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Autism-Like Presentation of Possible Autoimmune Encephalitis With Complete Recovery After Immunotherapy

Yongmoo Kim*
Yoonhyuk Jang*
Seolah Lee
Kon Chu

Department of Neurology,
Seoul National University Hospital,
Seoul, Korea

Dear Editor,

Autoimmune encephalitis is a neurological disorder characterized by an autoimmune response that leads to symptoms such as altered mental status, memory loss, clinical seizures, psychiatric symptoms, language dysfunction, and movement disorders including dyskinesia.[1,2] When patients exhibit symptoms indicative of autoimmune encephalitis but lack detectable autoantibodies, they can be classified as having seronegative autoimmune encephalitis based on specific criteria.[2] In such cases, immunotherapy has shown efficacy in improving the patient's condition.[3]

Autism spectrum disorder (ASD) is a developmental condition characterized by atypical social skills, repetitive behaviors, and challenges with verbal and nonverbal communication.[4] ASD is diagnosed based on the presence of observable behavioral traits, and its prevalence has increased in recent decades. The exact causes of this increase have not yet been established, but factors such as expansion of the diagnosis criteria for ASD have been suggested.[5] Moreover, multiple variables appear to be linked to the risk and onset of autism, including immune dysfunctions and early infections with viral agents such as the rubella virus and cytomegalovirus.[6] It is therefore crucial to conduct a thorough differential diagnosis in pediatric cases of autoimmune encephalitis presenting with cognitive impairment and psychiatric symptoms resembling autistic traits.[7] In this context, we present a case of a young patient exhibiting symptoms similar to autism in whom immunotherapy resulted in complete recovery.

A 15-year-old female was admitted to a psychiatry hospital due to visual hallucinations, disorganized speech, and abnormal behavior that had developed 1 month previously. At the age of 4 years she exhibited no problems when being separated from her parents, but faced difficulties when interacting with same-aged peers. In the first grade of elementary school she showed unclear pronunciation, reduced expressive abilities, and an IQ score of 44. Basic math and writing skills were present, and personal interests such as watching TV, listening to music, and playing the piano were maintained.

At the age of 15 years she experienced the sudden onset of an inability to concentrate when communicating and exhibited an unusual smile while talking to herself, along with visual hallucinations of seeing a ghost. Negativism and mutism were observed, along with catatonic features such as holding hands in odd positions and immobility (Supplementary Fig. 1 in the online-only Data Supplement). The addition of risperidone and olanzapine successfully resolved the irritability, but the visual hallucinations persisted. She also simultaneously experienced nausea and vomiting, and so was transferred to the neurology department since staring into space was suggestive of absence seizure.

A bedside examination revealed impaired comprehension of language but no other focal neurological deficit. She presented with a modified Rankin Scale (mRS) score of 3 and a score on the Clinical Assessment Scale for Autoimmune Encephalitis (CASE)[8] of 5. The cerebrospinal fluid profile showed a normal white blood cell count of 1/mm^3 and mild protein

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Correspondence
Kon Chu, MD, PhD
Department of Neurology,
Seoul National University Hospital,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea
Tel +82-2-2072-1878
Fax +82-2-2072-7424
E-mail stemcell.snu@gmail.com

*These authors contributed equally to this work.

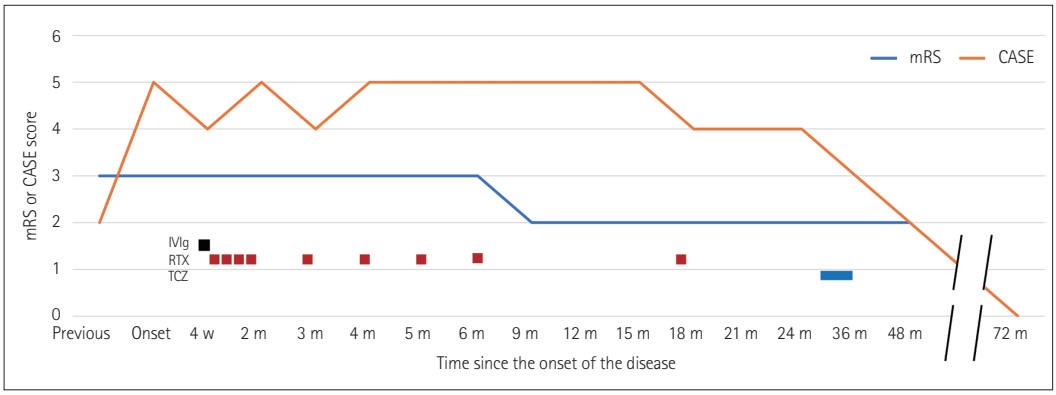

Fig. 1. Clinical course of the patient before and after immunotherapy. The patient's symptoms recovered gradually after sequential immunotherapy, as shown by scores on the mRS and the CASE. Two weeks after discharge from the hospital she exhibited disorganized thoughts, expressing a desire to go out and find her mother, even when her mother was standing right beside her. This was the first instance of aggravation since the discharge date. The frequency of abnormal speech improved after the fifth RTX treatment, but it worsened again with increased repetitive speech after 3 months. However, the overall mRS score decreased from 3 at baseline to 2 after the initiation of RTX and subsequent monthly maintenance. The final mRS score at 72 months from the onset of symptoms was 0. The administered doses for each treatment regimen were as follows: IVIg at 2 g/kg divided for 5 days, RTX at 375 mg/m^2 body surface, TCZ at 4 mg/kg for the first, fifth, sixth, and seventh doses, and at 8 mg/kg for the second, third, and fourth doses. CASE, Clinical Assessment Scale for Autoimmune Encephalitis; IVIg, intravenous immunoglobulin; m, months; mRS, modified Rankin Scale; RTX, rituximab; TCZ, tocilizumab; w, week.

elevation at 52.0 mg/dL. The findings of brain magnetic resonance imaging and electroencephalography were normal. Cancer screening revealed a 3.5-cm enhancing mass in the liver, suggesting focal nodular hyperplasia or adenoma. However, all synaptic and intranuclear autoantibody tests including for paraneoplastic autoantibodies were negative with the exception of the serum microsome antibody, which has inadequate clinical significance (Supplementary Material in the online-only Data Supplement).

The diagnosis was challenging since the patient was not fully consistent with the criteria for ASD.[4] Her symptoms met the criteria for possible autoimmune encephalitis,[2] and so intravenous immunoglobulin and rituximab were applied as initial immunotherapy, and tocilizumab was added for additional immune modulation (Fig. 1).[9] This sequential immunotherapy resulted in her hallucinations and abnormal behavior disappearing, and she fully recovered to an mRS score of 0 and a CASE score of 0. She subsequently joined a social workspace as a bakery staff member.

Patient with childhood encephalitis can not only present psychosis, language dysfunction, and behavior disorder, but also decreased social skills, which are common epidemiological features of ASD[8] (Supplementary Table 1 in the online-only Data Supplement).

Our patient demonstrated persistent deficits in social communication that were not attributable to emotional factors, and her nonverbal communication skills were not impaired. This discrepancy between the criteria outlined in Diagnostic and statistical manual of mental disorders, fifth edition[4] and fourth edition[10] for autism prompted further consideration of alternative diagnoses. The absence of autoantibodies in the present case along with the rapid progression of psychiatric symptoms, including episodes of staring into space and visual hallucinations, suggested autoimmune encephalitis (Supplementary Table 2 in the online-only Data Supplement). The patient's complete recovery following immunotherapy implies that her syndrome derived from inflammation or neural system activation mediated by autoantibodies. It is therefore important to exercise caution when making diagnoses, particularly in cases of childhood autism and childhood autoimmune encephalitis, since early clinical manifestations can vary due to the influence of development. Additional research may be warranted to explore the presence of antibodies associated with autoimmune encephalitis in individuals diagnosed with autism.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0245.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Yongmoo Kim https://orcid.org/0000-0003-4062-2616
Yoonhyuk Jang https://orcid.org/0000-0002-3346-3357
Seolah Lee https://orcid.org/0000-0002-1285-1334
Kon Chu https://orcid.org/0000-0001-5863-0302

Author Contributions

Conceptualization: Kon Chu. Data curation: Yongmoo Kim. Supervision: Yoonhyuk Jang, Kon Chu. Visualization: Yongmoo Kim. Writing—original draft: Yongmoo Kim. Writing—review & editing: Yongmoo Kim, Yoonhyuk Jang, Seolah Lee.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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