Cognitive Outcomes in Febrile Infection-Related Epilepsy Syndrome Treated With the Ketogenic Diet

abstract

Febrile infection-related epilepsy syndrome (FIRES) is a newly recognized epileptic encephalopathy in which previously healthy school-aged children present with prolonged treatment-resistant status epilepticus (SE). Survivors are typically left with pharmacoresistant epilepsy and severe cognitive impairment. Various treatment regimens have been reported, all with limited success. The ketogenic diet (KD) is an alternative treatment of epilepsy and may be an appropriate choice for children with refractory SE. We report 2 previously healthy children who presented with FIRES and were placed on the KD during the acute phase of their illness. Both children experienced resolution of SE and were maintained on the KD, along with other anticonvulsant medications, for several months. Both were able to return to school, with some academic accommodations. These cases highlight the potential value of the KD as a preferred treatment in FIRES, not only in the acute setting but also for long-term management. Early KD treatment might optimize both seizure control and cognitive outcome after FIRES.

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KEY WORDS
ketogenic diet, epilepsy, IQ

ABBREVIATIONS
FIRES—febrile infection-related epilepsy syndrome
FLAIR—fluid-attenuated inversion recovery
KD—ketogenic diet
SE—status epilepticus

Drs Singh and Shellhaas conceptualized and designed the study, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Joshi, Leber, Carlson, and Ms Potter analyzed and interpreted the data and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Febrile infection-related epilepsy syndrome (FIRES) is an epileptic encephalopathy that presents as pharmacoresistant status epilepticus (SE) in previously healthy school-aged children.1–3 At presentation, SE lasts for weeks and may result in death4 or evolve into treatment-resistant epilepsy with associated severe intellectual disabilities.1

The underlying pathophysiology may be immune-mediated, but adjunctive therapies to anticonvulsant medications, including immunotherapy with intravenous immunoglobulin, steroids, and plasmaphoresis, have been used with limited success.5,6 One group suggested the ketogenic diet (KD) may be effective in the acute SE phase of FIRES, based on experience with 9 patients, but cognitive outcomes were not described.7 The KD is a high-fat, adequate-protein, low-carbohydrate diet that can reduce seizure burden via incompletely understood mechanisms.8 We report 2 children with FIRES for whom the KD was initiated during the acute SE phase and was maintained during convalescence. Before their illnesses, both children performed at or above grade level without social or behavioral concerns. The KD controlled their seizures and may have contributed to their unusually good cognitive outcomes. Our institutional review board approved this study and granted a waiver of informed consent.

**CASE PRESENTATIONS**

**Patient 1**

A previously healthy 7-year-old boy presented with a seizure after 1 week of fever (38.3°C – 40.6°C), headache, malaise, papular rash, and erythematous oropharynx. He was diagnosed clinically with streptococcal pharyngitis and was taking amoxicillin. His first seizure was described as a self-limited generalized convulsion lasting 1.5 minutes. At a local hospital, head computed tomography scan and lumbar puncture were normal.

Because of persistent altered mental status, he was transferred to our PICU. Diagnostic tests excluded infectious, genetic, and autoimmune etiologies (Table 1). Brain MRI revealed increased fluid-attenuated inversion recovery (FLAIR) signal in bilateral medial temporal lobes (Fig 1A).

During the first night of admission, he had 6 clinical seizures characterized by oral automatisms and apnea with oxygen desaturations to the 70s. Continuous video-EEG monitoring demonstrated subclinical SE with seizures arising independently from all 4 quadrants. SE continued for 10 days despite sequential treatment with anticonvulsants (phenytoin, phenobarbital, levetiracetam, valproic acid, and topiramate), a 5-day course of intravenous methylprednisolone, and

| TABLE 1 Diagnostic Evaluations for 2 Patients With FIRES |
|-----------------|-----------------|
| **Patient 1**   | **Patient 2**   |
| Infectious      | Infectious      |
| HSV 1 and 2 DNA qPCR  | HSV 1 and 2 DNA qPCR |
| HSV 1 and 2 DNA PCR  | HSV 1 and 2 DNA PCR |
| HHV-6 DNA qPCR  | HHV-6 DNA qPCR |
| Enterovirus PCR  | Enterovirus PCR |
| CMV DNA qPCR  | CMV DNA qPCR |
| EBV DNA qPCR  | EBV DNA qPCR |
| Adenovirus DNA qPCR | Adenovirus DNA qPCR |
| Mycoplasma IgM, IgG antibody | Mycoplasma IgM, IgG antibody |
| Bartonella antibody panel | Bartonella antibody panel |
| Arbovirus panel | Arbovirus panel |
| West Nile Virus panel | West Nile Virus panel |
| Autoimmune      | Autoimmune      |
| C-reactive protein, ESR, thyrotropin, free T4 | C-reactive protein, ESR, thyrotropin, free T4 |
| Thyroglobulin antibody | Thyroglobulin antibody |
| Microsomal antibody | Microsomal antibody |
| Antinuclear antibody screen | Antinuclear antibody screen |
| ANA-2 nuclear antibody screen | ANA-2 nuclear antibody screen |
| ENA-11 antibody panel | ENA-11 antibody panel |
| Antidouble stranded DNA | Antidouble stranded DNA |
| Complement levels (C3,C4) | Complement levels (C3,C4) |
| IgG index | IgG index |
| Myelin basic protein | Myelin basic protein |
| Paraneoplastic   | Paraneoplastic   |
| NMDA-receptor antibody | NMDA-receptor antibody |
| Paraneoplastic autoantibody panel: | Paraneoplastic autoantibody panel: |
| CSF: ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2 | CSF: ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2 |
| PCAM, PCAM-Tr, Ampiphispy antibody, CRMP-5-IgG | PCAM, PCAM-Tr, Ampiphispy antibody, CRMP-5-IgG |
| Serum: ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, Ampiphispy antibody, CRMP-5-IgG | Serum: ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, Ampiphispy antibody, CRMP-5-IgG |
| Striatal (Striated Muscle) antibody, P/Q type calcium channel antibody, N-Type calcium channel antibody, ACh Receptor antibody, AchR | Striatal (Striated Muscle) antibody, P/Q type calcium channel antibody, N-Type calcium channel antibody, ACh Receptor antibody, AchR |
| Ganglionic neuronal antibody, Neuronal (V-G) K Channel antibody | Ganglionic neuronal antibody, Neuronal (V-G) K Channel antibody |
| Genetic/metabolic | Genetic/metabolic |
| Karyotype | Fatty acid profile |
| Acylcarnitine profile | Lactate |
| Initial MRI findings | Initial MRI findings |
| Increased FLAIR/T2 signal in bilateral medial temporal lobes | Normal |
continuous infusions (midazolam, pento-
barbital). His EEG reached burst sup-
pression with pentobarbital for 72 hours,
but as pentobarbital was weaned, the EEG
transitioned to generalized periodic epi-
leptiform discharges with the resurgence
of seizures.

On hospital day 13, he began the KD,
using an enteric formula (Ketocal
Nutricia, North America) with a 4:1 ratio
of fats to carbohydrates and protein.
Beginning with 50% of daily caloric
needs, the KD was titrated over 5 days to
100% of total caloric intake. Within 48
hours of KD initiation, he achieved ke-
tosis (serum β-hydroxybutyrate level
3.1), pentobarbital was weaned off, and
seizures resolved. He then required 3
weeks of inpatient rehabilitation. His
epilepsy treatment regimen was re-
fi
ned to include 3.25:1 KD, topiramate,
and phenobarbital. Initial neuropsycho-
logical assessments revealed euthymia
with emotional lability and signi
fi-
cant memory impairments.

Twenty months later, his epilepsy re-
mains quiescent with rare, self-limited,
focal seizures triggered by illnesses.
He is maintained on the KD, phenobar-
bital, and topiramate. He returned to
school with an individualized education
plan. Neuropsychometric testing re-
vealed moderate impairments in work-
ning memory, but average ability to recall
auditory verbal narratives and normal
fine-motor speed and dexterity (full scale
IQ 71). He also developed attention-
deficit/hyperactivity disorder. Repeat
MRI revealed FLAIR signal abnormalities
consistent with bilateral mesial tem-
poral sclerosis (Fig 1B).

Patient 2
A previously healthy 10-year-old girl
presented with new-onset seizures and
encephalopathy after 1 week of fevers
to 39°C, myalgias, abdominal pain, and
nausea. At school she had a 2-minute
seizure, described as emesis, tonic
stiffening, unresponsiveness, and uri-
nary incontinence, after which she did
not return to baseline mental status. At
her local hospital, she had a normal
head computed tomography scan and
lumbar puncture and was treated for
presumed meningocencephalitis. She
then had another seizure and was
transferred to our PICU.
Video-EEG monitoring revealed sub-
clinical focal SE arising from the
left frontal and temporal regions. Seizures
continued despite multiple
anticonvulsants, administered in se-
quential combinations (fosphenytoin,
phenobarbital, levetiracetam, lacosam-
ide, topiramate, valproic acid, and
lorazepam), and a course of intravenous
methylprednisolone. She continued
to have 3 to 8 seizures per hour, and
on the third hospital day the KD
was started. Ketosis was difficult to
achieve and seizures persisted. She
was placed on a pentobarbital infusion
for 72 hours of burst suppression. After
the pentobarbital was weaned, the
seizures returned with a new right
temporal focus. She was restarted on
pentobarbital for 10 days, while the KD
ratio was titrated upwards. Ketosis was
achieved by day 20 of hospitalization,
with a 6:1 KD ratio.
Infectious, rheumatologic, and auto-
immune investigations were all nega-
tive and MRI was normal (Table 1). She
was extubated on day 28, stabilized,
and transferred to inpatient reha-
bitation where she remained for 1
month. She was discharged on a 4:1
ratio KD, topiramate, phenobarbital,
and clobazam.
At her 1-month follow-up visit, she had
suffered 1 complex partial seizure.
Due to difficulty with compliance, the
KD was weaned 4 months after initial
presentation, and she had only 1
subsequent seizure. Her phenobarbital
has been discontinued, and topiramate
dose reduced. Eighteen months later,
she has ongoing challenges with
short-term memory, difficulty recalling
words, and is tangential in her con-
versation. Neuropsychological testing
reveals impaired phonics and fluency,
moderately-to-severely impaired pro-
cessing speed and recall of auditory
verbal narratives (full scale IQ 62). She
attends the fifth grade in a regular public
school classroom, but requires a modi-
fied curriculum with an individualized
education plan.
DISCUSSION

Care for a child with refractory SE requires a highly skilled multidisciplinary team with expertise in pediatric critical care, neurology, epileptology, pharmacy, nursing, and in our cases, dieticians. When diagnostic and therapeutic strategies suggest FIRES, and there are no contraindications, we suggest early consideration of KD in order achieve and sustain seizure control.

The KD has multiple mechanisms of action that confer anticonvulsant and neuroprotective properties. Commercially available KD formula simplifies its use among critically ill children. Several case series have revealed successful KD use in adults and children with SE due to cryptogenic etiology, viral and inflammatory encephalitis, hemimegalencephaly, Rasmussen syndrome, and head trauma. In each case, SE resolved 1 to 10 days after KD initiation, even though other treatments failed to abort the SE.

The largest study of FIRES included 77 children. The acute mortality rate was 11.7%, and 93% of survivors had refractory epilepsy. Only 12 survivors (18%) were cognitively normal; 11 (16%) had borderline cognition, 10 (14%) mild mental retardation, 16 (24%) moderate mental retardation, 8 (12%) severe mental retardation, and 11 (16%) were in a vegetative state. Four patients were treated with KD, of whom 1 had an immediate and sustained response. Cognitive outcomes for these 4 patients were not specifically described.

In a series of 9 children with FIRES, a 4:1 KD was initiated after a mean of 23 days, after a 24-hour fasting period. Ketosis (defined by ketonuria, without confirmation by serum β-hydroxybutyrate levels) was reached within 2 to 4 days. One patient failed to reach ketonuria, possibly due to concomitant high-dose steroids. Two patients’ seizures persisted; another child responded initially, but the diet was abruptly interrupted due to concerns of the ICU team, SE recurred, and the patient died 10 days later. The 6 responders remained on the KD for a mean of 1 year (range, 6 months to 2 years). Another report described 2 children treated with the KD in the acute phase with a 50% to 70% seizure reduction. Detailed cognitive outcomes were not reported in either study.

Challenges to KD initiation for refractory SE include occult carbohydrates in concurrently administered medications. For example, because pentobarbital is not water soluble, it is compounded with propylene glycol. The latter is metabolized into organic acids that act as carbohydrates and hinder ketosis. Additionally, interference of steroids with ketosis and the need to quickly rule-out contraindications (eg, fatty acid oxidation disorders) may be rate-limiting steps for KD initiation. All of the reported FIRES cases treated with KD used enteral administration. It is possible to formulate ketogenic total parenteral nutrition, but to our knowledge, ketogenic total parenteral nutrition has not been studied in FIRES.

As with any treatment of refractory SE, it is impossible to know whether KD truly alleviated our patients’ seizures or their SE resolved spontaneously. However, because many other interventions failed to provide adequate seizure control, and most concurrent anticonvulsants were successfully weaned after KD initiation, we postulate that KD had a significant impact on their severe epilepsy.

Our experience is unique because our patients with FIRES were not only placed on KD in the acute SE phase, but they also continued on KD for several months to 1 year afterward, and returned to school with only mild impairment in cognition. Although they did not return completely to their pre-FIRES baseline, our patients’ outcomes were much more positive than most of those reported in the literature, which highlights the potential value of the KD as a preferred treatment in FIRES, not only in the acute setting, but also to optimize seizure control and cognitive outcomes for the long term. Thus, early consideration of KD may be important in the acute management of children with FIRES.

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