Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2025.90277
J Pediatr Emerg Intensive Care Med

Successful Treatment of an 11-Year-Old Boy with Febrile Infection-Related Epilepsy Syndrome

On Bir Yaşında Febril Enfeksiyonla İlişkili Epilepsi Sendromu Tanılı Bir Erkek Çocuğun Başarılı Tedavisi

Mustafa Doğan Karabacak[1], Gülhan Atakul[1], Gülçin Akıncı[2], Mehmet Coşkun[3], Emre Sağlam[1], Selçuk Sinan Çelik[1], Aycan Ünalp[2], Hasan Ağın[1]

[1]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İzmir, Türkiye

[2]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Neurology, İzmir, Türkiye

[3]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Radiology, İzmir, Türkiye

Abstract

Febrile infection-related epilepsy syndrome (FIRES) is a subtype of new-onset refractory status epilepticus characterized by refractory status epilepticus following a febrile infection. It is associated with high morbidity and mortality, particularly in children and adults. However, its etiology often remains unclear. The ketogenic diet therapy (KDT), a proven treatment method for drug-resistant epilepsy, continues to be investigated for its mechanisms and efficacy.

This case report presents an 11-year-old male diagnosed with FIRES, successfully managed through a multidisciplinary approach and KDT. The patient initially received oral antibiotics for an upper respiratory tract infection but later developed altered consciousness and drowsiness, raising suspicion of encephalitis. He was transferred to the intensive care unit, where refractory status epilepticus occurred 11 days after the onset of fever. Given the clinical presentation, brain magnetic resonance imaging findings, and cerebrospinal fluid analysis consistent with autoimmune encephalitis, the patient was treated with intravenous immunoglobulin, pulse steroid therapy, and plasmapheresis. Despite these interventions, seizure activity persisted, prompting initiation of a classic ketogenic diet at a 3:1 ratio. Seizure activity ceased by the eighth day of KDT. Long-term follow-up revealed that the patient remained seizure-free without antiepileptic drugs, with improved electroencephalography findings.

This case highlights the potential role of the ketogenic diet in the early diagnosis and treatment of FIRES. KDT, in combination with immunotherapy, has demonstrated effectiveness in controlling

Öz

Febril enfeksiyonla ilişkili epilepsi sendromu (FIRES), yeni başlangıçlı dirençli status epileptikusun bir alt tipi olup, febril enfeksiyon sonrası başlayan refrakter status epileptikus kliniği ile karakterizedir. Bu durum, özellikle çocuklarda ve yetişkinlerde yüksek morbidite ve mortalite ile ilişkilidir. Ancak, etiyolojisi çoğunlukla belirsizdir. İlaca dirençli epilepsi hastalarında ketojenik diyet tedavisi (KDT) patogenezi araştırılmaya devam eden, etkinliği kanıtlanmış bir tedavi yöntemidir.

Bu vaka sunumunda, FIRES tanısı almış 11 yaşında bir erkek hastanın, multidisipliner yaklaşım ve KDT ile başarıyla yönetilmesi ele alınmıştır. Hasta, üst solunum yolu enfeksiyonu tanısıyla oral antibiyotik tedavisi almış ancak sonrasında kliniğinde bilinç bulanıklığı, uykuya eğilim gelişmesi nedenilye ensefalit şüphesiyle yoğun bakım ünitesine transfer edilmiştir. Hastada ateşin başlangıcıdan on bir gün sonra başlayan dirençli status epileptikus kliniği gelişti. Klinik değerlendirme, beyin manyetik rezonans görüntüleme ve beyin omurilik sıvısı analizleri sonucu otoimmün ensefalit ön planda düşünülmüş ve intravenöz immünoglobulin, pulse steroid tedavisi ile plazmaferez uygulanmıştır. İlk tedavilere rağmen nöbet aktivitesi devam eden hastaya klasik ketojenik diyet 3:1 oranında başlatılmıştır. KDT'nin başlamasından sonraki sekizinci günde nöbet aktivitesi durmuştur. Uzun dönem izlemde, hasta antiepileptik tedavi olmaksızın nöbetsiz kalmış ve elektroensefalografi bulgularında düzelme görülmüştür.

Bu vaka, FIRES'ın erken tanı ve tedavisinde ketojenik diyetin potansiyel rolünü vurgulamaktadır. KDT'nin, immünoterapilerle birlikte, özellikle akut fazda epileptik nöbetlerin kontrolünde etkili olabileceği ve uzun

Address for Correspondence/Yazışma Adresi: Mustafa Doğan Karabacak, University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İzmir, Türkiye
E-mail: mustafadogankarabacak@gmail.com **ORCID ID:** orcid.org/0000-0002-1923-7492
Received/Geliş Tarihi: 13.07.2024 **Accepted/Kabul Tarihi:** 03.03.2025 **Epub:** xxxxxxxx
Cite this article as: : Karabacak MD, Atakul G, Akıncı G, Coşkun M, Sağlam E, et al. Successful treatment of an 11-year-old boy with febrile infection-related epilepsy syndrome. J Pediatr Emerg Intensive Care Med. [Epub Ahead of Print]

Abstract

seizures during the acute phase and achieving long-term seizure-free outcomes.

Keywords: Status epilepticus, autoimmune encephalitis, limbic encephalitis, new onset refractory status epilepticus, febrile infection related epilepsy syndrome, ketogenic diet

Öz

dönemde nöbetsiz bir seyir sağlayabileceği gösterilmiştir.

Anahtar Kelimeler: Status epileptikus, otoimmün ensefalit, limbik ensefalit, yeni başlangıçlı refrakter status epilepticus, ateşli enfeksiyon ilişkili epilepsi sendromu, ketojenik diyet

Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a subcategory of new-onset refractory status epilepticus (NORSE) that requires a febrile infection occurring between 24 hours and 2 weeks before refractory status epilepticus (RSE), with or without fever at the onset of status epilepticus.[1]

In the treatment of patients with RSE, the ketogenic diet therapy (KDT) is gaining popularity, and its efficacy is still under investigation. The ketogenic diet was developed in the 1920s and is a high-fat, low-carbohydrate, moderate-protein diet.[2] In this treatment, the proportions of the ketogenic diet, and the needs for calories and protein are calculated individually and require close monitoring.

FIRES is associated with high morbidity and mortality in children and adults. Despite progress in the clarification of NORSE/FIRES as a clinical syndrome, understanding of the underlying pathogenic mechanisms is limited. A cryptogenic cause accounts for up to 50%[3] of cases, with these cases reported to have worstworse outcomes.[4] Due to the diagnostic challenges and the rarity of this condition, we present this case along with the successful treatment process implemented in the intensive care unit (ICU).

Case Presentation

An 11-year-old male patient presented with a sore throat, a maculopapular rash on the trunk, and axillary temperature exceeding 38 °C. During his initial outpatient clinic visit, he was diagnosed with an upper respiratory tract infection due to fever and sore throat that had started the same day. Oral amoxicillin-clavulanate was prescribed, and the patient was discharged. After three days of antibiotic therapy, the rash resolved, but due to persistent fever and fatigue, the patient returned to our hospital.

On the fourth day of oral amoxicillin-clavulanate therapy, the patient was hospitalized for further evaluation and management due to a refractory febrile state. Physical examination revealed hyperemia in the oropharynx, but the tonsils appeared normal. Other system examinations were unremarkable, with no findings suggestive of central nervous system infection. Intravenous (IV) ampicillin-sulbactam and IV hydration were initiated, and vital signs were closely monitored. Fever did not recur following admission. However, on the second day, the patient developed drowsiness and altered consciousness, raising suspicion of encephalitis. Consequently, he was transferred to the pediatric intensive care unit (PICU) for further management.

The patient's personal and family history revealed no significant findings. During hospitalization, his vital signs were as follows: body temperature, 36.6 °C; heart rate, 96/min; oxygen saturation, 98%; respiratory rate, 22/min; and blood pressure, 115/65 mmHg. Neurological examination findings were mostly normal, including intact eye movements and normal direct/indirect light reflexes, but with a Glasgow Coma Score of 13. No signs of meningeal irritation were noted. Deep tendon reflexes were normal in all extremities, with muscle strength assessed as 5/5. Head and neck examination revealed hyperemia in the oropharynx, but the tonsils appeared normal. No rash or other skin findings were observed. On presentation, biochemical analysis demonstrated normal hepatic and renal function. Electrolyte balance, coagulation status, and ammonia levels were within reference ranges. A mild systemic inflammatory response was suggested by a elevated CRP (15.9 mg/L). Peripheral blood analysis revealed mild leukopenia with a white blood count count of 2.85 x 10^9/L.

Brain magnetic resonance imaging (MRI) and diffusion-weighted imaging without contrast revealed mild T2-fluid-attenuated inversion recovery signal enhancement in the bilateral inferior caudate head, hippocampus, parahippocampal gyrus, and amygdala, consistent with limbic system involvement. The radiologist suggested autoimmune encephalitis or limbic encephalitis as differential diagnoses (Figure 1). Based on these findings, a lumbar puncture was performed to investigate the etiology of encephalitis or meningitis. IV vancomycin, ceftriaxone, and acyclovir were initiated for possible infectious causes. Oral clarithromycin was added as mycoplasma pneumoniae could not be excluded.

Cerebrospinal fluid (CSF) analysis showed no cells on direct examination. Biochemical parameters of CSF were as follows: glucose, 71 mg/dL; protein, 56.6 mg/dL; chloride, 121.1 mmol/L. Simultaneous capillary blood glucose was 116 mg/dL. A meningitis-encephalitis polymerase chain reaction panel

analyzed in the CSF sample was negative. Tests for limbic encephalitis panels, anti-neuronal antibodies, and myelin oligodendrocyte glycoprotein antibodies in CSF and serum were also negative (Table 1).

The patient's altered consciousness improved within two days of PICU admission, and fever did not recur during the hospital stay. However, on the fifth day, altered consciousness reappeared, along with orofacial dyskinesia and refractory seizure activity, accompanied by leftward deviation of the head and eyes and tonic contractions of both arms. Treatment for status epilepticus was initiated following the American Epilepsy Society guidelines. After treatment was started, consciousness levels fluctuated over this period, with intermittent psychiatric symptoms, including self-injury and swearing. Anti-convulsant therapy was tailored based on seizure recurrence, clinical progression, and electroencephalography (EEG) findings. During this period of resistant seizures, the patient received infusions of levetiracetam, valproic acid, phenytoin, oxcarbazepine, clobazam, midazolam, and ketamine. EEG findings revealed epileptic activity originating in the bilateral frontocentroparietal regions, more pronounced on the right side. Radiology board reviews of the patient's MRI confirmed bilateral limbic system involvement extending to the caudate nucleus.

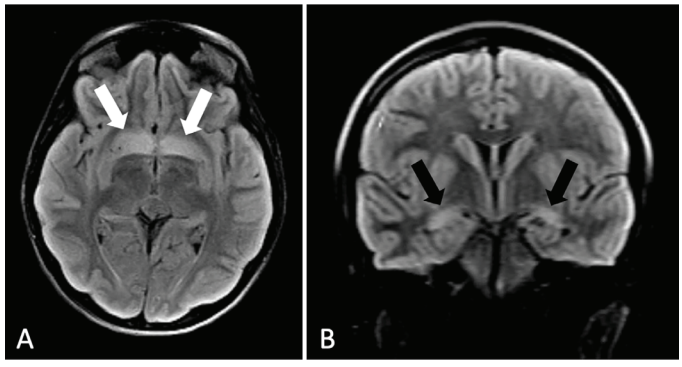

Figure 1. (A) Axial T2-FLAIR shows bilateral symmetric T2 signal enhancement in the globus pallidus (filled white arrows) **(B)** Coronal T2-FLAIR shows cortical swelling and T2 signal enhancement suggestive of bilateral hippocampal involvement (filled black arrows). T2-FLAIR: T2-fluid-attenuated inversion recovery

Based on MRI findings and negative infectious workup, autoimmune encephalitis was considered the leading diagnosis. Intravenous immunoglobulin (IVIG) was administered at 1 g/kg/day for two days. No microorganisms were identified in blood, urine, and CSF cultures. Acyclovir and vancomycin were discontinued, while ceftriaxone was continued for 21 days. Clarithromycin therapy was completed for seven days.

During follow-up, the patient was evaluated by the child and adolescent psychiatry team due to the development of sleep disturbances and delirium. To rule out paraneoplastic limbic encephalitis, abdominal and scrotal ultrasonography, as well as a whole-body contrast-enhanced MRI, were performed. These tests did not reveal any additional pathologies. Thyroid function tests and serum thyroid autoantibodies were unremarkable. Serum aquaporin-4 antibody, and West Nile virus antibody were negative. No pathology was detected in immunologic tests [immunoglobulin G-A-M-E, lymphocyte subset panel, regulatory T cell (Treg) flow cytometry panel, C3, C4, antinuclear antibody] performed in the pretreatment period.

The patient was diagnosed with FIRES following a multidisciplinary evaluation. There was no history of a diagnosed disease. Investigations into the etiology of RSE excluded any identifiable acute or active structural, toxic, or

Table 1. Parameters analyzed in the patient's CSF and serum samples

Autoimmune limbic encephalitis panel (CSF/serum)	Anti-neuronal antibodies (CSF)	Meningitis - encephalitis PCR panel (CSF)
		Escherichia coli
		Haemophilus influenzae
		Listeria monocytogenes
		Neisseria meningitidis
		Streptococcus agalactiae
		Streptococcus Pneumoniae
AMPA 1 (Glu1)		*Herpes Simplex Virus 1*
AMPA 2 (Glu2)		*Herpes Simplex Virus 2*
ANTI-CASPR2	Anti-Hu (ANNA-1)	*Human Herpesvirus 6*
ANTI-DPPX	Anti-Ri (ANNA-2)	*Human Parechovirus*
ANTI-GABA B	Anti-Tr (DNER)	*Enterovirus*
ANTI-LGI 1	Anti-Yo (PCA-1)	*Varicella Zoster Virus*
NMDAR antibody		*Cryptococcus neoformans/gattii*
		Cytomegalovirus

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, CASPR2: Contactin-associated protein-like 2, DPPX: Dipeptidyl-peptidase-like protein-6, GABA: Gamma-aminobutyric acid, GluR1/2: Glutamate receptors 1 and 2, LGI1: Leucine-rich, glioma-inactivated 1, NMDAR: N-methyl-D-aspartic acid receptor, ANNA: Anti-neuronal nuclear antibody, DNER: Delta and Notch-like epidermal growth factor-related, PCA-1: Purkinje cell cytoplasmic antibody type 1, CSF: Cerebrospinal fluid, PCR: Polymerase chain reaction

metabolic causes. There was a fever 11 days before the onset of RSE. The patient, whose clinical findings did not improve and whose seizure activity continued, was treated with IVIG, followed by pulse steroid therapy for 11 days, and then 6 cycles of plasmapheresis. Thiamine and biotin supplementation was given for possible thiamine-biotin responsive basal ganglia disease. A repeat EEG showed improved the background rhythm. Follow-up MRI showed regression of limbic system findings, although bilateral external capsule involvement persisted (Figure 2). Since the patient's seizure activities continued, KDT was initiated.

The classic ketogenic diet calculates the ratio of grams of fat to grams of carbohydrates plus protein. The most feasible ratios calculated to date are 3:1 or 4:1, with approximately 80-90% of the energy provided by fats and 10% by carbohydrates and proteins collectively. In our patient, the classic KD was initiated at a 3:1 ratio under the supervision of a dietitian, 18 days after the first seizure activity. During KDT, electrolytes, arterial blood gases, serum ketone bodies, and glucose levels were monitored. Ketosis was assessed through measurements of serum ketone levels. No KDT-related side effects were observed during follow-up.

From the eighth day of KDT onward, no further seizure activity was observed. Follow-up cranial MRI findings revealed normalization, while EEG demonstrated persistent multifocal epileptic abnormalities, albeit with reduced intensity. After resolution of the SE clinical presentation and a notable reduction in seizure frequency, the patient was transferred to the pediatric neurology ward following a one-month stay in the PICU. The patient continued receiving valproate, levetiracetam, and clobazam as anti-convulsant, alongside KDT and oral prednisolone. The treatment plan included gradual tapering and discontinuation of oral prednisolone, and the continuation of IVIG therapy at a dose of 1 g/kg per month.

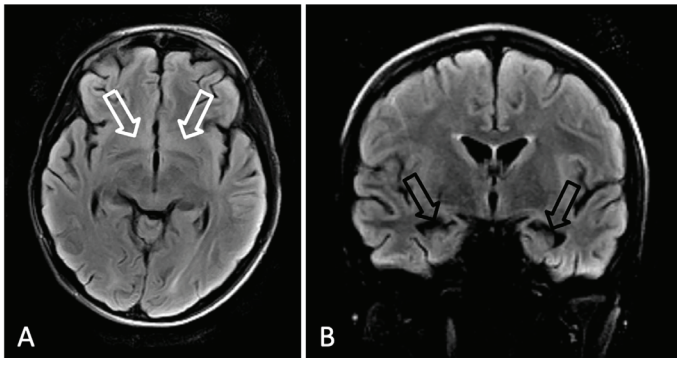

Figure 2. (A) Axial T2-FLAIR shows normalized signal in the globus pallidus (empty white arrows). **(B)** Coronal T2-FLAIR shows ventricular enlargement consistent with bilateral hippocampal atrophy (empty black arrows). T2-FLAIR: T2-fluid-attenuated inversion recovery

In the patient's long-term follow-up, anti-convulsant medications were discontinued after the seventh month. Although pathological findings such as the presence of spike-wave activity in the left parietoccipital and frontal areas on EEG persist;, he was followed up using KDT without seizures. At this time, second-line immunotherapy has not been started, as the patient, with the current clinical presentation, has responded well to first-line immunotherapy. Informed consent was obtained from the patient's family.

Discussion

We present a case of a rare epilepsy syndrome with unclear aetiology in a healthy boy whose seizures were eventually completely controlled after comprehensive treatment, especially first-line immunotherapy and KDT in the acute phase. In the long term, anti-seizure medications were discontinued.

If a previously healthy child presents with severe status epilepticus closely associated with a febrile illness, and after a short period of recovery infectious encephalitis is excluded, FIRES should be considered.[5] Although viral and autoimmune causes are often implicated in the etiology, most cases (up to 50%) remain cryptogenic despite extensive evaluation.[4,6] At this stage, preventing seizure recurrence is of utmost importance. In patients without clinical seizures, imaging, and laboratory evaluations should be performed at frequent intervals, and immunotherapy should be organized during the active phase of the disease to enable discontinuation of antiepileptic drugs.

In cases of seronegative autoimmune encephalitis, brain MRI has an important place in the differential diagnosis. MRI is an imaging modality that demonstrates inflammation-related changes in patients with autoimmune encephalitis. While different specific neuroimaging findings can be observed in various antibody-associated syndromes, as in our case, T2-weighted images typically demonstrate signal hyperintensity restricted to limbic regions.[7]

In addition to brain MRI, CSF examination is important to confirm the diagnosis and exclude infectious causes of encephalitis. Since the sensitivity and specificity of CSF and serum analysis differ between antibodies, it is recommended to perform antibody testing in both samples.[8] However, despite appropriate antibody screening tests, antibodies are reported to be negative in 7% of cases.[9] Comprehensive antibody screening in our patient revealed negative antibody results.

EEG is important in detecting and managing seizures and assessing their frequency in autoimmune encephalitis. although EEG abnormalities are seen in more than 75% of

patients, EEG findings may be completely normal.[10] In our case, although the EEG findings were useful for detecting seizure activity and assessing background rhythm, they were not decisive for making a differential diagnosis. In this regard, a retrospective study published in 2016 by Baysal-Kirac et al.[11] reported that there was no significant difference between the EEG findings of seronegative and anti-neuronal antibody-positive epilepsy patients. Therefore, we considered that EEG findings could be supportive of our diagnosis and treatment.

Various studies and case series have shown that the efficacy of antiepileptic drugs and other therapeutic agents in reducing seizure frequency and shortening the duration of the disease is controversial. Consequently, the epileptic process in FIRES may be considered self-limiting.[12] Nonetheless, the potential benefits of treatments employed during this process should not be underestimated.

In this case, the patient developed RSE 11 days following the onset of fever. Comprehensive investigations failed to reveal any underlying structural, metabolic, acute toxic, or infectious causes that could have precipitated RSE. Therefore, a diagnosis of FIRES was made, and the patient was managed in a multidisciplinary setting. In our patient, it is important to discontinue antiepileptic medication in the acute phase and maintain seizure-free clinical follow-up with KDT alone. The persistence of EEG findings can indicate that the existing autoimmune process continues, but clinical findings are not observed. Whether this is a response to first-line immunotherapy or a self-limitation of the existing autoimmune epileptic process remains controversial.

KDT is a treatment method with proven efficacy in patients with drug-resistant epilepsy, and although research on its mechanism of action is ongoing, its efficacy in the treatment of FIRES is still being studied.[13] Studies by Nabbout et al.[14] involving nine FIRES patients and Peng et al.[15] analyzing retrospective data from seven FIRES cases suggest that KDT is a safe and promising therapeutic option in FIRES, and that early initiation of the KDT provides a favorable prognosis.

Conclusion

In conclusion, the number of FIRES cases reported in the literature is steadily increasing. The majority of FIRES and NORSE cases have an average ICU stay of 20-40 days, and the mortality rate in children is around 12%.[12] The pathogenesis and exact mechanism of this catastrophic type of encephalopathy are not known. The efficacy of current therapies remains uncertain, as many patients exhibit inadequate responses to administered treatments. This case underscores the importance of early recognition of FIRES, timely initiation of immunotherapy, and the potential life-saving impact of KDT in refractory epilepsy syndromes.

Ethics

Informed Consent: Informed consent was obtained from the patient's family.

Footnotes

Authorship Contributions

Concept: M.D.K., G.A., H.A., Design: E.S., A.Ü., Data Collection or Processing: M.D.K., S.S.Ç., Analysis or Interpretation: G.Ak., M.C., A.Ü., Literature Search: M.D.K., G.A., G.Ak., Writing: M.D.K., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia. 2018;59:745-2.
2. Wilder RM. High fat diets in epilepsy. Mayo Clin Bull. 1921;2:308.
3. Tharmaraja T, Ho JSY, Neligan A, Rajakulendran S. The etiology and mortality of new-onset refractory status epilepticus (NORSE) in adults: a systematic review and meta-analysis. Epilepsia. 2023;64:1113-24.
4. Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. Neurology. 2015;85:1604-13.
5. van Baalen A, Vezzani A, Häusler M, Kluger G. Febrile infection-related epilepsy syndrome: clinical review and hypotheses of epileptogenesis. Neuropediatrics. 2017;48:5-18.
6. Husari KS, Labiner K, Huang R, Said RR. New-onset refractory status epilepticus in children: etiologies, treatments, and outcomes. Pediatr Crit Care Med. 2020;21:59-66.
7. Vogrig A, Muñiz-Castrillo S, Desestret V, Joubert B, Honnorat J. Pathophysiology of paraneoplastic and autoimmune encephalitis: genes, infections, and checkpoint inhibitors. Ther Adv Neurol Disord. 2020;13:1756286420932797.
8. Graus F, Vogrig A, Muñiz-Castrillo S, Antoine JG, Desestret V, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8:e1014.
9. Graus F, Escudero D, Oleaga L, Bruna J, Villarejo-Galende A, et al. Syndrome and outcome of antibody-negative limbic encephalitis. Eur J Neurol. 2018;25:1011-6. Erratum in: Eur J Neurol. 2018;25:1303.
10. Vogrig A, Joubert B, André-Obadia N, Gigli GL, Rheims S, et al. Seizure specificities in patients with antibody-mediated autoimmune encephalitis. Epilepsia. 2019;60:1508-25.
11. Baysal-Kirac L, Tuzun E, Altindag E, Ekizoglu E, Kinay D, et al. Are there any specific eeg findings in autoimmune epilepsies? Clin EEG Neurosci. 2016;47:224-34.

12. Kramer U, Chi CS, Lin KL, Specchio N, Sahin M, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia. 2011;52:1956-65.

13. Koh S, Dupuis N, Auvin S. Ketogenic diet and neuroinflammation. Epilepsy Res. 2020;167:106454.

14. Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia. 2010;51:2033-7.

15. Peng P, Peng J, Yin F, Deng X, Chen C, et al. Ketogenic diet as a treatment for super-refractory status epilepticus in febrile infection-related epilepsy syndrome. Front Neurol. 2019;10:423.