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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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ORIGINAL ARTICLE

# Beneficial effects on sleep of vagus nerve stimulation in children with therapy resistant epilepsy

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## KEYWORDS

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Arousal;  
Delta power;  
Behaviour

**Summary** The study purpose was to evaluate sleep structure following Vagus Nerve Stimulation (VNS) in 15 children with therapy resistant epilepsy and to correlate possible alterations with changes in epileptiform activity and clinical effects. Fifteen children were examined with ambulatory polysomnographic recordings initially, and after 3 and 9 months of VNS-treatment. Sleep parameters, all-night delta power activity and movement times (MTs), used to account for arousals were estimated. Epileptiform activity was evaluated by spike detection. Seizure frequency was recorded in a diary. The severity of the seizures was scored with the National Hospital Seizure Severity Scale (NHS3). Quality of life (QOL) was assessed by a visual analogue scale. Behaviour problems were quantified by using the total score of the Child Behaviour Checklist (CBCL). VNS induces a significant increase in slow wave sleep (SWS) and a decrease in sleep latency and in stage 1 sleep. The number and density of MTs during total night sleep were significantly increased. There was also a significant increase in the number of MTs immediately related to the VNS stimulation periods. Of the 14 children with increased MTs, 10 had a reduction in epileptiform activity, and in clinical seizures, all had an improvement in NHS3, and 11 in QOL. Of the 10 children with increased SWS, eight also improved in QOL and eight in behaviour. Our findings indicate that VNS counteracts known adverse effects of epilepsy on sleep and increases slow wave sleep. This possibly contributes to the reported improvement in well-being. We also see an increase in MTs. This arousal effect seems to be of minor importance for QOL and could possibly be related to the antiepileptic mechanisms in VNS.

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**Abbreviations:** CBCL, child behaviour checklist; CSF, cerebro spinal fluid; CSWS, continuous spike wave during slow wave sleep; DR, dorsal raphe nuclei; EMG, electromyogram; EOG, electrooculogram; GABA, gamma amino butyric acid; GRD, GABA<sub>A</sub> receptor density; LC, locus coeruleus; MSLT, multiple sleep latency test; MT, movement time; NCP, neuro cybernetic prosthesis; NHS3, national hospital seizure severity scale; PSG, polysomnography; QOL, quality of life; REM, rapid eye movement; SWS, slow wave sleep; TNS, total night sleep; VLPO, ventro-lateral preoptic thalamic nucleus; VNS, vagus nerve stimulation.

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**Table 1** Demographics and clinical characteristics of the study group

Patient no.	Age at epilepsy onset (years)	Epilepsy type/syndrome <sup>a</sup>	Seizure type <sup>a</sup>	Etiology	Previous epilepsy surgery	Changes in seizure frequency at 9 months (%)
1	0.25	Lennox-Gastaut	GTCS	Unknown	No	Increase (33%)
2	2.5	Partial, symptomatic	CPS	CD	L TL res	Seizure free (100%)
3	3	Partial, symptomatic	CPS	Encephalitis	No	Reduction (5%)
4	1	Partial, symptomatic	CPS	CD	R TL res	Reduction (4%)
5	5	Lennox-Gastaut	2°GTCS, AAbS	HIE	No	No change (0%)
6	4.5	CSWS	SPS, 2°GTCS	HIE	No	Reduction (55%)
7	5	Partial, symptomatic	SPS	HIE	No	Reduction (50%)
8	0.5	Lennox-Gastaut	2°GTCS	HIE	No	Reduction (50%)
9	9	Partial, symptomatic	CPS	CD	No	Increase (16%)
10	0.75	Partial, symptomatic	CPS, MS	Unknown	No	Reduction (35%)
11	2	Partial, symptomatic	2°GTCS	CD	L parieto-occ res	Reduction (5%)
12	0.25	Lennox-Gastaut	GTCS, AS, MS	CD	R frontal and occ res	Reduction (25%)
13	7	Partial, symptomatic	CPS	HIE	No	Reduction (78%)
14	3	Partial, symptomatic	CPS	Unknown	No	Reduction (57%)
15	5	CSWS	CPS	Unknown	No	Reduction (17%)

Abbreviations: AS, atonic seizure; AAbS, atypical absence seizure; CD, cortical dysplasia; CPS, complex partial seizure; CSWS, continuous spike wave during slow sleep; GTCS, generalized tonic-clonic seizure; 2°GTCS, secondary generalized tonic-clonic seizure; HIE, hypoxic ischemic encephalopathy; L, left; MS, myoclonic seizure; Occ, occipital; Res, resection; R, right; SPS, simple partial seizure; TL, temporal lobe.

<sup>a</sup> Epilepsy syndrome and seizure types according to the International Classification of the International League Against Epilepsy.

## Introduction

Repetitive vagus nerve stimulation (VNS) is a neurophysiologic method for treatment of refractory epilepsy. VNS has proved to be efficacious and well tolerated in adults.<sup>1,2</sup>

Paediatric studies have shown even better and more rapid response. More than 50% seizure reduction was reported in 27-57% of the children.<sup>3-6</sup> These uncontrolled open studies also showed an improvement in well-being and quality of life (QOL). In adults without epilepsy, VNS has caused a significant reduction in depressive symptoms.<sup>7</sup> Armitage et al.<sup>8</sup> presented an improvement in both depression and sleep architecture. Galli et al.<sup>9</sup> recently confirmed the positive effect of VNS on QOL in adults with epilepsy and learning disability and presented improvement in daytime vigilance. Mechanisms explaining the action of VNS on the Central nervous system (CNS) are still unknown. Over the last years VNS has been shown in several animal studies, and recently in some human studies to suppress both ictal and interictal epileptiform EEG activity.<sup>10-14</sup> In an earlier report we present the findings that VNS reduces interictal epileptiform discharges in Rapid eye movement

(REM) and slow wave sleep (SWS), and the number of electrographic seizures.<sup>15</sup>

The effects of VNS on sleep in patients with medically refractory epilepsy have only been elucidated in a few studies and so far not in children. Vaughn et al.<sup>16</sup> report, in a short abstract, a decrease in REM-sleep at high intensity and high frequency VNS and an increase in REM-sleep at low intensity and low frequency VNS. Malow et al.<sup>17</sup> described that VNS at low stimulus intensity counteracts daytime sleepiness, even in subjects without reduction in seizure frequency. Daytime REM-sleep was enhanced with VNS. Rizzo et al.<sup>18</sup> reported improved daytime alertness and reduced REM-sleep.

Microarchitectural studies of all-night delta power to reflect homeostatic regulation and restitution of sleep after sleep-deprivation is extensively studied and summarized by Finelli, Borbély and Achermann.<sup>19</sup> Huber et al.<sup>20</sup> described that sleep homeostasis can be induced on a local level and benefit or be triggered by a learning task or performance. Thus, SWS homeostasis may reflect synaptic changes underlying a cellular need for sleep. Increased delta power, following VNS, associated with increased wakefulness and anti-depressive effects were presented by Rizzo et al.<sup>18</sup> and Armitage et al.<sup>8</sup>

**Table 2A** Results of epileptiform activity from spike detection in 1 h of wake, REM-, sleep stage 2-, sleep stage 3 + 4, initially (baseline) and after 3 and 9 months of vagus nerve stimulation (VNS)

Activity stage	Before initiation (baseline), median (range)	3 Months after initiation, median (range)/p-value	9 Months after initiation, median (range)/p-value
<i>13 Children, excluding two with CSWS</i>			
Wake	50.5 (0-2115)	49 (0-1999)/0.64	39 (0-2182)/0.67
Sleep stage 2	515 (0-3839)	189 (2-4827)/0.17	463 (3-3330)/0.3
REM	95 (1-2445)	75 (0-2216)/0.08	46 (0-1688)/0.03
Sleep stage 3 + 4	550 (0-3176)	209 (3-2174)/0.10	155 (2-1295)/0.02
Total	968 (2-8133)	636 (8-6795)/0.15	636 (9.5-4802)/0.03
<i>15 Children, including two with CSWS</i>			
Wake	91 (0-2115)	87 (0-1999)/0.68	44 (0-2182)/0.79
Sleep stage 2	515 (0-3839)	189 (2-4827)/0.17	463 (3-3330)/0.3
REM	215 (1-2445)	79 (0-2216)/0.16	68 (0-2034)/0.08
Sleep stage 3 + 4	599 (0-5634)	264 (3-5678)/0.08	269 (2-4819)/0.008
Total	989 (2-10,430)	643 (8-12,795)/0.23	809 (9-11,923)/0.04

Abbreviation: CSWS, continuous spike-wave discharges during slow sleep.

In this study, we report changes in sleep structure and delta power following VNS in 15 children with therapy-resistant epilepsy, and how these changes correlate with epileptiform activity and clinical effects on seizure reduction and QOL.

## Methods

### Subjects

The study group comprises 15 children (10 boys and five girls) aged 4-17 years (median 11 years) with the diagnosis of therapy-resistant epilepsy with developmental impairment, and absence of non-epileptic seizures or specific sleep disorders. Epilepsy surgery had been performed in patient 2, 4, 11 and 12 and found not applicable in the others. Additional clinical features of the patients are given in Table 1. All patients had been on stable anti-epileptic drug medication for at least 3 months prior to the VNS initiation and during the 9 months of follow up. Written informed consent was obtained. The study was accepted by the Ethics Committee of the Faculty of Medicine of the Lund University.

### VNS

The VNS device (NCP System; Cyberonics, Houston, TX, USA) was implanted according to the established guidelines.<sup>21</sup> At the end of the surgical procedure, the device is programmed with the following parameters: output current 0.25 mA; signal frequency 30 Hz; pulse-width 500  $\mu$ s; stimulation on-time 30 s; stimulation off-time 5 min.

During the initial 4 weeks, the output current is increased in steps of 0.25 to 1-1.5 mA and is then kept stable during the 9 months of follow-up.

### Polysomnographic recordings

Continuous EEG recordings for polysomnography (PSG) were performed during 24 h initially, and after 3 and 9 months of VNS-treatment. The recordings were ambulatory with the children in their natural surroundings. Twenty-four hour recordings were performed to obtain enough artefact-free data and over-night sleep recording for quantification of sleep. Meals, naps, other activities, time of sleep and seizure events were registered in a diary. Via the Embla A10 Flaga-Medcare digital data recorder, data were recorded on a PC memory flash card. EEG was recorded on 11 scalp electrodes and a referential electrode (F3, F4, C3, C4, T3, T4, P3, P4, O1, O2, CZ, Ref.) placed according to the 10-20 International System. In addition, on the right side, electro-oculogram (EOG) and sub-mental electro-myogram (EMG) was applied. To detect the stimulus artefacts from the stimulation electrodes of the NCP device an electrode on the left side of the patient's neck, over Erbs point, with a reference on the right side, was attached. The digitalized data were transferred to Somnologica 3.1 (Flaga hf. Medical Devices) for PSG analysis. The recording before VNS initiation was used as baseline and compared with registrations 3 and 9 months after VNS initiation. Sleep parameters were scored according to Rechtschaffen and Kales criteria<sup>24</sup> in Somnologica both automatically and manually. We used the Somnologica automatic sleep scoring

hypnogram with necessary corrections for overestimated SWS and underestimated REM. Sleep stage 3 and 4 were treated together as SWS.

## Monitoring

Initially and after 3 and 9 months of VNS-treatment, epileptiform activity was counted in comparable assessment periods according to time of day and activity stage. Two hours of artefact-free EEG was selected from wake and 1 h of artefact-free EEG was selected from three different sleep stages defined as rapid eye movement (REM), sleep stadium two, with theta activity, sleep spindles and <50% slow wave sleep, and sleep stadium 3+4 with >50% slow wave sleep (Table 2A).

During 3 months before VNS 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.<sup>22</sup> QOL was assessed by a visual analogue scale and parents' perception of the children's general behaviour problems were quantified by using the total score of the Child Behaviour Checklist (CBCL). Follow-up assessments were performed at 3 and 9 months after VNS initiation (Table 2B).<sup>23</sup>

## Delta power

The digitalized data were converted to Nervus Taugagreining EEG format (Valor-format) for delta power and spike detection. Delta power in the 0.5-4.0 Hz interval of consecutive 30 s epochs was computed for 4 s epochs using the fast fourier transform (FFT) algorithm with a Hamming window overlapping every 2 s. Either C3-P3 or C4-P4 was chosen individually depending on which was least affected by epileptiform activity and artefacts. Patients 6 and 15 with continuous spike wave during slow sleep (CSWS) were excluded. Epochs (30 s) containing artefacts were excluded and

interpolated by the mean delta power in the epochs preceding and following those with artefacts. Sleep stadium 3 and 4 according to Rechtschaffen and Kales criteria<sup>24</sup> in the first and second sleep-cycle were analysed.

## Movement time

Movement time (MT) is assigned to epochs in which the EEG and EOG tracings are obscured in more than half the 30 s scoring epoch by electromyographic and movement related artefacts. Because MT involves more than half an epoch of movement artefact and hence relatively large movements in most cases, the criteria for scoring MT will usually satisfy the criteria for body movement and movement arousal. In the visual sleep scoring all MTs associated with wake, seizures or electrode artefacts were deleted. Besides total number of MTs, number per hour total night sleep (TNS), number per sleep stage and number of MTs immediately related to the VNS-stimulation periods were analyzed.

## Statistical evaluation

Wilcoxon signed rank test was used for comparison of data from the hypnogram and delta power analysis. Median time in minutes and percent of TNS were analysed in REM, stage 1 sleep, stage 2 sleep, SWS and sleep stage latency, before VNS initiation and 3 and 9 months later. Total number of MTs, MTs per hour TNS and number per sleep stage were also analyzed. Total delta power during night-sleep, delta power during SWS in the first and second sleep cycle, according to Rechtschaffen and Kales sleep criteria<sup>24</sup> were analyzed. Friedmans test and Wilcoxon signed rank test were performed to analyze the relation between MTs and VNS stimulation period. A binomial test was used in order to analyze concordance in direction of changes between increased SWS and MTs and reduction in epileptiform activity, seizure frequency, improvement in seizure severity and

**Table 2B** Effects on clinical seizures, seizure severity (NHS3), quality of life (QOL) and behaviour (CBCL), before and after 3 and 9 months of vagus nerve stimulation (VNS)

	Before VNS-initiation, median (range)	3 Months after VNS-initiation, median (range) <i>p</i> -value	9 Months after VNS-initiation, median (range) <i>p</i> -value
Clinial seizures	51 (2-200)	18 (2-141) <i>p</i> =0.02	19 (2-112) <i>p</i> =0.04
NHS3	12 (4-19)	9 (1-16) <i>p</i> <0.001	9 (1-16) <i>p</i> <0.001
QOL	10 (10-10)	15 (5-20) <i>p</i> =0.04	13 (2.5-17.5) <i>p</i> =0.04
CBCL	49 (19-94)	50 (19-102) <i>p</i> =0.69	43 (18-92) <i>p</i> =0.10

Abbreviations: NHS3, national hospital seizure severity scale; QOL, quality of life; CBCL, child behaviour check list.

**Table 3** Sleep parameters and delta power before and after 3 and 9 months of vagus nerve stimulation (VNS)

	Before VNS-initiation, median (range)	3 Months after VNS-initiation, median (range) p-value	9 Months after VNS-initiation, Median (range) p-value
TS (min)	587.5 (503-781.5)	585 (443.5-739) $p=0.6$	603.5 (474-771.5) $p=0.5$
TNS (min)	522 (437.5-609.5)	547.5 (443.5-701.6) $p=0.3$	548.5 (467-701.6) $p=0.15$
TDS (min)	69.5 (0-202)	22.5 (0-180) $p=0.07$	0 (0-216.5) $p=0.16$
Stage 1 (min)	0 (0-14)	0 (0-22) $p=0.4$	0 (0-7.5) $p=0.03$
Stage 1 (% TNS)	0 (0-2.6)	0 (0-3.8) $p=0.4$	0 (0-1.4) $p=0.03$
Stage 2 (min)	275.5 (99-395.4)	239.5 (75.5-361.4) $p=0.2$	260.5 (105-472.5) $p=0.3$
Stage 2 (% TNS)	54.8 (18-77.9)	44.4 (13.4-70.5) $p=0.08$	43.8 (18.4-80.1) $p=0.08$
Stage 3+4 (min)	146.5 (32.5-370.5)	144 (38-426.5) $p=0.1$	180.5 (24.5-486) $p=0.03$
Stage 3+4 (% TNS)	26.1 (6.8-62.5)	25.8 (8.2-75.7) $p=0.1$	35.8 (4.1-78.3) $p=0.04$
REM (min)	81.5 (21-299)	93.5 (25-287.5) $p=0.4$	97.5 (17.5-266) $p=0.7$
REM (% TNS)	14.6 (4-55.2)	17.7 (4.1-49.6) $p=0.5$	20.4 (2.9-50.9) $p=0.9$
Delta power night	120,253 (9248-852,468)	113,607 (12,823-140,750) $p=0.81$	135,321 (21,251-616,542) $p=0.31$
Delta power sleep cycle I	12,016 (180-85,263)	5811 (365-63,934) $p=0.55$	13,222 (501-37,498) $p=0.65$
Delta power sleep cycle II	4697 (84-30,321)	1400 (183-176,100) $p=0.5$	7306 (643-1,242,687) $p=0.05$
MT (n/h TNS)	2.98 (0-12.71)	4.57 (0-9.82) $p=0.09$	4.52 (1.65-11.60) $p=0.009$
Stage shifts (n)	31 (11-68)	33 (17-58) $p=0.75$	25 (15-65) $p=0.26$
Sleep latency (min)	0 (0-15.5)	0 (0-26) $p=0.57$	0 (0-7.5) $p=0.04$

Abbreviations: REM, rapid eye movement; Sleep latency, (min) time from lights-off to the first occurrence of stage 2; Stage1/2/3+4, sleep stage 1/2/3+4; TDS, total day time sleep; TNS, total night sleep; TS, total sleep (TNS+TDS); MT, movement time.

improvement in QOL and behaviour. Spearman rank correlation coefficient ( $r$ ) was used to calculate the correlation in degree of improvement between MTs and epileptiform activity, clinical seizures, NHS3 and QOL and SWS and QOL and CBCL. The level of significance was set at  $p < 0.05$ .

## Results

All 15 children completed the study without any changes in VNS stimulus parameters or medication, except patient 12 who received rapid stimulation (stimulation on-time 7 s, stimulation off-time 12 s) after 6 months. This child was excluded from the analysis of VNS stimulus related MTs.

### Sleep scoring

The medians and ranges of PSG sleep macro-architecture variables are shown in Table 3.

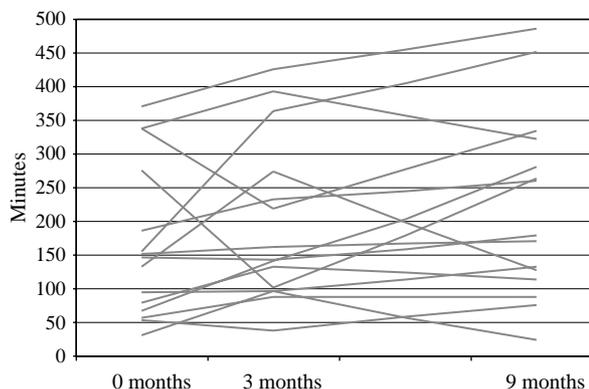
Significant differences, with an increase in SWS in both duration ( $p=0.03$ ) (Fig. 1) and percentage ( $p=0.04$ ) and a decrease in stage 1 sleep in both duration ( $p=0.03$ ) and percentage ( $p=0.03$ ) were seen at 9 months of VNS. A significant decrease was seen in sleep latency after 9 months of VNS ( $p=0.04$ ) and a non-significant decrease of daytime sleep was seen at 3 and 9 months ( $p=0.07, 0.16$ ).

### Delta power

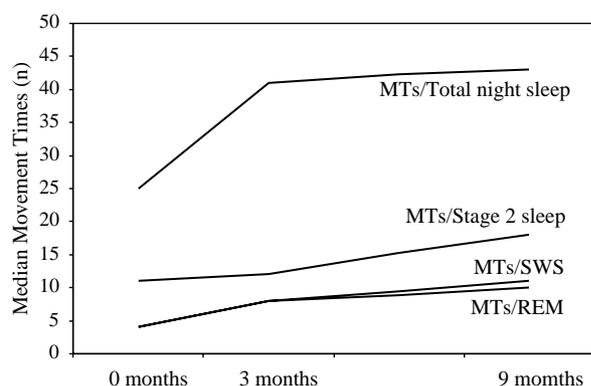
There was a tendency towards increase in total delta power and delta power in the first two sleep cycles, significantly so in sleep cycle 2 after 9 months of VNS ( $p=0.05$ ) (Table 3).

### Movement time

The total number MTs ( $p=0.08, 0.01$ ) and the number per hour TNS ( $p=0.09, 0.009$ ) (Table 3) were increased, significantly so at 9 months. When considering MTs in the different sleep stages



**Figure 1** Slow wave sleep in minutes initially and after 3 and 9 months of Vagus nerve stimulation (VNS) in 15 children. The increase was significant at 9 months ( $p=0.03$ ).



**Figure 2** Movement time (MT), with body movement artefact in more than half the 30 s scoring epoch, was used to account for an arousal. There was an increase in the median MTs after 3 and 9 months of Vagus nerve stimulation (VNS) during total night sleep ( $p=0.08$ ,  $0.01$ ). When considering median MTs in the different sleep stages separately, there was a tendency of increase in all stages and significantly so in sleep stage 2, and Slow wave sleep (SWS) at 9 months. Median number MTs in Rapid eye movement (REM) sleep ( $p=0.16$ ,  $0.28$ ). Median number MTs in stage 2 sleep ( $p=0.12$ ,  $0.02$ ). Median number MTs in SWS (stage 3 and 4 sleep) ( $p=0.06$ ,  $0.03$ ).

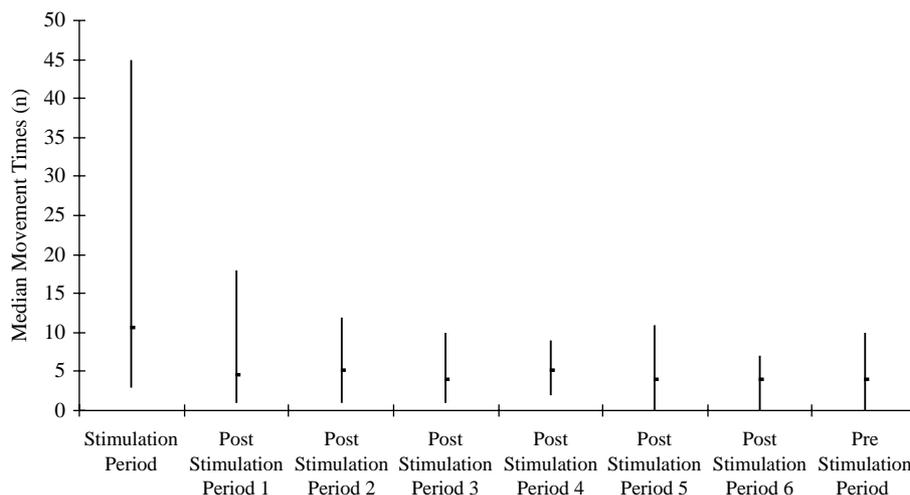
separately, there was a tendency towards increase in all stages and significantly so in sleep stage 2 ( $p=0.02$ ) and SWS ( $p=0.03$ ) at 9 months (Fig. 2). The difference in total number of MTs between the VNS stimulation periods and post-VNS stimulation periods was highly significant at both 3 and 9 months ( $p<0.001$ ). The median number of MTs was significantly larger during the VNS stimulation period compared with the pre- and post-stimulation periods, respectively ( $p=0.002$ ,  $0.007$  at 3 months

and  $p=0.005$ ,  $0.005$  at 9 months). The median and range of the different children's VNS stimulus related MTs are presented in Fig. 3. A case with exceptional high stimulus related MTs is described in Table 4.

There were concordance in direction of changes between increased MTs and decreased epileptiform activity and clinical seizures in 10 of 15 children and between increased MTs and decreased NHS3 in 14 of 15 children ( $p=0.001$ ) and between increased MTs and QOL in 11 of 15 children. Concerning SWS there were concordance in direction of changes between enhanced SWS and QOL in nine of 15 children and enhanced SWS and improved CBCL in 11 of 15 children. MTs exhibited no significant correlation in the degree of increase with extent of improvement in epileptiform activity (Spearman  $r=-0.09$ ,  $p>0.3$ ), clinical seizures ( $r=-0.2$ ,  $p>0.3$ ), QOL ( $r=-0.08$ ,  $p>0.3$ ), or NHS3 ( $r=-0.09$ ,  $p>0.3$ ). SWS exhibited no significant correlation in degree of increase with extent of improvement in QOL (Spearman  $r=-0.45$ ,  $p=0.1$ ); and CBCL ( $r=-0.01$ ,  $p>0.3$ ).

## Discussion

In our data, VNS treatment of therapy-resistant epilepsy is associated with a longer nocturnal sleep and increased slow wave sleep (SWS). The sleep latency was significantly reduced. There was a tendency towards decrease in daytime sleep, although we did not use an objective PSG measure like MSLT. To avoid first night laboratory effects the recordings were performed ambulatory with the children in their natural surroundings.



**Figure 3** Median movement times (MTs) after 9 months of Vagus Nerve Stimulation (VNS). The difference is significant between the Stimulation period and pre- and post-stimulation periods ( $p=0.005$ ) during total night sleep. The vertical lines illustrate the ranges.

**Table 4** Patient 7 had the largest increase of total and stimulus related MTs. In all VNS-stimulation epochs he had increased MTs

	Before VNS-initiation	3 Months after VNS-initiation	9 Months after VNS-initiation
TNS (min)	543.00	580.00	523.00
TDS (min)	107.50	0.00	0.00
REM (%)	55.20	49.60	50.90
Sleep stage 2 (%)	31.90	35.10	35.10
SWS (%)	7.10	15.30	17.10
MT (n)	66.00	95.00	83.00
Awakenings (n)	0.00	0.00	0.00

This patient had a non-transient pain and paresthesia in the neck that was so disabling that mood, behaviour score and QOL was affected and the stimulator was withdrawn after the study had finished, despite increased SWS, decreased total daytime sleep and 50% reduction of seizure frequency.

In general, 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 REM sleep.<sup>25,26</sup> Our findings show a VNS induced improvement of sleep quality with increased SWS, a tendency to decrease in sleep fragmentation (see stage shifts, Table 3) and a tendency towards reduction in daytime sleep, probably contributing to improved well-being.<sup>27-29</sup> In our study, the improvement in QOL was significant for the whole group ( $p=0.03$ ). There was concordance in direction of changes between enhanced SWS and QOL in nine of 15 children. We could not prove any direct quantitative correlation between improved QOL and increased SWS. This may be due to the small number of patients and the fact that increased SWS is only one of several contributing factors to improved QOL together with decreased epileptiform activity, seizure frequency and severity. Parker et al.<sup>5</sup> and George et al.<sup>30</sup> reported that the effects of VNS are positively correlated to the length of the treatment period. In this view 9 months may still be a too short observation time to find effects on sleep architecture in addition to effects on epileptiform activity. Rizzo et al.<sup>18</sup> and Armitage et al.<sup>8</sup> reported increased delta power associated with increased wakefulness and anti-depressive effects, following VNS. Slow wave sleep as a neurophysiologic marker of sleep homeostasis<sup>27,28</sup> is enhanced by VNS. In this study, we only see a tendency of increased delta power especially

in sleep cycle 2 ( $p=0.05$ ). This might be due to the small number of patients with severe epileptic encephalopathy and enhanced background delta during wake, even though patients 6 and 15 with CSWS were excluded, and artefacts were carefully provided for. One should also note that SWS is classified as sleep stadium 3 and 4 according to Rechtschaffen and Kales criteria,<sup>24</sup> and includes both delta and theta frequencies. Delta power include only delta (0.5-4 Hz). The enhancement of deep non-REM sleep seen after VNS might be produced by other mechanisms than that produced by simple sleep deprivation. Such mechanisms may be related to a GABA mediated thalamic influence further discussed below.

We used the MT as a sign of arousal. We show that MTs increase in total number, number/hour TNS and particularly in sleep stage 2 and SWS during long time VNS treatment. The finding of a highly significant increase of MTs in immediate association to the VNS stimulation, support the theory that MTs seems to be directly related to the VNS-stimulation. These findings differ from the gradual increase in SWS indicating different mechanisms of effect of VNS, see Table 3. MT and arousals following VNS may be one of several antiepileptic mechanisms of VNS. It is well known that arousals during sleep can be pro-epileptic.<sup>31</sup> It is also well known that deliberate alerting can produce a reduction in epileptic seizures.<sup>32,33</sup> Nagai et al.<sup>34</sup> describes the therapeutic potential of biofeedback in reducing seizure frequency in patients with therapy-resistant epilepsy. Both epilepsy and increased arousals can lead to sleep deprivation and fragmentation possibly associated with degraded QOL. Despite these possible adverse effects we see an improvement in QOL in the whole group at 9 months and a decrease in epileptiform activity, seizure frequency and severity (Table 2B). We could not prove a significant quantitative relation between each parameter and the increased MTs except in seizure severity. There were concordance in direction of changes between increased MTs and decreased epileptiform activity and clinical seizures in 10 of 15 children and between increased MTs and decreased NHS3 in 14 of 15 children ( $p=0.001$ ) at 9 months and between increased MTs and QOL in 11 of 15 children. Despite the effects of MTs the overall effects of each parameter seems to contribute to the improved QOL. Eleven of 15 children had concordant changes in MTs and QOL. This indicates that MTs are at least not contributing to a reduced QOL, except in patient 7 as described above and in Table 4.

The Vagus nerve has direct projections to the reticular formation via the nucleus of the solitary

tract to the VLPO, and via the parabrachial nucleus to the locus coeruleus (LC) and the dorsal raphé nucleus (DR). These regions are strongly implicated in mood as well as in sleep regulation.<sup>35</sup> Saper et al.<sup>36</sup> describes a reciprocal relationship between a VLPO promoting non-REM sleep and inhibiting influence on LC and DR on one hand, and a LC and DR promoting wake state and inhibiting influence on VLPO on the other hand. In our study the increased SWS could be due to a GABA mediated VLPO influence through VNS stimulation. Ben-Menachem et al.<sup>37</sup> showed an increased concentration of GABA in cerebrospinal fluid (CSF) during VNS-treatment. Marrosu et al.<sup>38</sup> presented normalization of GABA<sub>A</sub> receptor density (GRD) after 1 year of VNS stimulation correlated to improvement in seizure frequency. The increased MTs could be due to VNS mediated mono-aminergic influence from LC and DR as an antiepileptic arousal effect. Krahl et al.<sup>39</sup> showed that LC lesion suppresses the seizure-attenuating effects of VNS.

In conclusion, the aim of this study was to evaluate changes in sleep structure following VNS. We see that VNS counteracts known adverse effects of epilepsy on sleep and increases SWS. This possibly contributes to improved well-being. We also see an increase in MTs. This arousal effect seems in most cases to be of minor consequence for QOL and may even be one of several antiepileptic mechanisms in VNS.

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