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Review article

Ketogenic diet in 3 cases of childhood refractory status epilepticus

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ABSTRACT

Introduction: Refractory status epilepticus (RSE) in children is associated with a significant risk of death or neurological morbidity. Recently attention has been drawn to the ketogenic diet (KD) as an acute treatment, as it has shown promise in controlling seizures in otherwise refractory status epilepticus in several cases. We have listed these and reviewed all cases of KD used in RSE at our centre. KD was given as 4:1 fat:carbohydrate-protein solution.

Results: A 3-year-old girl with RSE due to Hemiconvulsion-Hemiplegia Epilepsy syndrome. KD was instigated on day 6. Seizures stopped with ketosis on day 7.

A 10-year-old boy rapidly developing RSE. After months a mitochondrial disorder was discovered. KD was tried twice with severe side-effects but no seizure control.

11-year-old healthy boy with RSE as FIRES. On KD seizures stopped for 24 h one day after reaching ketosis. He improved over 3–4 weeks.

Discussion: KD was efficient in two of three cases of RSE. The non-responder had severe side-effects and proved to have a mitochondrial disorder which is arguably a contraindication for KD.

More studies are needed to prove efficacy of KD in RSE, to define optimal timing of KD and possible contraindications for KD in RSE.

Contents

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1. Introduction

Status epilepticus (SE) in children is a severe condition associated with a significant risk of death or subsequent neurological morbidity and cognitive problems.[1] Prolonged, pharmacoresistant or refractory status epilepticus (RSE) therefore represents a very serious challenge. As a supplement to traditional antiepileptica various other means of treatment have been used for RSE. These include supplemental pharmacological treatment such as pulse-steroid and immunoglobuline (IVIG). Non-pharmacological measures include plasmapheresis, electro-convulsive therapy (ECT) and controlled hypothermia. However, results are very inconsequent.[2]

The ketogenic diet (KD) has been used successfully to treat or control otherwise intractable epilepsy in children. In 2009 Villeneuve et al.[3] showed markedly better effects of KD in epileptic children with a current increase in seizure frequency and repetitive seizures compared to those with a stable seizure frequency. This has drawn attention to KD as a possible early means of treating acute RSE in both children and adults.

Bodenant et al.[4] had already described effect of KD on RSE in an adult male. Wusthoff et al.[5] then reported seizure control by KD in two adults with non-convulsive RSE. Kumada et al.[6] published 2 cases of effective seizure control in children with non-convulsive RSE using a modified Atkins diet similar to KD. Nabbout et al.[7] have investigated the effects of KD in 9 children with RSE in the form of FIRES ("Febrile Infection-Related Epilepsy Syndrome").[8,9] Only 8 of the 9 children with FIRES reached ketosis, but in 7 of those 8 cases seizures completely stopped a few days after reaching ketonuria on KD.[7] Ismail et al.[10] also described seizure control with KD in a 14-year-old girl with FIRES. In 2011 Nam et al.[11] reported termination of SE or marked seizure reduction using KD in four children and one adult with RSE. Cervenka et al.[12] reported SE termination with KD in an adult male refractory to both medical treatment and surgery. Recently Vaccarezza et al.[13] found that KD terminated RSE in 4 out of 5 paediatric cases. (The cases are summarized in Table 1.)

To supplement these studies we reviewed all cases from the last five years, in which KD was attempted in treating RSE in children at our centre.

In all cases KD was given via gastric tube as a commercially available formula (KetoCal, SHS, Liverpool, Great Britain) with a fat to carbohydrate and protein ratio of 4:1. Prior to initiating KD all patients were screened for contraindications i.e. beta oxidation defects, pyruvate carboxylase deficiencies and porphyria by a standard urine metabolic screening and carnitine profile.

All glucose administration was removed, including what was contained in different kinds of medicine. We did not start KD before corticosteroid treatment had finished and propofol was not allowed during the KD as this combination has been associated with liver failure.[2] Sedation was upheld by the very high doses of either Phenobarbital or Midazolam that were used as anticonvulsants.

2. Results

2.1. *Case 1*

A 3 year old girl presented with generalized tonic-clonic seizures progressing to acute onset SE following one day of fever and vomiting, which proved to be caused by pneumococcal septicaemia.

As new born she was diagnosed with adrenogenital syndrome (AGS). The AGS condition was consistently well controlled with hormonal substitution therapy, and the child was otherwise healthy and normally developing.

Broad-spectrum antibiotics were given to treat the septicaemia. Two separate spinal taps revealed normal CSF with no signs of inflammation. CT scan on day 3 showed hypointensities in the left cerebral hemisphere.

Seizures were treated with Diazepam (DZP), Valproic acid (VPA) and Phenytoin (PHT) but progressed to SE with right-sided motor seizures over a few days, and the girl was sedated and intubated. In spite of propofol sedation and treatment with high doses of the antiepileptic drugs VPA, PHT, Levetiracetam (LEV), Topimarate (TPM) and both Midazolam (MDZ) and Phenobarbital (PB) as intravenous infusion she remained in status epilepticus.

MRI on day 5 showed oedema of the entire left cerebral hemisphere.

The characteristic clinical symptoms and radiological findings led to the diagnosis of Hemiconvulsion-Hemiplegia Epilepsy syndrome, probably facilitated by the initial septicaemia.

Ketogenic diet was initiated on day 6. On day 7, with moderate ketosis appearing, the seizures stopped completely. She slowly recovered over 2–3 weeks. On day 21 the girl was extubated as her medication had been gradually reduced to a maintenance treatment consisting of Oxcarbazepine (OXC), PHT and TPM. At the time of extubation the KD was weaned for compliance reasons as the girl returned to oral feeding. On day 28 she was discharged to a different hospital for neurorehabilitation as she had a permanent right-sided hemiplegia. The girl developed daily focal seizures 6 months later. KD was reintroduced resulting in more than 50% reduction in seizure frequency lasting 3 months after which seizures again recurred. Epilepsy surgery is currently considered.

2.2. *Case 2*

A 10 year old, previously healthy boy was admitted after having 3 generalized tonic-clonic seizures. Preceding this he had had a common cold for 2 weeks and high fever the last 5 days.

Short generalized tonic-clonic seizures were followed by focal twitches of the face with secondary generalization. Refractory doses of DZP, infusion of MDZ and i.v. loading with Fosphenytoine (FOS) had no effect. Two hours after admission seizure activity necessitated sedation with Propofol.

Extensive investigations for bacterial, viral, autoimmune and metabolic causes were all negative and MRI of the brain was normal.