Original article

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Ketogenic parenteral nutrition in three paediatric patients with epilepsy with migrating focal seizures

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ABSTRACT – *Aims.* Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare epilepsy syndrome, characterized by an onset of multifocal seizures before the age of six months and a rather typical ictal EEG pattern. The ketogenic diet (KD) has been shown to be a treatment option in these patients with variable results. The KD is generally given by enteral formula or solid food, however, patients on the KD often have coexisting medical disorders that may impair the gastrointestinal tract and, in these cases, parenteral nutrition support may be needed. We present our experience with three patients who had been on the KD because of EIMFS, who were acutely unable to absorb nutrients through the intestinal tract.
Results. For these patients, we were unable to reach ketogenic ratios higher than 1.5:1 because of the limited fat intake *via* the parenteral route. This ratio, nevertheless, was adequate for maintenance of seizure control while allowing short-term bowel rest.
Conclusion. Even though our report is limited as it provides no controlled evidence, ketogenic parenteral nutrition should be considered in children on the KD when enteral nutrition is not feasible. Special care should be taken to maintain ketosis and avoid undesired carbohydrates. Patients may respond well to ketogenic parenteral nutrition in spite of a lower ketogenic ratio.

Key words: epilepsy of infancy with migrating focal seizures, EIMFS, ketogenic diet, ketogenic parenteral nutrition

Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare epileptic syndrome, characterized by an onset of multifocal seizures before the age of six months and a typical ictal EEG pattern, consisting of seizures that arise independently and sequentially from both hemispheres (Coppola *et al*., 1995). The seizures are refractory to antiepileptic drugs (AEDs) and cause subsequent severe intellectual disability (Coppola *et al*., 1995; Caraballo *et al*., 2008). The ketogenic diet (KD) has been shown to be a treatment option in these patients (Caraballo *et al*., 2015) with variable results (Caraballo, 2018). Mutations in the *SCN2A*, *KCNT1*, *KCNQ2*, and *CLCN4* genes were identified in patients with EIMFS (Zhou *et al*., 2018).

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The KD is a high-fat, restricted-carbohydrate regimen used for the treatment of drug-resistant epilepsy. The diet has been shown to work particularly well in certain epilepsy syndromes, such as Dravet syndrome, infantile spasms, febrile infection-related epilepsy syndrome (FIRES), and super-refractory status epilepticus (SRSE) (Kossoff *et al*., 2018) and is the first-line therapy for certain inborn errors of metabolism, such as glucose transporter type 1 deficiency and pyruvate dehydrogenase deficiency.

The KD is generally given by enteral formula or solid food, however, patients on the KD often have coexisting medical disorders that may impair the gastrointestinal tract, and in these cases, parenteral nutrition support may be needed. From a therapeutic point of view, in patients with refractory epilepsy on the KD, the primary aim of ketogenic parenteral nutrition (KPN) is to maintain the level of ketosis, defined as serum Betahydroxybutyrate levels (BHB) > 2 mmol/L, (Van Delft *et al*., 2010) and seizure control when enteral nutrition is not possible.

Several medical conditions require complete bowel rest, such as a gastrointestinal tract that is not absorbing food, gastrointestinal feeding causing respiratory distress or poor gut motility, or ileus. These conditions may require intravenous (IV) KD administration, due to transient intestinal failure. KPN has also been reported for the treatment of patients with super-refractory status epilepticus (Lin *et al*., 2015).

Therefore, KPN is used in the immediate postoperative period in patients who underwent surgery and in whom the enteral route is temporally contraindicated, as a bridge to the enteral KD, but may also be applied for the initiation of the KD. In the neonatal and paediatric intensive care unit (PICU), the combination of antiepileptic drugs, general anaesthetics, and mechanical ventilation may warrant initiation of the IV KD as well (Chiusolo *et al*., 2016; Farias-Moeller *et al*., 2017).

Although beneficial effects of KPN have been reported in several studies with short-term outcomes (Jung *et al* 2012; Strzelczyk *et al*., 2013; Lin *et al*., 2015; Chiusolo *et al*., 2016), currently there are no official guidelines for the use of the KPN. The use of KPN is based on case reports and personal experience, varying from institution to institution. Nevertheless, Dressler *et al*. have recently developed an algorithm based on ESPGHAN guidelines to standardize feeding regimens in order to calculate the individual components of KPN (Dressler *et al*., 2017).

Here, we present three patients who had been on the KD because of EIMFS, who were acutely unable to absorb nutrients through the intestinal tract because of appendicitis and intestinal bleeding - that were unrelated to the diet - and required complete bowel rest.

Case reports

Case 1

The patient was a 15-month-old girl who was referred to our centre for multidisciplinary evaluation because of chronic encephalopathy and seizures, and a suspicion of a neurometabolic disease.

At the Department of Neurology, the patient was diagnosed with EIMFS and was put on levetiracetam, lorazepam, oxcarbazepine, and sulthiame.

Shortly after, the patient was admitted to the PICU because of status epilepticus and respiratory distress. Pharmacological treatment with phenobarbital was started and subsequently phentanyl and a continuous intravenous drip of midazolam were added. The patient required mechanical ventilation without inotropic support.

As the patient did not respond to multiple AEDs, the classic ketogenic diet was initiated.

Because of swallowing difficulties, the KD was administered through a nasogastric tube at a 3:1 ratio with good tolerance. Three days after diet initiation, ketonaemia was within the necessary range (blood β-hydroxybutyrate level: 5.2- 5.8 mmol/L) without hypoglycaemia.

The KD was initially administered with a total volume of 115 mL/kg, contributing 60 cal/kg and proteins 1.2 g/k/day. The patient had an excellent response to the diet without further evidence of seizures since the second day after KD initiation.

Because of hyperketosis (BHB: 8 mmol/L) and weight loss, the ketogenic ratio was reduced to 2.5:1 and total calorie intake was increased to 100 cal/kg /d, with 1.6 g/kg proteins.

One month after KD initiation, the patient had an upper gastrointestinal haemorrhage requiring fasting. Therefore, parenteral administration was decided on at a ratio of 1.5:1 (*table 2*).

After three days, a continuous enteral drip was initiated with a ketogenic formula at a 1:1 ratio, gradually increasing the volume up to the level the patient was receiving previous to the GI haemorrhage. The girl was kept on KPN for 10 days. On KPN, β-hydroxybutyrate levels were maintained at 2.3 mmol/L, and were raised to 4.7 mmol/L when enteral formula was added.

The child was slowly weaned from parenteral nutrition. On enteral KD, levetiracetam at 100 mg/kg/day, and sulthiame at 13 mg/kg/day, she was transferred back to the ICU at the centre of her home town with support from the multidisciplinary team through our telemedicine program.

Case 2

The patient was a 14-year-old boy with EIMFS of neonatal onset, followed at our institution since birth.

He had been shown to be refractory to multiple AED schemes. Based on the experience of our team with the KD for different types of epileptic encephalopathy, the patient was finally put on the classic KD at 12 years and 10 months, receiving mixed feeding with KD formula *via* nasogastric tube for liquids and semisolid foods orally because of swallowing difficulties. At diet onset, the boy was receiving topiramate, levetiracetam, lacosamide, clobazam, lorazepam, and zonisamide. He responded well to the diet with a seizure reduction of >50%.

On the diet, the boy's nutritional parameters improved significantly. Weight-for-height went from 73.8% to 90.4%, after 11 months on the KD.

At that moment, the child required surgery because of peritonitis and an appendiceal mass was found. The patient recovered well from the surgery, however, on the third postoperative day, he developed pneumonia and was admitted to the PICU where he was put on mechanical ventilation without the need for inotropic support.

As the patient was still on the KD, but unable to tolerate enteral nutrition due to ileus, KPN was started (*table 2*). The KPN was infused continuously over 16 hours and stopped for eight hours during night time.

As serum protein levels were low, amino acids were calculated at 2g/kg, resulting in a ketogenic ratio of 0.57:1 and very low plasma ketones bodies, which, to our surprise was enough to control the seizures. On Day 8, trophic enteral feeding with a 1:1 ketogenic ratio was initiated. Tolerance was good and serum protein normalized.

After four days, the child was successfully weaned from ventilation.

Over the following seven days, KPN was progressively switched to enteral KD nutrition. Currently, the boy is fed by nasogastric tube and remains seizure-free.

Case 3

The patient was a one-year, seven-month-old girl with neonatal-onset EIMFS, followed at the Neurology Department of our institution since she was six months old.

She had been shown to be refractory to multiple AED schemes. She was started on the classic KD, receiving feeding with KD formula 2:1 with good tolerance, *via* nasogastric tube because of swallowing difficulties. At diet onset, the girl was receiving vigabatrin, topiramate, levetiracetam, and sodium diphenyl hydantoinate.

The child responded well to the diet with a seizure reduction of >50% and was discharged one month after initiation of the KD. She was followed as an outpatient for six months. She only had seizures during infectious episodes.

Ten months after diet initiation, the girl was admitted because of dehydration due to vomiting, acidosis, and fever. She required surgery because of appendicitis (peritonitis). The patient recovered well, however, KPN was started as she was unable to tolerate enteral nutrition postoperatively (*table 2*).

KPN was administered through continuous infusion with a glucose flux of 1.5 mg/kg/min, 0.9 gr/kg amino acids, and 2 g/kg lipids at 31 cal/kg/day. On Day 11, trophic enteral feeding at a 1:1 ketogenic ratio of half the total enteral volume was initiated. Tolerance was slow and she could be weaned off KPN on Day 13.

Discussion

Here, we present three patients with EIMFS in whom KPN was shown to be safe and well tolerated as a transient treatment when administration of the KD *via* the enteral route was not possible. In all three children, seizure control was maintained when transitioning from enteral to parenteral nutrition and also when switching back from parenteral to enteral nutrition. The diet has shown to be effective in seven patients with EIMF reported by our group (Caraballo *et al*., 2015; Caraballo, 2018). KPN was used according to the algorithm by Dressler *et al*. (2017).

Indeed, in our patients we could not reach ratios higher than 1.5:1 because of the limited fat intake and the need to reach adequate allowances of proteins. This ratio, nevertheless, was adequate for maintenance of seizure control while allowing short-term bowel rest.

The macronutrient content of the typical parenteral nutrition solutions differs greatly from the high-fat, low-carbohydrate profile of the classic KD (*table 1*). To achieve ketosis, at least 60% of energy should be provided as lipids. Nevertheless, IV lipids may cause liver toxicity and/or cholestasis (Koletzko *et al*., 2005) and a high ketogenic ratio is difficult to achieve. Exceeding

Table 1. Differences in macronutrient content between the typical parenteral nutrition and the ketogenic parenteral nutrition schemes.

Macros/ %total calories	TPN	KPN
Carbohydrates (%)	50-60	10 Glycerol from SMOF 25%/L- Intralipid 20%/L
Amino acids	10-20	10-20
Lipids	20-30	60-80
Calories target	60-90*	50

*depending on age. Ref ESPGHAN.

Table 2. Differences in constitution of the KPN in our series of patients.

	Patient 1	**Patient 2**	**Patient 3**
	Intravenous only KD	**Intravenous only KD**	**Intravenous only KD**
Ketogenic ratio	1.5:1	0.57:1	0.6:1
Glucose (g/kg)**	0.35	1.5	2.1
Glucose flux (mg/kg/min)	0.24	1	1.5
Aminoacids (g/kg)*	1	2	0.9
Lipids (g(kg) *** DHA+EPA/100ml	2 130.5mg	2 130.5mg	2 130.5mg
beta-hydroxybutyrate (mmol/L)	1.8	0.5	1.6
% calorie target (Schofield Formula)	53	94	60

*Parenteral Aminoacids Supply: Aminoven Infant 10%.
**Parenteral Glucose Supply (body weight per day).
*** Lipids: SMOF Lipid 20 % (Fresenius Kabi): 30% soybean oil, 30% MCT oil 25% olive oil 15%Fish oil, W6:W3 ratio 0.5:1, 150 mg DHA+EPA /100ml.

the IV dose of lipids in paediatrics to more than 2 g/kg implies an increased risk of complications.

When prescribing the KPN in children, maintaining the level of ketosis and seizure control should be weighed against lipid reduction to avoid liver toxicity, resulting in lower ratios than the 3:1 and 4:1 of the classic KD. Ratios in the 2:1 or 1:1 range are feasible.

Jung *et al*. (2012) retrospectively analysed 10 patients who were put on KPN at 4:1 and 3:1 ratios. All patients showed transient hypertriglyceridaemia and one had severe hypertriglyceridaemia; discontinuation of the diet was required for the latter. In our study, the first and third patient (both infants) developed transient hypertriglyceridaemia (up to 449 mg/dL), which returned to normal without any intervention.

Regarding the mechanisms of action, the relationship between seizure control and the most commonly measured metabolite of the diet, the ketone body (KB) betahydroxybutyrate (BHB), is controversial (Buchhalter *et al*., 2017). The role of KBs as either mediators or indicators of seizure control is seriously questioned by the low-glycaemic-index diet, which has no apparent relationship to levels of KBs, yet appears to have efficacy equivalent to that of the classic KD (van Delft *et al*., 2010; Pfeifer and Thiele, 2005). In fact, our patients had low plasma ketone bodies (mean <2 mmol/L) during KPN, but they did respond to the diet.

In addition to KBs, several other metabolic changes have been implicated in KD action, including glycolytic restriction, increased fatty acids, and increased bioenergetic reserves, among others (Masino and Rho, 2012).

EIMFS is caused by genetic defects in various ion channels, the most common being the sodium-activated potassium channel (*KCNT1*), found in up to 50% of cases (Madaan, 2018). Omega 3 polyunsaturated fatty acids (PUFAs) in the diet might have anticonvulsant properties due to inhibitory effects on voltage-dependent ion channels (Taha *et al*., 2010). Unfortunately, no genetic studies could be performed in our patients. Genetic studies on epileptic encephalopathies in Latin America are currently being conducted.

Two of our patients were infants who were already receiving the KD *via* enteral formula according to the European guidelines for infants with refractory epilepsy with very good tolerance (van der Louw *et al*., 2016). The KPN is not included in these guidelines, however, in their study of 17 patients treated with KPN, Dressler *et al*. (2017) included two neonates with Ohtahara syndrome and an infant with EIMFS (of unknown aetiology). Nevertheless, in the child with EIMFS, the KPN did not control seizures. Although the authors did not specify the lipid emulsion used in this child, we wonder whether the efficacy of the KPN in our cases may be due to the content of PUFAs and especially DHA in the SMOF SC IV lipid emulsion used at our centre.

Relevant ketosis in that study (Dressler *et al*., 2017) was reached in 10 children, but not in seven, the mean of parenteral fat:non-fat ratio was 0.9. Our mean parenteral fat:non-fat ratio was 0.89. A low ketogenic ratio is to be expected due to the limit of the fat intake *via* the parenteral route. Only mild and transient adverse effects were seen in that cohort with low ratio KPN as was seen also in our case reports.

In patients on KPN, early introduction of enteral KD formula at a slow rate, *i.e.* trophic feeding, should be considered to prevent liver dysfunction and impaired bile flow (Zupec-Kania *et al*., 2011). In our three patients, a slow switch to the enteral route was made as soon as possible with good tolerance, and thereby ketosis was increased and the calorie target was reached, achieving nutritional catch up.

Stress hyperglycaemia may be an obstacle to reach and maintain ketosis in a critically ill patient. Lin *et al*. (2015) described a patient on KPN for the treatment of SRSE, in whom the 5% dextrose water had to be switched to a sugar-free solution for the KPN because of hyperglycaemia of more than 150 mg%. As for all KD treatment, care should be taken to avoid carbohydrates in intravenous fluids. Glycerol is a solvent used in parenteral lipid emulsions, which is a trihydroxy-alcohol derived from fats that is converted into a carbohydrate. Therefore, when preparing a KPN solution, this source of carbohydrate should be taken into account. We found that the ratio in our patients was even lower when glycerin carbohydrate was accounted for. However, even at this lower ratio, ketosis was maintained and seizures were controlled.

Based on the above, the question arises as to whether KPN ketogenic ratios as high as those in enteral nutrition are necessary. Our three patients maintained ketosis and seizure control at much lower ratios. This may be explained by the SMOF lipid emulsion used, which contains a higher percentage of medium chain triglycerides and Omega 3, resulting in a stronger antiseizure effect, as hypothesized by other authors (Augustin *et al*., 2018).

Additionally, there may be a certain degree of fat malabsorption in patients on the KD *via* the enteral route that is avoided in KPN and leads to a greater effectivity of IV lipids. If this is the case, it may not be necessary to reach the 4-g/kg IV lipid level during KPN. However, the disadvantage would be that caloric intake is lower and therefore this type of KPN can only be maintained for short periods (3-4 days).

The use of KPN in our three as well as previously reported patients calls for a consensus involving a multi- and interdisciplinary team in the PICU.

Here we report the clinical efficacy and safety of the KPN in three patients with EIMFS. Even though our report is limited as it provides no controlled evidence, KPN should be considered in children on the KD when enteral nutrition is not feasible. Special care should be taken to maintain ketosis and avoid undesired carbohydrates. Patients may respond well to KPN in spite of a lower ketogenic ratio. □

Disclosures.
None of the authors have any conflict of interest to declare.

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