



Review article

How effective is the ketogenic diet for electrical status epilepticus of sleep?

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ABSTRACT

Electrical status epilepticus of sleep (ESES), with the activation of profuse amounts of epileptiform discharges in sleep, may lead to intractable epilepsy and neurocognitive decline in children. Numerous varied treatments including antiseizure medications, steroids, and surgery have been investigated as possible treatment options. The ketogenic diet (KD) is an additional treatment option which may add to our treatment armamentarium for ESES. The KD may theoretically improve ESES by affecting GABA systems and reducing inflammation. Clinical reports of the KD for ESES have been heterogeneous, but to date 38 children have been described in six publications. Overall, 53% had EEG improvement, 41% had >50% seizure reduction, 45% had cognitive improvement, but only 9% had EEG normalization. This review will assess the efficacy of the KD in the treatment of ESES based on known data as well as possible mechanisms of action and the need for future study.

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1. Introduction

Electrical status epilepticus of sleep (ESES) is a cause of childhood-onset intractable epilepsy in which the vast majority of the EEG during non-REM sleep is filled with electrographic spikes with a resultant decline in neurocognitive function. A variety of approaches have been tried to treat this disorder including anti-seizure medications and steroids (Loddenkemper et al., 2011a; Caraballo et al., 2013). Unfortunately, at this time there are no controlled studies assessing these treatments and there are rela-

tively small numbers of patients studied. ESES is often resistant or partially responsive to anti-seizure medication and those patients who respond to steroids often recur when medications are weaned (Veggiotti et al., 2012).

The ketogenic diet (KD) has been used for nearly 100 years in the treatment of intractable epilepsy (Winesett et al., 2015). Researchers have identified several indications recently for which the KD may be particularly effective (Kossoff et al., 2009). In Table 1 of the 2009 Expert Consensus Statement, several indications were highlighted, including those with “suggestion of benefit” from one case report or series (Kossoff et al., 2009). At that time, Landau-Kleffner syndrome, a syndrome in which ESES is present on the EEG, was mentioned as a possible indication due to a single case series 10 years prior (Bergqvist et al., 1999). Since that time, five

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Table 1

Summary of studies looking at the use of the Ketogenic diet in ESES.

Study	Prospective/ Retrospective/ Case Report	Year	ESES Definition (Spike-wave Index)	Number of patients	Improvement in seizure control (>50%)	EEG improvement	EEG normalization	Neurocognitive improvement
Bergqvist et al	R	1999	>50%	3	3/3 (100%)	2 (67%)	0 (0%)	3 (100%)
Kang et al	C	2006	>85%	1	N/A*	1 (100%)	1 (100%)	1 (100%)
Nikanorova et al	P	2009	>85%	5	N/A**	3 (60%)	1 (20%)	1 (20%)
Raha et al	R	2012	>50%	4	1/4*** (25%)	Not reported	Not reported	2 (50%)
Ville et al	R	2015	>50%	13	5/11**** (45%)	8 (62%)	0 (0%)	8 (62%)
Reyes et al	R	2015	>85%*****	12	4/12 (33%)	4 (33%)	1 (8%)	2 (17%)
Total				38	13/32 (41%)	18/34 (53%)	3/34 (9%)	17/38 (45%)

* Patient did not have clinical seizures; ** All 5 patients were already seizure-free with valproate or oxcarbazepine at the time of KD initiation; *** inferred age, exact number not reported **** 2 patients considered responders were seizure-free prior to KD onset; ***** Seen in 8 of 12 patients.

other papers have been published describing the use of the KD for other conditions in which the EEG demonstrates ESES (Kang et al., 2006; Nikanorova et al., 2009; Raha et al., 2012; Ville et al., 2015; Reyes et al., 2015). In our personal experience, we have received increasing consults requesting KD therapy for ESES, perhaps reflecting both the more widespread acceptance of KD therapy for epilepsy overall as well as lack of benefit from other treatments for ESES. We therefore conducted a PubMed search using the keywords “ketogenic,” “ESES,” “CSWS,” and “Landau-Kleffner” to find studies addressing the use of the ketogenic diet in ESES. In this review, we will discuss the current evidence for the treatment of ESES with the KD, as well as potential mechanisms for its action.

2. Background of ESES

ESES was initially described in 1971 (Patry et al., 1971). Within the literature there are varying definitions but it is consistently described as epileptiform activity that activates with sleep. When associated with neurocognitive changes it is referred to as encephalopathy with continuous spike wave of sleep. The epileptiform activity on EEG is present in a significant portion of non-REM sleep (Loddenkemper et al., 2011b). The percentage of affected sleep that defines ESES varies in the literature, but typically ranges from 50 to 85%. The ILAE has proposed that any time greater than 50% of the record has seizure activity a work-up for ESES should be completed (Scheltens-de Boer, 2009). Most, but not all, of these children will have clinical seizures and many will have a decline in neurocognitive function and neuropsychological regression. ESES may encompass more severe cases such as Landau-Kleffner Syndrome (LKS) and Continuous Spike-Wave of Sleep (CSWS) in the literature as well (Veggiotti et al., 2012). In LKS, children lose speech and in some cases the ability to recognize sounds in the setting of having focal or generalized ESES on their EEG. The majority of these children also have clinical seizures (Nickels and Wirrell, 2008). CSWS encompasses an encephalopathy associated with ESES. The terms CSWS and ESES are often used interchangeably. In ESES the EEG activity may be lateralized or bilateral and may be idiopathic, due to an underlying structural abnormality, or genetic etiology. In tertiary care centers ESES can be seen in as many as 0.6% of childhood epilepsy cases (Scheltens-de Boer, 2009).

ESES may have its detrimental effect on neurocognition due to the disruption of normal sleep architecture which prevents normal memory formation and consolidation during sleep (Holmes and Lenck-Santini, 2006). Studies have found that the frequency of nocturnal spikes correlates with amount of neurocognitive dysfunction (Weglage et al., 1997). Animal studies have additionally demonstrated that prolonged interictal spiking may have long term effects on cognition, for example impairing memory and decreasing neurogenesis (Khan et al., 2010). However, spiking is likely not the only reason for cognitive changes. Even though current therapies are aimed at reducing spike burden, improvement in cognition

does not always correlate with this change (Bolsterli et al., 2011). The EEG abnormality itself does typically resolve on its own around puberty, however cognitive deficits often remain (Kramer et al., 2009a).

3. Current medication treatments for ESES

Several case reports exist looking at different options for the treatment of ESES (van den Munckhof et al., 2016). There have been no controlled or randomized studies evaluating the best treatment option. The case studies in the literature describe patients who are on multiple medications and have a wide range of symptoms and severities of the disorder making it difficult to compare the treatments.

A recent pooled analysis compared the most commonly used treatments for ESES (van den Munckhof et al., 2015). This study looked at anti-seizure medications as a group, benzodiazepines, steroids, and surgery. The KD was not studied in this particular analysis. In this evaluation, the authors looked at EEG and cognitive outcomes. While the study was limited by the heterogeneity present in the ESES patients, as well as small samples sizes, publication bias, and the fact that many of the studies reviewed were retrospective in nature, the authors found that antiseizure medications as a group were less effective than benzodiazepines or steroids.

Other studies have looked more specifically at individual anti-seizure drugs such as valproic acid and levetiracetam to assess epileptiform discharge clearance rates after initiation of medication. In children with new onset epilepsy (not ESES) epileptiform discharges resolved during sleep 50% of the time on valproate in one study (Libenson and Caravale, 2001). In CSWS specifically, the combination of valproate and ethosuximide was effective for a small proportion of children in a prospective study (Liukkonen et al., 2010) but in other retrospective studies valproate alone or in combination with benzodiazepines was not found to be effective in reducing spiking (Scholtes et al., 2005; Kramer et al., 2009b). Levetiracetam was found to be effective in decreasing epileptiform discharges in 41% of patients with ESES (Kramer et al., 2009b). Recent studies have advocated the use of both high dose diazepam as well as the use of clobazam (Vezzani and Granata, 2005; Lowenstein, 2009). A study in 2014 looked at the treatment choices for CSWS among North American epileptologists and found that high dose benzodiazepines followed by valproic acid and then corticosteroids were the preferred treatment choices (Sanchez Fernandez et al., 2014). In this survey, the KD was deemed more effective than surgery when ESES was pharmacoresistant.

4. Effects of the KD on seizures and cognition

The KD is a high fat, low carbohydrate, and adequate protein dietary therapy which has been used since the 1920s for the treat-

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