Ketogenic Diet for a Young Adult Patient With Chronic-Phase Febrile Infection-Related Epilepsy Syndrome

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Abstract

Febrile infection-related epilepsy syndrome (FIRES) is a rare disease, whereby refractory status epilepticus (a severe epileptic syndrome) occurs in previously healthy individuals following a febrile illness. Here, we report a patient with FIRES who received ketogenic diet (KD) therapy initiated in the chronic phase. A 21-year-old man presented with status epilepticus, following fever and headache. In the acute phase, his seizures were refractory to conventional antiepileptic drugs and were suppressed only by intravenous anesthetics. In the chronic phase, he showed frequent seizures with concurrent severe cognitive decline. Twenty-seven months after onset, the patient was started on KD. Consequently, his seizure frequency rapidly reduced while his cognitive function slowly improved, albeit incompletely. Recently, KD has been shown to both reduce seizures and improve cognitive prognoses in children with FIRES. Although early KD may help in both seizure control and cognitive prognosis, it is likely that KD can be applied to adult patients with chronic FIRES.

Categories: Neurology, Psychology, Nutrition

Keywords: refractory epilepsy, ketogenic diet, fires, febrile infection-related epilepsy syndrome, adult

Introduction

Febrile infection-related epilepsy syndrome (FIRES) is an epileptic encephalopathy in which previously healthy individuals present with prolonged status epileptics (SE) following a febrile illness [1-3]. The SE is refractory to conventional antiepileptic drugs (AEDs) and immunotherapies [2-3]. Although seizure frequency gradually decreases in the chronic phase of FIRES, in many cases, these last throughout the patient’s lifetime and is accompanied by cognitive decline [2-3]. Recently, several small case studies report that the ketogenic diet (KD) both reduces seizures in FIRES and improves cognitive prognosis in children and in the acute phase of this disease, with incompletely understood mechanisms [4-5]. We report a young adult man with FIRES, who showed great seizure reduction and mild improvement of cognitive function with long-term KD despite delayed initiation in the chronic phase.

Case Presentation

A previously healthy, 21-year-old man presented with fever and headache. Three days later, he exhibited a disturbed consciousness level, frequent twitching of the ipsilateral face and upper limb, and apneic spells. Brain magnetic resonance imaging (MRI) showed no abnormalities. A cerebrospinal fluid (CSF) study disclosed slight lymphocytic pleocytosis with 8 leukocytes/mm², including 75% lymphocytes and total protein 0.4 g/l (normal <0.5 g/l). No organism was isolated on Gram staining and culture of the CSF, and the polymerase chain reaction was negative for herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and human herpesvirus 6. A CSF panel of autoimmune encephalitis, including anti-N-methyl-D-aspartate receptor, gamma-aminobutyric acid B receptor, leucine-rich glioma-inactivated 1, and contactin-associate protein 2 antibodies were all negative. As his seizures periodically repeated every five to 10 minutes, he was intubated and ventilated using a mechanical respirator and treated with midazolam. Five days after the onset, he was given fosphenytoin and levetiracetam sequentially in addition to midazolam, but his seizures were not controlled. Eight days after the onset, he was controlled with burst-suppression on electroencephalogram (EEG) using a continuous infusion of midazolam, propofol, and thiamylal sodium. However, the seizures and continuous epileptic discharge often recurred when these anesthetics were tapered (Figure 1A).
He was started on glucocorticoid pulse therapy, plasma exchange (PE), and high-dose intravenous immunoglobulin (IVIG) sequentially. Three months after onset, his frequency of seizures decreased under oral administration of six AEDs (levetiracetam 5,000 mg/day, lamotrigine 100 mg/day, perampanel 12 mg/day, topiramate 600 mg/day, phenobarbital 120 mg/day, and potassium bromide 2.25 g/day), and his intravenous anesthetics and artificial ventilator could be discontinued. There was persistent weakness in both lower limbs, probably due to critical illness neuropathy. Seven months after the onset, he was transferred to our hospital. At the same time, a physical examination revealed a temperature of 36.6 °C, a pulse of 82 beats/min, a blood pressure of 128/62 mmHg, a height of 163 cm, and a bodyweight of 62 kg. On
neurological examination, he was alert but apathetic. Muscle weakness (2/5 on the Medical Research Council muscle grading scale) and moderate hypesthesia and areflexia were observed in bilateral lower limbs. Laboratory studies were unremarkable. At our hospital, he presented apneic spells and impaired consciousness 15–20 times a week and tonic-clonic seizures two to three times a month. AED adjustments did not reduce the frequency or duration. In addition to his lack of spontaneity, he became agitated and impulsive and showed behavioral problems such as sexual disinhibition and stereotyped tool use, which were resistant to all administered antipsychotic drugs. Fourteen months after the onset, interictal EEG showed repeated slow waves in the frontoparietal region (Figure 1B). Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV) showed full-scale IQ 52. Wechsler Memory Scale—Revised (WMS-R) was less than 50 in all categories (Table 1).

| After ketogenic diet initiation (month) | Before | 3   | 9   | 16  |
|----------------------------------------|--------|-----|-----|-----|
| After the onset (month)                | 14     | 30  | 36  | 43  |
| Wechsler Adult Intelligence Scale - Fourth Edition |        |     |     |     |
| Full-scale IQ                          | 52     | 55  | 61  | 67  |
| Verbal comprehension index             | 67     | 68  | 68  | 81  |
| Perceptual reasoning index             | 58     | 69  | 78  | 82  |
| Working memory index                   | 67     | 60  | 69  | 67  |
| Processing speed index                 | 54     | 57  | 57  | 57  |
| Wechsler Memory Scale - Revised        |        |     |     |     |
| Verbal memory index                    | <50    | <50 | <50 |     |
| Visual memory index                    | <50    | 76  | 90  |     |
| General memory index                   | <50    | <50 | 50  |     |
| Attention and concentration index      | <50    | 54  | 69  |     |
| Delayed recall index                   | <50    | <50 | <50 |     |

**TABLE 1: Neuropsychological tests**

Twenty-seven months after onset, brain magnetic resonance imaging (MRI) showed atrophy of the bilateral frontal lobes and mesial temporal lobes and dilatation of the lateral ventricles (Figure 2A).
FIGURE 2: MRI and SPECT

The findings of brain magnetic resonance imaging (MRI) and cerebral blood flow single-photon emission computed tomography using N-isopropyl-p-[123I] iodoamphetamine (SPECT). Twenty-seven (27) months after the onset: (A) MRI shows atrophy of the bilateral frontal lobes and mesial temporal lobes and dilatation of the lateral ventricles. (B) SPECT reveals hypoperfusion in the right-dominant frontal and parieto-temporal cortices (arrows). Thirty-six (36) months after the onset and nine months after the ketogenic diet initiation: (C) MRI shows no changes compared to (A) before the introduction of the ketogenic diet. (D) SPECT shows the improvement of hypoperfusion in the frontal and parieto-temporal cortices. The Z-score on SPECT is higher as the degree of decrease in cerebral blood flow is larger than that of an age-matched normal database.

Single-photon emission CT using N-isopropyl-p-[123I] iodoamphetamine (IMP-SPECT) revealed hypoperfusion in the right-dominant frontal and parieto-temporal cortices (Figure 2B). Then, we started the patient on a 2:1 (fat:carbohydrate and protein) ratio KD of 1,350 kcal. Within 48 hours of the KD initiation, he achieved a urine ketone of 3+. One month after KD initiation, laboratory tests showed elevated total
We reported that a young adult patient with FIRES showed a significant decrease in seizure frequency due to our case. Neurology, epileptology, nutritional science, and cooperation of the family offering KD at home such as in the application of more liberal regimens, multidisciplinary teams with expertise in pediatric and adult some adult patients discontinuation antiepileptic effect can persist in some children with refractory epilepsies, including FIRES, after its...The appropriate duration of KD in refractory epilepsies, including FIRES, is controversial...Putative mechanisms of KD include anti-inflammatory effects and neuroprotective properties in addition to anticonvulsant effects. These various effects of KD may contribute to both seizure reduction and cognitive improvement in children with refractory epilepsies including FIRES [4-5]. Compared to children, the use of the KD in adolescents and adults has been more restrained due to reasons such as an inability to adhere to the diet or a medical team that is not proficient in administering the diet [8]. However, the emergence of more liberal regimens (e.g., the modified Atkin’s diet, the low-glycemic index treatment, and the medium-chain triglyceride diet) has allowed adolescents and adults to participate in diet therapies more tolerably, and these regimens may reduce seizures similar to classic KD with 4:1 ratio of fat to protein and carbohydrate [8]. Consequently, growing evidence indicates that the KD and its variants can be effective for adolescents and adults with refractory epilepsy as well as in children [8-11]. The seizure frequency of our patient was also sufficiently reduced on KD with lower ratios, such as 2:1 or 1.5:1, compared to the classic 4:1...KD should be initiated as early as possible in order to achieve and sustain seizure control, particularly status epileptics in the acute phase of FIRES, which can lead to deleterious cognitive outcomes [5,8]. Moreover, it has been reported that KD shows a better response in patients with recently increased seizure frequency, than in patients with stable sporadic seizures [12]. However, our patient showed a great decrease in seizure frequency with mild cognitive improvement despite the initiation of KD in the chronic phase. Even in patients with chronic epilepsy resistant to multiple AEDs, KD should be fully considered to reduce seizure frequency and prevent further cognitive decline...The appropriate duration of KD in refractory epilepsies, including FIRES, is controversial [8]. The antiepileptic effect can persist in some children with refractory epilepsies, including FIRES, after its discontinuation [5,13]. In addition, stopping KD may lead to increased seizure frequency and recurrent SE in some adult patients [10]. We consider that the following points are important to successfully continue KD: the application of more liberal regimens, multidisciplinary teams with expertise in pediatric and adult neurology, epileptology, nutritional science, and cooperation of the family offering KD at home such as in our case...Conclusions We reported that a young adult patient with FIRES showed a significant decrease in seizure frequency due to long-term KD despite initiation in the chronic stage, while his cognitive function incompletely improved. Although early initiation of KD in FIRES is desirable to optimize both seizure control and cognitive outcome,
we consider that KD can be applied for adult patients with chronic refractory epilepsy as well.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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