9

Ketogenic Diet in Status Epilepticus

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INTRODUCTION

Status epilepticus (SE) is defined by continuous epileptic status with alteration of consciousness. Status epilepticus might be a single prolonged seizure or recurrent seizures repeated frequently without recovery of consciousness between the seizures. The incidence of SE is 3–41/100,000 individuals per year (Chin et al., 2006, Raspall-Chaure, 2007, Dham, 2014) and it is the second most common neurologic emergency in adults and the first in children. The duration of SE was long debated, and an operational definition is proposed for tonic clonic status defining T1 as the time that emergency treatment should be started and T2 as the time at which long-term consequences on the brain might be expected (Trinka et al., 2015). For instance, T1 is from 5 minutes and above and T2 is over 30 minutes of duration (Trinka et al., 2015). 12%–43% of patients with SE fail to respond to first- and second-line therapy, and they enter refractory SE (after 2 hours of the onset of SE). Super-refractory SE (SRSE) is defined by the persistence of SE over 24 hours (Ferlisi and Shorvon, 2012). Overall, ~15% of SE cases admitted to the hospital become super-refractory (DeLorenzo, 1995; Krumholz et al., 1999; Ferlisi and Shorvon, 2012).

In adults, SRSE presents a high rate of mortality (>60%) (Ferlisi and Shorvon, 2012). Although the risk of death is low in the pediatric population, the risk of subsequent neurological morbidity and cognitive problems is high (Scott, 2009). The therapeutic intervention aims to reduce SRSE duration, mortality, and short- and long-term comorbidities.

Status epilepticus can be tonic clonic, tonic or myoclonic. It can be associated with acute or chronic brain disease or can occur in patients with known epilepsy. It might occur at the onset or in the course of the disease (Trinka et al., 2015). For instance,inaugural convulsive SE without previous known epilepsy occurs in CNS infections (encephalitis, meningitis), autoimmune epilepsies, epilepsies with presumed immune etiology such as FIRES and NORSE, metabolic disorders, and stroke. SE might occur during the course of epilepsy syndromes; tonic clonic or clonic in Dravet syndrome, tonic in Lennox Gastaut syndrome. In myoclonic atonic epilepsy (Doose syndrome), myoclonic status might occur at onset or during the first months. Myoclonic nonconvulsive status is frequent in some genetic syndromes such as Angelman syndrome, and in mitochondrial diseases (Trinka et al., 2015).

Identifying a possible underlying cause and treating it is an important step in the treatment of SE. An etiology-targeted therapy should be instituted as soon as the etiology is identified (antibiotics for CNS infections, antiviral agents for encephalitis, immune therapy for auto-immune encephalitis).

Benzodiazepines are the first-line therapy in SE, with different molecules used and different routes of administration; buccal, intra rectal or intra muscular. If benzodiazepines fail to stop the SE, phenytoin is usually the second-line drug. The use of other AEDS with IV formulations is the usual next step after the failure of phenytoin (Shorvon and Ferlisi, 2011). Barbiturate anesthesia is the most common third-line drug and is used in adults more often than in children. Propofol and ketamine can also be used (Ferlisi et al., 2015). The failure rate of anesthesic barbiturate and the frequent recurrence after withdrawal with associated high mortality and morbidity make it essential to develop other therapies for medication-resistant SE.

The KD has reported efficacy in SE (Kossoff and Nabbout, 2014). The multiple mechanisms of action of KD make it a good choice for refractory SE. The inherent combination of these mechanisms can mimic AED polytherapy, an approach that is suggested to be a good choice for RSE (Löscher, 2015, Gama et al., 2015, Lusardi et al., 2015).

KETOGENIC DIET IN CONVULSIVE STATUS EPILEPTICUS

The first report of efficacy of KD in a series of patients with highly recurrent seizures was in 2009 by Villeneuve et al. (Villeneuve et al., 2009). The authors reported KD response in a retrospective pediatric series of patients with focal pharmacoresistant epilepsies. The efficacy of KD was higher in patients who presented with SE or recent worsening of seizure frequency (Villeneuve et al., 2009). In this first series, efficacy was reported in different etiologies such as Sturge-Weber syndrome, FIRES, and cryptogenic focal SE (Villeneuve et al., 2009). A second paper in 2010 reported an international series of nine patients with SRSE due to FIRES with 7/9 responders to KD (Nabbout et al., 2010). The KD was well tolerated via nasogastric tube in the pediatric ICU setting. Ketosis was achieved mostly within 24 hours and SE stopped during the first days of the diet and in all responders within the first week (Nabbout et al., 2010).

Other reports of SE due to FIRES or similar immune entities were further reported in the literature, including pediatric (Vaccarezza et al., 2012, Nam et al., 2011, Sort et al., 2013, O'Connor et al., 2014) and adult patients (Cervenka et al., 2011, Thakhur et al., 2014). The pathophysiology of FIRES, based on activation of an inflammatory cascade (Nabbout et al., 2011), makes this syndrome a possible specific target for KD. The majority of patients reported had RSE due to inflammatory etiologies (Table 9.1). This trend is confirmed by the largest pediatric series with FIRES (Nabbout et al., 2010) and in adult series (Thakur et al., 2014). In this last series of 10 patients, 4 patients presented with NORSE, 2 with anti-NMDA encephalitis, and 1 with LGI1 encephalitis.

Other etiologies, possibly involving inflammation cascades, were reported as a possible indication for KD in SE; the over representation of these inflammatory etiologies might be due to their frequency in SRSE. Patients with Rasmussen syndrome, an encephalitis involving the activation of the T cell pathway were reported as responders in a few pediatric (Villeneuve et al., 2009) and adult patients (Wusthoff et al., 2010).

SE in mitochondrial diseases as in Alpers disease with POLG1 mutations (Martikainen et al., 2012) and with stroke-like accidents as in MELAS syndrome (Steriade et al., 2014) are good candidates for KD to be introduced early at onset (Desguerres et al., 2014). Other small series of patients with focal SE due to structural lesions were also reported as responders to KD in pediatric (Villeneuve et al., 2009, Caraballo et al., 2014, Lin et al., 2015) or adult series (Bodenant et al, 2008).

KETOGENIC DIET IN NONCONVULSIVE STATUS EPILEPTICUS

The efficacy of KD is not restricted to convulsive SE. The efficacy of KD was reported in myoclonic

TABLE 9.1 REPORTS OF EFFICACY OF KETOGENIC DIET (KD) IN SE IN CHILDREN AND ADULTS. *KD WAS INTRA VENOUS (IV)

Author	Population	Diet	Etiology	Time to response
Bodenant (2008)	1 adult	KD	Partial	7 days
Villeneuve (2009)	5 children	KD	SWS, encephalitis...	1–10 days
Kumada (2009)	2 children	MAD	Frontal lobe, heterotopia	5–10 days
Wusthoff (2010)	2 adults	KD	Rasmussen, head trauma	8–10 days
Nabbout (2010)	9 children	KD	FIRES	4–6 days
Cervenka (2011)	1 adult	KD	Idiopathic, autoimmune	7 days
Ismail (2012)	1 child	KD	FIRES	10 days
Nam (2012)	4 children, 1 adult	KD	Encephalitis	1–19 days
Vaccarezza (2012)	5 children	KD	FIRES, partial status	?
Sort (2013)	3 children	KD	FIRES, HHE, mito	1–6 days
Thakur (2014)	10 adults	KD	Super refractory SE (70% "encephalitis")	1–7 days
O'Connor (2014)	5 children	KD	Mito, myoc, FIRES?	2–8 days
Caraballo (2015)	10 children (7/10)	KD	Focal seizures	5–7 days
Lin (2015)	1 child	KD*	Focal with Gen	2–3 days
Caraballo (2015)	2 children	KD	Myoclonic status (EE in 1)	3 days

SE of mitochondrial diseases and POLG mutations (Martikainen et al., 2012, Desguerres et al., 2014) and of myoclonic astatic epilepsy, or Doose syndrome (Kelley et al., 2010, Caraballo et al., 2013,), and in patients with myoclonic SE from unknown etiologies (Caraballo et al., 2015). KD efficacy was also reported in patients with electrical SE during slow sleep (ESES) (Reyes et al., 2015; Veggiotti et al., 2012).

CHALLENGES OF KETOGENIC DIET USE IN STATUS EPILEPTICUS

The challenges of the KD might raise some concerns that limit its widespread use for SE in ICUs. Implementation of the diet could be a complex issue in ICUs, especially in centers lacking KD teams. The availability of the KD team and the daily communication between the neurologists, child neurologists, dietitians, and ICU teams are strongly recommended, enabling initiation of the diet under optimal conditions. This daily communication makes it possible to respect the follow-up of the diet, thus avoiding any additional glucose load from fluids and concomitant medications. Enteral feeding should be privileged, since parenteral feeding cannot achieve a high-ratio KD. Enteral feeding is usually well tolerated in our experience, especially when initiated with continuous infusion slowly increasing the feeding rate to achieve the total caloric intake within 48–72 hours. The major steps for successful implementation in the ICU are summarized in Figure 9.1.

Another limiting factor for the use of the diet might be the time lag for efficacy. In the reported series, ketosis appears within 24 to 72 hours and seizure reduction within the first week (Table 9.1). This time lag is difficult to accept in a severe condition such as SE. Although many studies confirmed the main role of underlying etiology in the cognitive outcome of SE, the long duration of SE might also negatively impact the long-term outcome (Kilbride et al., 2013). However, after the first- and second-line therapies for SE, treatment alternatives are scarce and the use of an anesthetic agent is usually the main strategy left (Ferlisi and Shorvon, 2012). Anesthetic agents are potent seizure suppressors and might help to shorten the SE but their use is based on expert opinion and is not evidence based. In addition, some concerns have been raised about possible worsening of the outcome of refractory SE after the use of anesthetic agents (Sutter et al., 2014, 2015, Ferlisi et al., 2015). Limiting dextrose containg IV fluids early in the course of the SE

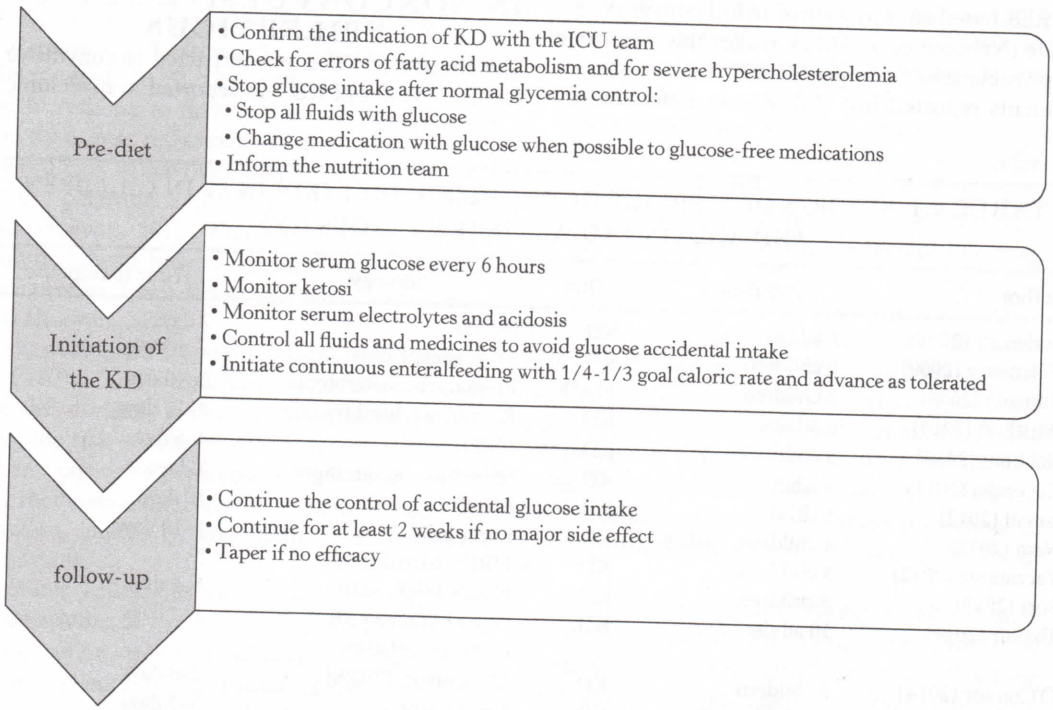

FIGURE 9.1 Steps to implement the diet in ICU.

after blood glucose has been controlled, and initiating the diet as soon as inborn errors of fat metabolism are ruled out might help to shorten the delay of ketosis and improve the efficacy of KD. Along these lines, some medications used in the setting of SE and refractory SE, such as steroids, can delay ketosis. They should be avoided when medically unnecessary (Nabbout et al., 2010).

The reports of KD in SE are mainly retrospective, reporting small numbers of individuals treated and rarely referring to patients where the diet failed. In addition, comedication and changing doses of comedication with the possible time to achieve efficacy of the diet might make causal attribution debatable. Finally, reports lack the long-term follow-up studies reporting cognitive and neurological outcome, which is, apart from mortality, the major endpoint of any treatment of refractory SE. Indeed, KD reports share the same weakness with all third-line therapies in refractory SE where no drug or therapy has achieved a high level of evidence-base medicine (Ferlisi and Shorvon, 2012).

The KD is well tolerated with low rates of side effects in the short and long term in the ICU setting, as detailed in different reports (Table 9.1). The increasing number of reports worldwide demonstrates its possible implementation in ICUs. Its efficacy in inflammatory SE or in SE from other etiologies, convulsive and nonconvulsive, should make it a therapeutic option in the treatment of refractory SE. Recently a few data on possible improvement of cognitive outcome are emerging in patients with FIRES (Kramer et al., 2011, Singh et al., 2014).

A prospective, randomized controlled trial is necessary to validate this treatment option, as for all third-line therapies for refractory SE. This is important for physicians—at least one patient has died after the KD was stopped following seizure arrest because "this indication was not considered as good clinical practice" (Nabbout et al, 2010). This trial should evaluate efficacy and tolerance and would be mandatory for the acceptance of KD by physicians and by health authorities and institutions. Outcomes should be evaluated in the short term - aiming for control of SE - and also in the long-term (at a few months or longer) to evaluate seizure control as well as cognitive outcomes. Pending the results of such a trial, KD should be available in ICUs and be part of the treatment arsenal of refractory SE, a critical situation where evidence-based medicine is dramatically lacking to date.

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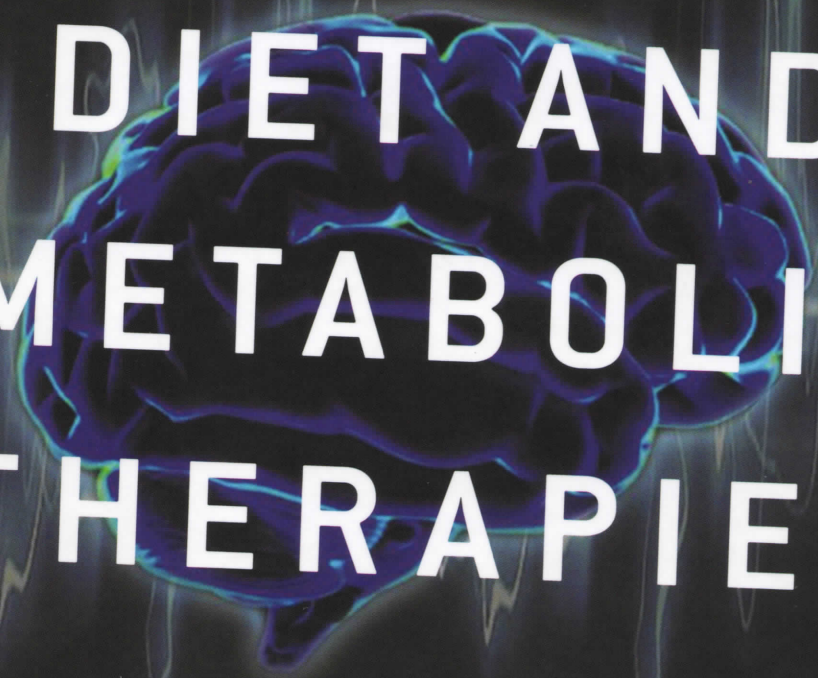
KETOGENIC DIET AND METABOLIC THERAPIES



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