibodies were reported after treatment of the first episode when only partial clinical remission had been obtained.[2] However, in our patient, serum titers decreased but were still positive when clinical recovery was remarkable whereas cerebrospinal fluid titers became negative. Recent data demonstrated that assessment of outcome and planning of treatment should be based on clinical findings rather than antibody titers, which invariably decrease with immunotherapy.[4]

Persistent cognitive deficits, especially in attention, executive functions, and memory are the well-known major long-term morbidity of anti–NMDA receptor encephalitis.[1,2,8,9] Early and aggressive therapy is related to good cognitive outcome. Similar findings were reported in 2 pediatric cases.[10] There is evidence that cognitive recovery can be incomplete or delayed by many months. The limited recovery of cognitive functions in our patient can be secondary to the late onset of immunotherapy and also progressive cortical atrophy.

Contrary to a previous study that reported cortical atrophy in 2 cases in the active phase of the disease and improvement of atrophy 5 to 7 years later,[11] we observed cortical atrophy in the late recovery period when serum and cerebrospinal fluid titers became negative. Generalized atrophy was reported in a series of children with probable autoimmune encephalopathies.[6] The lack of cortical atrophy in the active phase of the disease is

contrary to the possible acute effects of high-dose methylprednisolone or recurrent seizures. However chronic low dose corticosteroids could also contribute to irreversible loss of tissue secondary to steroid-induced protein catabolism.[12] Cerebral effects of glucocorticoids in later childhood as apparent brain atrophy and cognitive dysfunctions have been reported in various neurologic and nonneurologic diseases.[13-15] Chronic valproate therapy can also have possible effect for atrophy.[16] We expect that long-term follow-up in our patient might enlighten the future of cortical atrophy.

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Author Contributions

All authors contributed to the data collection. DT had the primary responsibility for writing the article. ACO contributed to the first draft of the article.

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