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LETTER TO THE EDITOR / EDİTÖRE MEKTUP

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Pediatric Refractory Anti-GAD65 Positive Autoimmune Encephalitis Successfully Treated with Rituximab

Rituximab ile Başarıyla Tedavi Edilen Pediyatrik Dirençli Anti-GAD65 Pozitif Otoimmün Ensefalit

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Anahtar Kelimeler: Anti-GAD65, otoimmün ensefalit, rituksimab, status epileptikus

Dear Editor,

Autoimmune encephalitis (AE) is a group of encephalitides caused by an autoimmune response targeting antigens of the central nervous system. The incidence in the pediatric population is 1/100.000. AE has a wide spectrum of clinical manifestations. Children with AE may develop significant neurological symptoms within a short period, including cognitive dysfunction, behavioral changes, movement disorders, seizures, and disturbances of consciousness[1,2]. The diagnosis of AE is supported by clinical findings, neuroimaging, cerebrospinal fluid (CSF) analysis, and antibody tests. Recently, many AE-associated antibodies have been identified; anti-glutamic acid decarboxylase 65 (GAD65) is one of them. GAD65 antibodies are associated with neurological conditions such as stiff-person syndrome, AE, and cerebellar ataxia[3]. Here, we will present an anti-GAD65-positive AE case that developed into super-refractory status epilepticus (SE) while being followed for focal epilepsy and which we successfully treated with rituximab.

A previously healthy 18-month-old female patient presented with a focal tonic seizure. Prenatal and postnatal histories were unremarkable. Neurodevelopment was normal. At 18 months of age, brain magnetic resonance imaging (MRI) was normal, and electroencephalography (EEG) showed focal spike-and-slow-wave discharges in the right temporal area. Follow-up MRI at 9 years of age showed focal cortical dysplasia (FCD) involving the right frontoparietal region (Figure 1A). Valproic acid was given as the first anti-seizure medication (ASM). The patient continued to have focal seizures during follow-up; therefore, carbamazepine, lamotrigine, levetiracetam, and topiramate were added.

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At 14 years of age, she presented to the emergency department with seizures. Seizure semiology was characterized by right-sided myoclonic-clonic movements of the face and arm, with impaired consciousness. Due to ongoing seizures, the patient was diagnosed with SE and managed according to current protocol[4]. Brain MRI performed during this period showed an edematous appearance in the right cerebral hemisphere and hyperintensity in the right occipital cortical area on T2A and fluid-attenuated inversion recovery (FLAIR) sequences (Figure 1B, C). The EEG performed on the first day showed epileptiform discharges originating from the temporal region of the right hemisphere, and these discharges occasionally spread intrahemispherically. A few days later, EEG monitoring in the pediatric intensive care unit revealed epilepsia partialis continua (Figure 2).

The patient had seizures that could not be controlled with ASM for more than 24 hours. Follow-up was initiated for the patient receiving mechanical ventilation. Therefore, it was classified as super-refractory SE. Because of suspected autoimmune involvement, intravenous immunoglobulin (IVIg) was administered at a dose of 1 g/kg. The patient responded well to this treatment, with seizures decreasing by more than 50%. A few days later, because of persistent seizures, pulse methylprednisolone therapy was initiated at 1.000 mg/day for 10 days. After this treatment, there was an improvement in consciousness and the general condition. We added lacosamide at 4 mg/kg/day to the treatment regimen to benefit from its effects on focal seizures. CSF AE panel was unremarkable, which includes AMPA1, AMPA2, anti-GABA B, anti-DPPX, anti-NMDA, anti-CASPR, and anti-LGI1 antibodies. The CSF AE panel, which included antibodies to AMPA1, AMPA2, GABA B, DPPX, NMDA, CASPR, and LGI1, was unremarkable. Thyroid and celiac

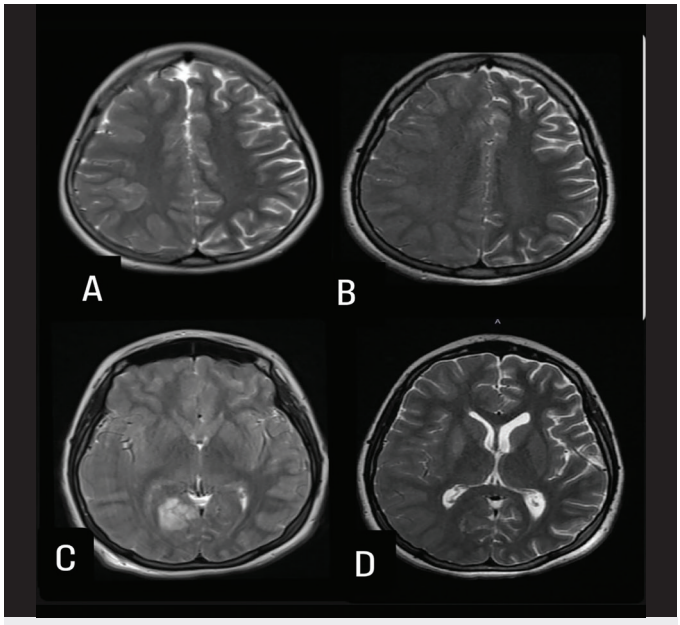

Figure 1. A) Cortical thickening and dysgyria are observed in the right frontoparietal area. This is considered to be focal cortical dysplasia. B, C) The right hemisphere of the brain appears edematous compared with the left hemisphere. Hyperintensity is observed in the right occipital cortex on T2A and FLAIR sequences. D) On the control MRI performed after immunotherapy, we observed that the hyperintensity on T2 and FLAIR imaging in the right occipital region disappeared

FLAIR: Fluid-attenuated inversion recovery, MRI: Magnetic resonance imaging

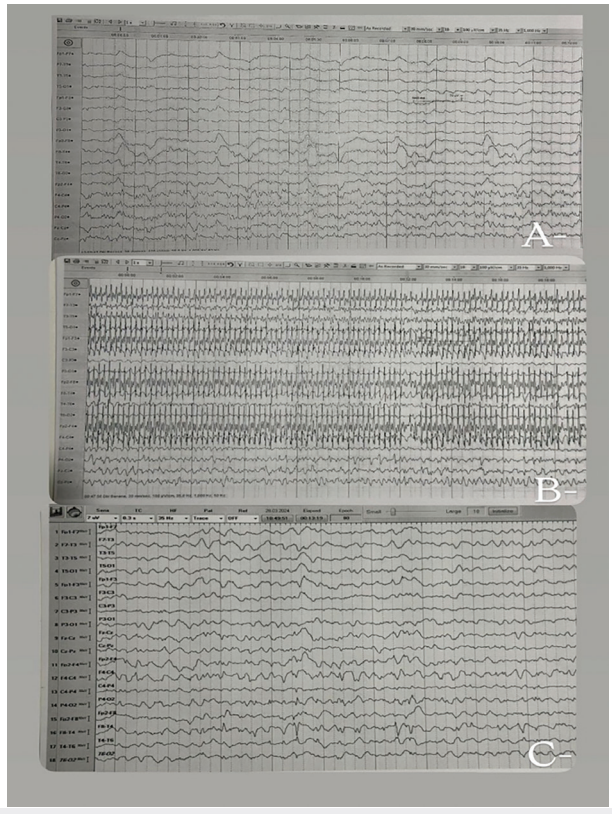

Figure 2. EEG images. A) Asymmetry between the right and left hemispheres is observed. The frequency and amplitude are higher in the right hemisphere than in the left hemisphere. B) Ictal EEG recording was performed during status epilepticus while intubated. C) After the rituximab treatment, phase-matching spike slow wave discharges are observed in the area corresponding to the right T4 electrode

EEG: Electroencephalography

antibodies, myelin oligodendrocyte glycoprotein antibody, aquaporin-4 antibody, ANA, and anti-dsDNA were negative. Serum anti-GAD65 antibody, measured by enzyme-linked immunosorbent assay, was 35 IU/mL (normal range <10 IU/mL). Other CSF studies, including glucose, protein, leukocyte count, culture, polymerase chain reaction, cytology, and oligoclonal bands, were unremarkable. CSF GAD65 antibody testing was planned for definitive diagnosis; however, it could not be performed due to financial constraints and limitations in health insurance coverage.

The patient was diagnosed with probable anti-GAD65-positive AE. We decided to administer rituximab to the patient who experienced recurrent seizures after a temporary seizure-free period following steroid treatment. Comprehensive evaluations were performed, including serological testing, measurement of Ig levels, lymphocyte panel, vaccination status, and chest X-ray. She had no active, serious infection that would prevent her from receiving rituximab. Then, we administered rituximab 375 mg/m^2 weekly for 4 weeks. After the first dose, we achieved complete resolution of seizures, and she was extubated. She was free from seizures after four weeks of treatment. We planned monthly IVIg treatment for the patient for at least 6 months, with rituximab treatment to commence after that period. On the control MRI, we observed that the hyperintensity in the right occipital area on T2 and FLAIR sequences had resolved. (Figure 1D). She was discharged in good general condition with spontaneous breathing and enrolled in a home-based rehabilitation and physical therapy program.

The diagnostic process for AE in children is challenging due to the wide clinical spectrum. Antibody detection plays a critical role in this process. Anti-GAD65 AE should be considered in the evaluation of all suspected cases. Seizures are typically refractory in anti-GAD65-positive AE. Steroids, IVIg, and plasmapheresis are first-choice treatments. If there is no response to first-line treatments, different treatment options should be considered. Rituximab is an anti-CD20 monoclonal antibody that targets CD20-positive B cells. While rituximab is an anti-B-cell therapy, it has indirect effects on T cells. B cells often act as "antigen-presenting cells" that activate T cells. By depleting B cells, rituximab deprives T cells of this activating signal, thereby attenuating an overactive T-cell response in autoimmune conditions. It is a safe and effective treatment for many patients with AE[5-7]. In our patient, we administered rituximab after IVIg and steroid therapy because the seizures were refractory. In a review in 2025, rituximab was shown to have a favorable prognosis rate of 80% in cases of AE that did not respond to first-line treatments, especially in patients under 18 years of age or with disease duration ≤180 days[8]. After this treatment, not only seizure resolution but also an improvement in the general clinical condition of our patient were seen.

Although CSF GAD65 antibody testing could not be performed because of financial constraints, the clinical features were highly suggestive of AE. In conjunction with serum GAD65 antibody positivity and a favorable response to immunotherapy, these findings strongly supported a diagnosis of probable GAD65-associated AE.

Our patient had a pre-existing diagnosis of FCD and subsequently developed AE during follow-up. Although chronic neuroinflammatory changes and blood-brain barrier disruption have been reported in FCD, a causal relationship between these findings and the development of AE has not been established. The possible interaction between FCD-associated neuroinflammation and autoimmune processes remains speculative and represents an emerging area of research[9].

Before rituximab treatment, the patient should be free of active or serious infections. A comprehensive evaluation by the immunology and infection departments is recommended. This evaluation includes tests such as a complete blood count, a lymphocyte panel, Ig levels, detailed serology, and a chest X-ray. Post-treatment monitoring is conducted jointly with the immunology department. During this period, attention should be paid to the risk of infection, and live vaccines should be avoided during the first year[10].

Seizure control in anti-GAD65-positive AE cases can be challenging. Rituximab should be considered a safe and effective treatment for patients with AE who have SE that is resistant to first-line treatment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Concept: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Design: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Data Collection or Processing: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Analysis or Interpretation: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Literature

Search: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U., Writing: G.D., Ö.Ö.M., S.S.K., Y.G., F.B., G.S.U.

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