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Effects of Vagus Nerve Stimulation and Ketogenic Diet on Quality of Life and Changes in EEG and Sleep

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Ketogenic Diet Improves Sleep Quality in Children with Therapy Resistant Epilepsy

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SUMMARY

Purpose: The study purpose was to evaluate sleep structure during ketogenic diet (KD) treatment in children with therapy resistant epilepsy and to correlate possible alterations with changes in clinical effects on seizure reduction, seizure severity, quality of life (QOL) and behaviour.

Methods: Eighteen children were examined with ambulatory polysomnographic recordings initially and after three months of KD treatment. Eleven children continued with the KD and were also evaluated after 12 months. Sleep parameters were estimated. Seizure frequency was recorded in a diary and seizure severity in the National health seizure severity scale (NHS3). QOL was assessed with a visual analogue scale. Child Behaviour Checklist and Ponsford and Kinsella's Rating-Scale of Attentional Behaviour were used.

Results: KD induced a significant decrease in total sleep ($p=0.05$) and total night sleep ($p=0.006$). Slow wave sleep was preserved, rapid eye movement (REM) sleep increased ($p=0.01$), sleep stage two decreased ($p=0.004$) and sleep stage one was unchanged. Eleven children continued with the KD and were also evaluated after 12 months. They showed a significant decrease in daytime sleep ($p=0.01$) and a further increase in REM sleep ($p=0.06$). Seizure frequency ($p=0.001$, $p=0.003$), seizure severity ($p<0.001$, $p=0.005$) and QOL ($p<0.001$, $p=0.005$) were significantly improved at three and twelve months. Attentional behaviour was also improved, significantly so at three months ($p=0.003$). There was a significant correlation between increased REM sleep and improvement in QOL (Spearman $r=0.6$, $p=0.01$) at three months.

Conclusion: Ketogenic Diet decreases sleep and improves sleep quality in children with therapy resistant epilepsy. The improvement in sleep quality, with increased REM sleep, seems to contribute to the improvement in QOL.

Key Words: sleep, REM sleep, slow wave sleep, children, epilepsy, ketogenic diet, EEG, quality of life, attention, behaviour

INTRODUCTION

Ketogenic diet (KD) is a high fat, low carbohydrate and low protein diet that has been used for childhood therapy resistant epilepsy since the 1920s. It was developed to mimic the ketotic state of starvation (1, 2). A standard approach to KD treatment includes a 2-year diet period with a 6- to 12- months wean (3). Fasting and fall in blood glucose reduces plasma insulin production and stimulates lipolysis and production of fatty acids. Fasting is also up-regulating the MCT-1, monocarboxylic transport system of ketone bodies to the brain. Ketone bodies can pass directly into the neuronal mitochondria. Once in the mitochondria, beta-hydroxybutyrate is converted to acetoacetate and acetoacetate-CoA for the ATP production in the tricarboxylic acid cycle. Efficacy and safety have been demonstrated in several studies. At least 50% of children with therapy resistant epilepsy achieve more than a 50% reduction in seizure frequency (4, 5). The reported improvement in attention, cognition and behaviour seems to be unrelated to the level of attained seizure control (6). The basis for the improvement in both seizure control and behaviour is still unclear. There are different theories of the anti epileptic mechanisms of ketogenic diet. Increased cerebral energy reserves with decreased ictal excitability, decreased rate of glutamate transamination to aspartate and, possibly, enhancement in the rate of

glutamate decarboxylation to GABA, may be some of the important mechanisms behind the increased resistance to seizures in ketotic brain tissue in response to starvation or KD (7, 8).

The effects of KD on sleep have not yet been elucidated as far as we know. Patients with frequent or medically intractable seizures have multiple sleep abnormalities including increased latency to sleep onset, increased number and duration of awakenings, decreased sleep efficiency, increased number of stage shifts and decreased or fragmented rapid eye movement (REM) sleep (9, 10). Inadequate sleep can exacerbate daytime-drowsiness, memory dysfunction, defective attention and behavioral problems thus affect quality of life (QOL) (11). Influences of sleep on epilepsy are also well known. The different sleep stages have a different effect on interictal discharge production. In non REM sleep, particularly in sleep stage two, a synchronizing effect is shown with an increase and a spreading of the interictal abnormalities and seizures. In contrast, REM sleep, with its asynchronous cellular discharge patterns and skeletal motor paralysis, increases the resistance to propagation of epileptic EEG discharges and to clinical motor accompaniment (12-14).

The study purpose was to evaluate sleep structure following KD in children with therapy resistant epilepsy and to correlate possible alterations with changes in clinical

effects on seizure reduction, seizure severity, QOL, attention and behaviour. This study includes all children put on KD from December 1999. The first 18 children are presented in this study.

METHODS

Subjects

Eighteen children (nine boys and nine girls) aged 2 -15 years (median 7.5 years) with the diagnosis of therapy resistant epilepsy with developmental impairment, and absence of non-epileptic seizures or specific sleep disorders were started on KD. Epilepsy surgery had been performed

in one patient (# 4) and found not applicable in the others. Additional clinical features of the patients are given in Table 1. All children were controlled in the same epilepsy center with the same KD-nurse. Patients remained on stable anti-epileptic drug medication for at least three months prior to the KD initiation and during the follow up. Plasma-concentrations of anti epileptic drugs (AED) were taken every third month and found not changed. Written informed consent was obtained. The study was accepted by the Ethics Committee of the Faculty of Medicine of the Lund University.

Table 1

Pat No	Age at KD-onset (yr)	Age at epilepsy onset (yr)	Etiology	Epilepsy type/syndrome	AED	Seizure type	Changes in seizure frequency at 3 months (%)	Changes in seizure frequency at 12 months (%)
1	7	3	Unknown	Generalized	SUX	AD GTCS	Decreased 99%	Decreased 99%
2	14	5	Unknown	MAE	CLON VPA LTG	Tonic/Gen	Decreased 90%	Decreased 40%
3	2	0,13	Unknown	IS, L-G	CLON LTG Sulth CLOB	AA GTCS	Decreased 72%	Decreased 30%
4	11	0,25	Asphyxia	IS, L-G	Nitra LTG VPA CLON	TC/2°GTCS	Unchanged 0%	
5	5	2,5	Encephalitis	Generalized, L-G	OXC LTG	AA AD TD	Decreased 90%	Decreased 89%
6	4	0,75	Unknown	Partial Crypt	VPA CBZ	Tonic/Gen	Decreased 96%	Decreased 90%
7	8	5	Unknown	Partial Crypt	AZT	TC/2°GTCS	Increased 50%	
8	4	Neonatal	Asphyxia	Generalized	LTG Nitra	TD MC	Decreased 100%	Decreased 80%
9	5	2	Encephalitis	Generalized	VPA OXC	TC/2°GTCS	Decreased 22%	
10	9	Neonatal	Asphyxia	IS, Partial Crypt	LTG GBP CLOB	Tonic/Gen MC	Decreased 72%	Decreased 85%
11	5	Neonatal	Asphyxia	IS, Partial Crypt	VGB VPA CLON	AA TD MC	Decreased 40%	Decreased 88%
12	3	0,67	Unknown	Partial Crypt	LTG Sulth CLOB	Tonic/Gen	Decreased 100%	Decreased 100%
13	9	Neonatal	Asphyxia	IS, L-G	VPA Nitra	Tonic/Gen	Decreased 30%	Decreased 37%
14	9	Neonatal	Unknown	Partial Crypt	LTG TPA	TC/2°GTCS	Decreased 80%	
15	14	6	Sp tumor, HC	Partial Sympt	OXC CLON	TC/2°GTCS	Unchanged 0%	
16	13	2,5	CMV	Partial Sympt	TPA	GTCS	Decreased 67%	
17	6	1	Asphyxia	L-G	LTG Sulth CLOB	TD MC	Decreased 100%	Decreased 100%
18	15	0,5	GLUT-1	Generalized	LTG	AD	Decreased 100%	

Abbreviations: AA, Atypical Absence; AD, Atonic Drop; AED, Anti Epileptic Drugs; AZT, Acetazolamide; CBZ, Carbamazepine; CLOB, Clobazepam; CLON, Clonazepam; CMV, Cytomegalovirus; Crypt, Cryptogenic; GBP, Gabapentin; GLUT-1, Glut-1 deficiency; GTCS, Generalized Tonic Clonic Seizures; HC, Hydrocephalus; IS, Infantile Spasms; L-G, Lennox-Gastaut; LTG, Lamotrigine; MAE, Myoclonic Astatic Epilepsy; MC, Myoclonic; Nitra, Nitrazepam; OXC, Oxcarbamazepine; Sp, Spinal; Sulth, Sulthiame; SUX, Suxinutrin; TC, Tonic Clonic; TD, Tonic Drop; TPA, Topiramate; VPA, Valproate

Ketogenic Diet

All children were admitted to the hospital and started gradually on the diet following a 12-hour out patient fast. The children were started on the classical KD. Fifteen received a 4:1 and three a 3.5:1 ratio implying 4 g or 3.5 g of fat to 1 g of combined protein and carbohydrates. Sixteen children were kept stable and two more changed from ratio 4:1 to 3.5:1 during the first three months and were then kept stable. The children also received the recommended daily intake of vitamins and minerals and were supplemented with calcium, magnesium, phosphorous, potassium and carnitine. The children were closely monitored to exclude intake of extra carbohydrates. In two children the diet was introduced via a gastrostomy tube, using Ketocal and a soy milk based ketogenic formula.

Polysomnographic recordings

Ambulatory polysomnographic recordings (PSG) with the children in their natural surroundings were performed initially and after three and twelve months of KD treatment. The Embla A10 Flaga-Medcare digital data recorder, using sampling rate 200 Hz with 16 bits resolution was used. The digitalized data was transferred to Somnologica 3.1 (Flaga hf. Medical Devices) for PSG analysis. Sleep parameters were scored according to Rechtschaffen and Kales criteria (15) both automatically and manually. We used the

Somnologica automatic sleep scoring hypnogram with necessary corrections for overestimated slow wave sleep (SWS) and underestimated REM sleep. Sleep stage 3 and 4 were treated together as SWS.

Monitoring

During three months before KD initiation, a diary of seizure frequency and severity was collected together with clinical data. The severity of the seizures was scored with the National Hospital Seizure Severity Scale (NHS3), a further development of the Chalfont Seizure Severity Scale described by O'Donoghue et al (16). QOL was assessed with a visual analogue scale and parents' perception of the children's general behaviour and attention were quantified by using the total score of the Child Behaviour Checklist (CBCL) (17) and Ponsford and Kinsella's rating scale of attentional behaviour (18). Follow-up assessments were performed after three and twelve months of KD.

Statistical Evaluation

Wilcoxon signed rank test was used for comparison of data from the hypnogram. Median time in minutes and percent of total night sleep were analysed in REM sleep, sleep stage one, sleep stage two and SWS, initially and after three and twelve months of KD treatment. Wilcoxon signed rank test was also used for comparison of the clinical data on seizure frequency, seizure severity, QOL, attention and

behaviour before KD initiation and three and twelve months later. Spearman rank correlation coefficient (r) was used to calculate the correlation in degree of improvement between sleep parameters and clinical effects. The level of significance was set at $p < 0.05$.

RESULTS

Sleep scoring

KD induced a significant decrease in total sleep ($p=0.05$) and total night sleep ($p=0.006$). SWS was preserved, REM sleep increased ($p=0.01$) (Fig. 1 and 2), sleep stage two decreased ($p=0.004$) and

sleep stage one was unchanged. Eleven children continued with the KD and were also evaluated after 12 months. They showed a significant decrease in daytime sleep ($p=0.01$) and a further increase in REM sleep ($p=0.06$). The medians and ranges of PSG sleep variables are shown for all 18 children, initially and after three months of KD in Table 2 and for the 11 children that continued, initially and after three and 12 months of KD in Table 3. Median and range of the beta hydroxybutyrate levels initially and after three and 12 months in the two groups are also shown in Table 2 and 3.

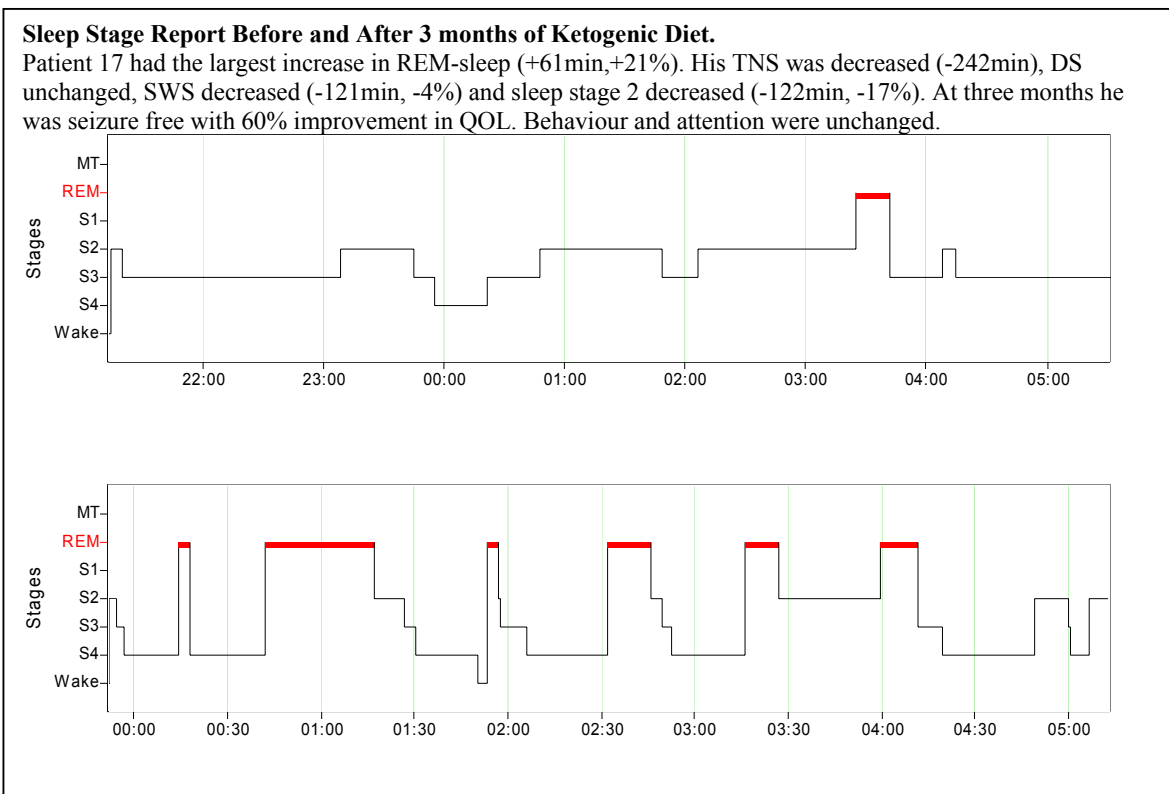


Figure 1

Sleep Stage Report Before and After 3 months of Ketogenic Diet.

Patient 3 had a large increase in REM-sleep (+75min, +14%). His TNS was decreased (-40min), DS unchanged, SWS decreased (-61min, -6%) and sleep stage 2 decreased (-52min, -7%). At three months he had a 75% seizure reduction with 60% improvement in QOL. Behaviour and attention were also improved.

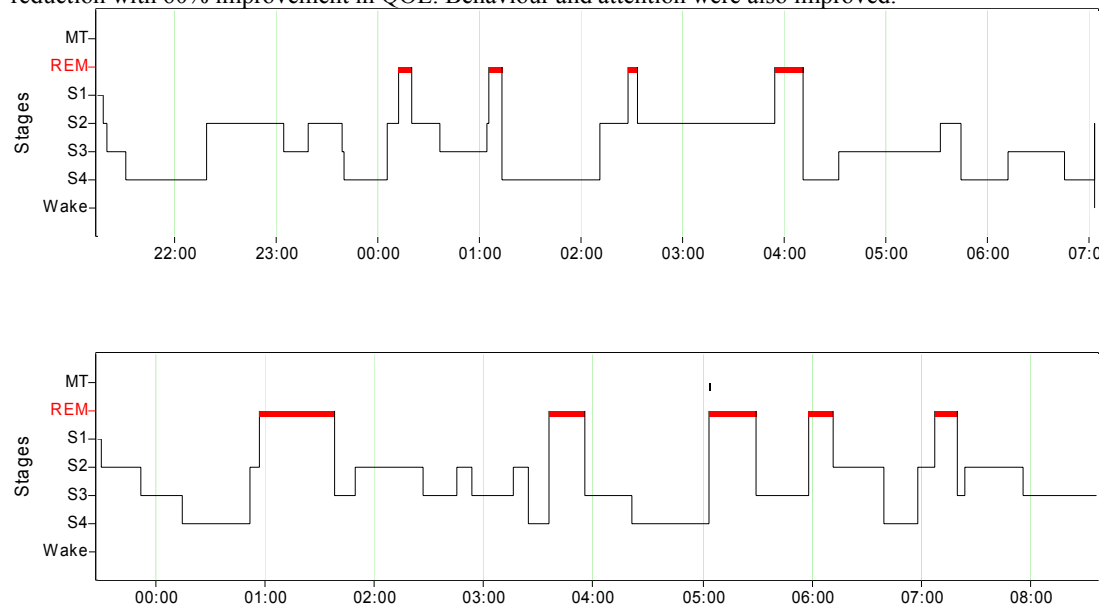


Figure 2

Table 2

11 pat	Before KD Median (range)	After 3 months of KD Median (range) / p	After 12 months of KD Median (range) / p
TS (min)	657 (492,5 - 924)	588,5 (321,5 - 766) / 0,08	573 (342 - 708,4) / 0,09
TNS (min)	600,40 (492 - 821)	546,55 (169 - 683) / 0,04	573 (342 - 708,4) / 0,5
TDS (min)	62,5 (0 - 118,5)	53,75 (0 - 250) / 0,58	0 (0 - 36) / 0,01
Stage 1 (min)	0 (0 - 8,5)	1 (0 - 2) / 1	0 (0 - 9) / 0,9
Stage 1 (% TNS)	0 (0 - 1,4)	0,2 (0 - 0,4) / 0,86	0 (0 - 1,3) / 0,83
Stage 2 (min)	188,5 (120 - 497)	141,75 (20 - 346) / 0,05	158 (70,9 - 388,4) / 0,1
Stage 2 (% TNS)	37,1 (14,7 - 84,2)	26,5 (3,8 - 66) / 0,05	30,1 (13,8 - 54,8) / 0,2
Stage 3+4 (min)	294 (27 - 613,5)	278 (25 - 463,5) / 0,37	215 (155 - 350,5) / 0,4
Stage 3+4 (% TNS)	54,1 (4,6 - 74,8)	53,8 (7,5 - 82,7) / 0,8	39,6 (21,9 - 67) / 0,5
REM min	69,5 (17,5 - 117)	97 (42 - 197,5) / 0,18	116 (44 - 194) / 0,04
REM %	11,2 (3,5 - 23,9)	19,55 (8 - 37,6) / 0,11	20,2 (9,9 - 36,9) / 0,06
Stage shifts (n)	28 (12 - 42)	28 (16 - 44) / 0,76	37 (24 - 50) / 0,3
Sleep latency (min)	0,5 (0 - 2)	0,1 (0 - 0,5) / 0,13	0 (0 - 116,5) / 0,2
Clinical seizures	122,6 (58 - 21604)	22 (0 - 900) / 0,002	49,6 (0 - 180) / 0,003
NHS3	12 (3 - 31)	5 (1 - 11) / 0,005	5 (1 - 14) / 0,005
QOL	10 (10 - 10)	15 (12 - 16,5) / 0,003	16 (12 - 20) / 0,005
CBCL	39 (13 - 61)	36 (6 - 67) / 0,18	34,5 (10 - 66) / 0,54
PK	27 (7 - 36)	17 (3 - 28) / 0,03	15 (0 - 38) / 0,08
Beta hydroxybutyrate	1 (0,1-3,2)	4,2 (2,6-7,7) / 0,003	5,2 (2,7-7,2) / 0,003

Abbreviations:

KD, Ketogenic diet; TS, Total sleep; TNS, Total night sleep; TDS, Day sleep; Stage 1,2,3+4, Sleep stage 1,2,3+4; REM, Rapid eye movement; NHS3, National health seizure severity scale; QOL, Quality of life; CBCL, Child behaviour checklist; PK, Ponsford and Kinsella's rating-scale of attentional behaviour

Table 3

18 pat	Before KD Median (range)	After 3 months of KD Median (range) / p
TS (min)	675,75 (492,5 - 924)	589,25 (321,5 - 776) / 0,05
TNS (min)	612,10 (346,5 - 821)	546,55 (169 - 683) / 0,006
TDS (min)	53,75 (0 - 169,5)	53,75 (0 - 250) / 0,67
Stage 1 (min)	0 (0 - 8,5)	0,75 (0 - 5,5) / 0,48
Stage 1 (%TNS)	0 (0 - 1,4)	0,15 (0 - 1,6) / 0,38
Stage 2 (min)	195,25 (49 - 497)	141,75 (20 - 346) / 0,002
Stage 2 (%TNS)	36,3 (7,9 - 84,2)	26,5 (3,8 - 66) / 0,004
Stage 3+4 (min)	274,25 (27 - 613)	278 (25 - 463,5) / 0,5
Stage 3+4 (%TNS)	47,05 (4,6 - 77,9)	53,8 (7,5 - 82,7) / 0,29
REM (min)	86,5 (17,5 - 189,5)	97 (42 - 197,5) / 0,23
REM (%TNS)	14,15 (3,5 - 28,20)	19,55 (8 - 37,6) / 0,01
Stage shifts (n)	33 (12 - 44)	28 (16-44) / 0,59
Sleep latency (min)	0,5 (0 - 2)	0,05 (0 - 0,5) / 0,06
Clinical seizures	75,3 (1 - 21604)	15,8 (0 - 900) / 0,001
NHS3	12,5 (3 - 31)	6 (1 - 19) / <0,001
QOL	10 (10 - 10)	14 (10 - 18) / 0,001
CBCL	40 (13 - 19)	38 (6 - 73) / 0,08
PK	28 (7 - 21)	17 (3 - 35) / 0,006
Beta hydroxybutyrate	1 (0,1-3,2)	4,2 (2,6-7,7) / 0,003

Abbreviations:

KD, Ketogenic diet; TS, Total sleep; TNS, Total night sleep; TDS, Day sleep; Stage 1,2,3+4, Sleep stage 1,2,3+4; REM, Rapid eye movement; NHS3, National health seizure severity scale; QOL, Quality of life; CBCL, Child behaviour checklist; PK, Ponsford and Kinsella's rating scale of attentional-behaviour

Monitoring

At three months there was a significant reduction in seizure frequency ($p=0.001$). Eight children (44%) showed 90% or more reduction in seizure frequency, four (22%) became seizure free, four (22%) had a 50-90% seizure reduction, five (28%) less than 50% seizure reduction and one (6%) increased in seizure frequency. Eleven children (61%) continued with the diet. They were also evaluated after 12 months. They had a significant reduction in seizure frequency ($p=0.003$). Four (36%) had a 90% or more reduction of seizures, two (18%) were seizure free, four (36%) had a 50-90% seizure reduction and three (27%) less than 50% seizure reduction.

Seizure severity and QOL were significantly improved at three and twelve months ($p<0.001$, $p=0.005$). Attentional behaviour was also improved, significantly so at three months ($p=0.006$, $p=0.08$). Changes in sleep parameters were compared with clinical seizure reduction, improvement in seizure severity, attentional behaviour and QOL. There was a significant correlation between increased REM sleep and improvement in QOL at three months (Spearman $r=0.6$, $p=0.01$). No other significant correlations were seen. The three children that continued KD despite less than 50% seizure reduction described an improvement in seizure severity, a decrease in total sleep and an improvement in attentional behaviour and QOL. One of the three children that

stopped the KD despite good antiepileptic effect experienced ataxia and lethargy. These side effects outweighed the antiepileptic effect. In the other two there were problems with compliance.

DISCUSSION

In this study we saw decreased total sleep (TS) and total night sleep (TNS) and at 12 months a decreased total daytime sleep (TDS). REM sleep increased, sleep stage two decreased and SWS was preserved. We also saw an improvement in seizure frequency, seizure severity, attentional behaviour and QOL.

To avoid first night laboratory effects the recordings were performed ambulatory with the children in their natural surroundings. PSG was performed on the left side. In a few children the right side was used because of artifacts from a loose lead or because of abundant epileptiform activity. All PSG recordings were interpretable with the Somnologica automatic sleep scoring hypnogram with necessary corrections manually for overestimated SWS and underestimated REM sleep. AED were kept stable throughout the study. The good antiepileptic effect and a slight fall off in efficacy during the study could justify this. On the other hand, despite a good antiepileptic effect or even seizure freedom we did not reduce or taper the AED until 12 months. This is in accordance with the recommendations after epilepsy surgery,

where AED are kept stable for at least one year.

The changes in sleep parameters cannot solely be explained by age dependent changes. Total sleep time does not change with age from early childhood to adolescence. It is related to environmental factors rather than biologic changes. At birth the amount of REM and non REM sleep is about equal. The amount of REM sleep gradually decreases to 20-25% before the age of five. There are no significant changes in REM sleep with age from 5 years of age. SWS decreases during childhood and this continues steadily until old age. The amount of sleep stage two increases with age from early childhood (10, 19-20). Sleep is strongly influenced by epilepsy and seizures. Sleep disturbances are common in patients with epilepsy (11, 12). Altered sleep organization and microarchitecture with increased awakenings during sleep, decreased sleep efficiency, decreased and fragmented REM sleep and increased sleep stage two are seen (9, 10). Cortesi et al showed in a study on 89 children with idiopathic epilepsy that children with epilepsy had more sleep problems and decreased QOL than controls (21). In an earlier study we presented sleep changes after VNS treatment in a group of 15 children with therapy resistant epilepsy and cognitive impairment. These children exhibited similar sleep disturbances before treatment and showed similar benefits on sleep

architecture with decreased TS, TNS and TDS and an increase in REM sleep and a significant increase in SWS (22). In this study we see a normalization of abnormal sleep patterns in most of the children. Initially, TS, TNS and TDS are pathologically increased, REM sleep is decreased, sleep stage two and the number of sleep stage shifts are increased. The increase in REM sleep seems to be a normalization of the initially pathologically decreased percentage of REM sleep. The decreased TS, TNS and TDS, seen in our study, are probably due to the improved sleep structure and sleep quality including increased REM sleep, decreased sleep stage two and preserved SWS, following KD. We infer that the increased REM sleep is an important marker for improved sleep quality. This was significantly correlated to the improved QOL.

Sleep is also known to have both precipitating and protecting effects on seizures. Generalized tonic-clonic or myoclonic convulsions occur mainly during non REM sleep and "drowsy wakefulness" (12, 23). Epileptiform discharges are likely to propagate during non REM sleep, in particular in sleep stage two because the electroencephalographic (EEG) background activity is more synchronized with transients such as k-complexes and sleep spindles, and in transitional "drowsy" EEG arousal periods. In contrast the antiepileptic nature of REM

sleep has been demonstrated in several reports linking sleep and epilepsy. The desynchronized low-amplitude activity during REM sleep decreases seizure susceptibility and those that do occur generalize in fewer cases (24-26).

The antiepileptic effect of KD was very good in this study. At three months 44% and at twelve months 36% of the children had > 90% reduction in seizure frequency. The presumed antiepileptic effects of KD are increased cerebral energy reserves and decreased ictal excitability, decreased rate of glutamate transamination to aspartate and, possibly, enhancement in the rate of glutamate decarboxylation to GABA (7, 8). The role of caloric restriction, direct anticonvulsant action of ketone bodies, polyunsaturate fatty acids, norepinephrine, galanin and neuropeptide Y (NPY) is also discussed (8). Dahlin et al 2005 found, significantly increased GABA and decreased glutamate levels in CSF in a study of KD in children with refractory epilepsy (27). Galanin is a widespread neuropeptide in the CNS. It is found in many brain regions including hypothalamus, dorsal raphe nucleus (DR) and locus coeruleus (LC). It is known to regulate food consumption, energy expenditure and pain, but also to decrease hippocampal excitability and glutamate release (28, 29). Expression of galanin and NPY is shown to increase in starvation and high fat intake with decreased leptin and insulin levels, a situation identical to KD

(30, 31). The dorsomedial hypothalamic nucleus (DMH) plays a role in the circadian control of sleep-wake cycling. It sends GABAergic projection to the sleep and REM promoting ventrolateral preoptic nucleus (VLPO) and promotes wakefulness via the ascending arousal system, among other cell-groups the monoaminergic DR and LC, and the lateral hypothalamic area (LHA) with stabilizing orexine/hypocretine influence (31). VLPO withhold sub-regions that are specialized for the control of REM versus nonREM via LC (32, 33). Since VLPO contains GABA and galanin, one could speculate that besides the anticonvulsant effects, the increase or normalization in REM sleep, of KD, is induced by changes in GABAergic and galaninergic functioning.

In conclusion, in our study, KD decreases sleep and improves sleep quality and in particular increases REM sleep, in children with therapy resistant epilepsy. We also see an improvement in seizure frequency, seizure severity, attentional behaviour and QOL and a significant correlation between increased REM sleep and QOL at three months.

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