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# **Long Term Effects on Epileptiform Activity with Vagus Nerve Stimulation in Children**

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**Key Words:** Epilepsy; Vagus Nerve Stimulation; EEG; Seizure frequency; Spike detection; Children

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## **Summary**

### **Purpose**

Long-term Effects on Epileptiform Activity with Vagus Nerve Stimulation in Children  
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We report long-term effects of Vagus Nerve Stimulation (VNS) on epileptiform activity in 15 children, and how these changes are related to activity stage and to clinical effects on seizure reduction, seizure severity (NHS3) and quality of life (QOL).

## Methods

Initially, and after three and nine months of VNS-treatment, 15 children were investigated with 24 hours ambulatory EEG monitoring for spike detection. The number of interictal epileptiform discharges (IED) and the inter spike intervals (ISI) were analysed during two hours in the awake state, and one hour of rapid eye movement (REM)-, spindle- and delta-sleep, respectively. Total number and duration of electrographic seizure episodes were also analysed.

## Results

At nine months the total number of IEDs was significantly reduced ( $p=0.04$ ). There was a tendency of reduction in all activity stages, and significantly so in delta-sleep ( $p=0.008$ ). Total electrographic seizure number was significantly reduced in the 24 hour EEG at three and nine months ( $p=0.03, 0.05$ ). There was a significant concordance in direction of changes in epileptiform activity and electrographic seizures at nine months ( $p=0.04$ ). Concordance in direction of changes was seen in 9 of 15 children between clinical seizures and IED ( $p>0.3$ ), in 10 of 15 children between QOL and IED ( $p=0.3$ ) and in 8 of 15 children between NHS3 and IED ( $p>0.3$ ). There was no direct correlation between the extent of improvement in these clinical data and the degree of spike reduction.

## Conclusion

This study shows that VNS reduces IEDs especially in REM and delta sleep, as well as the number of electrographic seizures. It also shows a concordance between reduction in IEDs and electrographic seizures.

## 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 [1,2]. Paediatric studies have shown even better and more rapid response. More than 50% seizure reduction was reported in 27-57% of the children. Interestingly, these uncontrolled open studies also showed a dramatic improvement in well-being and QOL [3-6]. The most commonly used parameter for evaluation of the efficacy of an anti-epileptic treatment is clinical seizure frequency. However, in this group of children with therapy-resistant epilepsy and developmental impairment, seizures can be subtle and difficult to distinguish from other behavioural abnormalities. An accurate seizure registration may therefore be difficult to attain. Quantification of epileptiform activity in long-term digital EEG recordings is one way to assess effects and to elucidate the influence of VNS on cerebral function [7-10].

Over the past several years VNS has been shown in several animal studies to suppress both ictal and interictal epileptiform EEG activity. Zanchetti and Chase showed induced synchronization and desynchronization of the background EEG, depending on the stimulus frequency and stimulation intensity [11-13]. Human studies have not been able to reveal such changes [14,15]. Until recently the only documented acute effect of VNS in humans has been occasional observations of abrupt termination of ictal events with VNS [15]. Olejniczak et al. reported, in a case study, an immediate VNS effect with significant decrease in epileptiform sharp waves recorded directly from invasive EEG in the left hippocampus despite absence of a clinical VNS effect [16]. Koo has shown that VNS does cause EEG changes over time, and Kuba has shown an immediate effect on interictal and ictal epileptiform discharges [17,18]. When analysing EEG, spontaneous fluctuations in the frequency of epileptiform discharges is a problem described both in anti-epileptic drug studies [19] and in routine EEG recordings [20]. A short EEG recording may not be sufficient. A greater consistency of the epileptiform

activity is seen in long-term EEG monitoring, including different stages of sleep [21]. Binnie et al described transitory cognitive impairments (TCI) produced by subclinical EEG IEDs, and emphasized the need for testing the relation between psychosocial function and reduction of IEDs [22].

We report long-term effects of VNS on epileptiform activity in 15 children with medically refractory epilepsy, and how these changes are related to activity stage and to clinical effects on seizure reduction, seizure severity and effects on 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. Epilepsy surgery had been performed in four patients and found not applicable in the others. Age of epilepsy onset was between four months and nine years (median three years). The duration of epilepsy was 4 -12 years (median 8.5 years). The aetiology was cortical dysplasia in five, encephalitis in one and hypoxic ischemic encephalopathy in five. The aetiology was unknown in four subjects. One showed right anterior hippocampus atrophy, and in three there were no MRI abnormalities. All patients had been on stable anti-epileptic drug medication for at least three months prior to the VNS implantation and during the nine 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

Vagus nerve stimulation is delivered via the Neuro Cybernetic Prosthesis (NCP) System, Cyberonics, Inc. The NCP is an implantable, multi-programmable pulse generator that delivers current electrical stimulation to the vagus nerve. The VNS can be programmed externally and individually. It can also be activated by a hand-held magnet.

The Vagus Nerve Stimulator is implanted subcutaneously below the clavicle on the left side. At the end of the surgical procedure the device is programmed with the following parameters: output current 0.25mA; signal frequency 30Hz; pulse-width 500µsec; stimulation on-time 30sec; stimulation off-time 5min. During the initial 4 weeks, the output current is increased in steps of 0.25mA to 1-1.5mA and is then kept stable during the nine months of follow-up.



## EEG monitoring

Continuous EEG recordings were performed during 24 hours initially, and after three and nine months of VNS treatment. The recording was 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, using sampling rate 200 Hz with 16 bits resolution, data were recorded on a PCMCIA memory flash card. The EEG was recorded with 11 scalp electrodes and a referential electrode (F3, F4, C3, C4, T3, T4, P3, P4, O1, O2, CZ, Ref.) according to the 10-20 International System. An additional electrode was applied to the left side of the patient's neck, over Erb's point, with a corresponding reference on the right side, to pick up the stimulus artefacts from the stimulation electrodes of the NCP device. The digitalized data were converted to Nervus Tauragreining EEG format (Valor format).

The 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 one hour of artefact-free EEG was selected from three different sleep stages, defined as rapid eye movement (REM), non-REM (NREM) with theta activity and sleep spindles (ss) and <50% slow wave sleep and delta- sleep (>50% slow wave sleep). Periods of sleep during daytime, seizure events or disturbances in the recordings due to movement artefacts or technical problems were not selected. For three children, selected channels with continuous artefacts were excluded.

The spike counting was based on the Persyst® Spike Detector version 3.0. In order to justify the use of automatic spike detection, a single blind pilot study comparing visual detection and

the Persyst® Spike Detector system was performed. We analysed seven children encompassing altogether 21 hours of EEG. A Common Average montage was used. The visual identification of epileptiform activity was performed with a 5 Hz high pass filter and a 50 Hz low pass filter in consecutive 10s periods. Each solitary spike or sharp wave with peak amplitude at least twice the local background activity was supplied with an event mark. The automatic spike detection was performed in its most sensitive setting. All events were visually evaluated and edited for false detections.

The total number of epileptiform discharges and the inter-spike interval determined on each assessment in the four activity stages were used for comparison. The recording before VNS initiation was used as baseline and compared with those at three and nine months after VNS initiation.

We also compared seizure pattern as number and duration of clinical, electrographic and combined clinical and electrographic seizures. An electrographic seizure event was defined as an abrupt onset of rhythmic epileptiform activity of >10s duration. The whole material was visually analyzed, and no software for automated electrographic seizure detection was used. During three months before initiation, a diary of seizure frequency and severity was collected together with clinical data. Follow-up assessments were performed at three and nine months after VNS initiation. The types of seizures, epilepsies and epileptic syndromes were defined according to the classification of the International League Against Epilepsy, including seizure semiology and electroencephalogram characteristics before study entry [23,24]. 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 (1996) [25]. QOL was assessed by a visual analogue scale. These data are reported in an earlier article in this number of Seizure [26].

## Statistical Evaluation

The pilot study, i.e. the comparison between manual visual inspection and the Persyst® Spike Detector system, was single blinded, i.e. the scorer was kept blinded to the identity of the recorded subject and to the order of the recording. Wilcoxon signed rank test was used for comparisons of the total and median number of IEDs and the median inter-spike interval in the different activity stages before VNS initiation, and three and nine months later. In order to investigate possible changes in the variability of the inter-spike intervals, the standard deviation of the inter-spike intervals was calculated for each patient before VNS initiation and three and nine months after. Wilcoxon signed rank test was also used for comparison of total and median number and duration of seizures during the 24 hour monitoring before VNS initiation and three and nine months later. A binomial test was used in order to check concordance in direction of changes in IEDs and electrographic seizures during the 24 hour monitoring at baseline and nine months of VNS stimulation. Spearman rank correlation coefficient ( $r$ ) was used to calculate the correlation between extent of reduction in IEDs and seizure frequency, improvement in seizure severity and improvement in QOL. The level of significance was set at  $p < 0.05$ .

## RESULTS

### Interictal Epileptiform Activity

The epileptiform activity consisted of focal or multi-focal spike or sharp-wave complexes in 14 children. One child had generalised spike-and-slow-waves. In three children the epileptiform activity was sparse and appeared as solitary discharges. In seven children it was abundant, and in two more than 85% of non-REM-sleep consisted of epileptiform activity, they were classified as continuous spike-wave discharges during slow sleep (CSWS).

### The Pilot Study

The Pilot Study showed a high correlation between the visual inspection and Persyst® Spike Detector system (PSDS) ( $r=0.99$ ). This suggests a low rate of false positives in the visual inspection and that PSDS tends to underestimate changes in epileptiform activity.

Proportionally, the PSDS never underestimated the visual inspection by more than 25%.

Wilcoxon signed rank test showed a systematic difference between the visual inspection and the Persyst Spike Detector system ( $p=0.04$ ). The difference was never more than 78 spikes/h, and in 50% never more than 14 spikes/h (quartiles 0 and 14) (Table 1). Of the 21 analyzed recordings, the visual inspection and the PSDS scored identical in five. In 12, the visual inspection scored higher, and in four, lower.

### EEG recording

On reviewing the baseline EEGs, it was found that two children had CSWS. This is a typical, therapy-resistant, neurophysiologic and clinical entity with epileptiform activity in >85% of non-REM sleep [27]. The further analysis is presented both with and without these two children.

After nine months of VNS stimulation, the total number of epileptiform discharges was significantly reduced ( $p=0.03$  in the 13 children without CSWS and  $p=0.04$  in all 15 children) (Figure 1). When considering the four activity stages separately, there was a tendency towards

reduction of median number of spikes in all stages, and significantly so in REM ( $p=0.03$ ) and delta sleep ( $p=0.02$ ) in the 13 children without CSWS (Table 2). See also Table 2 for results in all 15 children. The total electrographic seizure number was significantly reduced in the 24 hours of EEG monitoring at both three and nine months ( $p=0.03, 0.05$ ) in the 13 children without CSWS. In all 15 children  $p=0.07$  and  $0.13$  at three and nine months. There was a non-significant tendency of reduction of seizure time.

In the 24 hours of EEG monitoring there was a significant concordance in direction of changes in epileptiform activity and electrographic seizures at nine months in 12 children.

Three children did not have any electrographic seizures, and could not contribute to the analysis ( $p=0.04$ ) (Figure 2). Ten children had concordant changes. Eight showed a decrease in both IEDs and seizure number, seven also in seizure time. Two children showed increased IEDs, seizure number and seizure duration. There was no direct correlation between the extent of electrographic seizure reduction and the degree in IED reduction ( $r=0.28, p>0.3$ ).

As we have reported [26] there was a reduction of clinical seizures at three (median 65%) and nine months (median 63%), and a significant improvement in NHS3 and QOL in the 15 children. Concordance in direction of changes was seen in 9 of 15 children between clinical seizures and IED ( $p>0.3$ ), in 10 of 15 children between QOL and IED ( $p=0.3$ ) and in 8 of 15 children between NHS3 and IED ( $p>0.3$ ). There was no direct correlation between the extent of improvement in these clinical data and the degree of spike reduction (Spearman:  $r=-0.15, -0.04, -0.018, p>0.3$ ).

No significant changes of median inter-spike interval were found at three and nine months ( $p=0.27, 0.10$ . In wake  $p=0.58, 0.16$ ; in ss  $p=0.43, 0.86$ ; in REM  $p=0.09, 0.14$  and in delta sleep  $p=0.43, 0.07$ ). In delta sleep there was a significant increase of the standard deviation of inter-spike interval at three and nine months, indicating that VNS produces more variable

spike patterns at this sleep stage ( $p=0.04, 0.03$ ). Overall, the standard deviation was high in comparison to the median ISI.

## DISCUSSION

In the present study 24-hour EEG recordings were performed in order to select long artefact-free recordings with comparable periods during the same real time of day, activity stage and in the natural environment. Efforts were made to select accurate overnight sleep recordings for quantification of sleep. Taking these factors into account, a comparison of the EEG in a particular patient would be more accurate.

The pilot study showed a systematic difference between the visual detection and the Persyst, automated spike-detection. The Persyst, automated spike-detection tends to underestimate changes in epileptiform activity. The observation that the automated spike detection has a higher false negative detection rate with high IED frequencies than with low frequencies may indicate that the effect of VNS on IEDs was somewhat underestimated. The analysis is presented both with and without the two children with CSWS, due to the difficulties in distinguishing between seizures and IEDs in this therapy resistant syndrome. One of these children showed an increase, and the other a decrease in electrographic seizures and in IEDs in all sleep stages with VNS. They did not influence the comprehensive results of the group (Fig.1).

The total number of epileptiform discharges was significantly reduced after nine months of VNS stimulation. There was a trend towards smaller median value in all sleep stages, but this was only significant in REM and delta sleep. The total electrographic seizure number was significantly reduced in the 24 hour EEG monitoring at both three and nine months. These findings are in agreement with previous animal studies on VNS [12,13]. So far, our findings are not previously and consistently reported in human studies [14,15]. This could be explained by longer and more comprehensive recording, including different activity stages in our study. Another possible explanation is that, contrary to other studies, we only investigated children.

In pharmacological studies, concomitant suppression of seizures and IEDs has been demonstrated in generalized epilepsy [28]. For partial epilepsies the relationship is more controversial [29]. Lamotrigine and Levetiracetam have been shown to reduce IEDs [30,31]. Clonazepam, Diazepam, Phenobarbital and Phenytoin show a correlation between suppression of IEDs and anti-epileptic drug plasma concentration, while carbamazepine and valproate show variable correlation [32-37]. So far, few long-term studies have investigated this possible relationship between electrographic seizures and IED, especially in children. In the 12 children with electrographic seizures in the 24-hour EEG monitoring, there was a significant concordance in direction of changes in interictal epileptiform activity and electrographic seizures at nine months. In our long-term data for all 15 children, there was no concordance in direction of changes in epileptiform activity and clinical effects on seizure reduction, seizure severity and quality of life, and there was no direct correlation between the extent of improvement in these clinical data and the degree of spike reduction. These data are in agreement with the literature, which has suggested that EEG IEDs are not directly related to clinical seizure frequency [29]. The method commonly used for evaluation of the anti-epileptic effect in children with epilepsy is parents seizure frequency reports. These are uncertain measures with a high rate of missed subtle seizures and undetected seizures during sleep. This could explain the lower concordance between IEDs and clinical seizures compared to IEDs and electrographic seizures during the 24 hour EEG.

The concomitant reduction in IEDs, electrographic seizures and to a lesser extent in clinical seizures seen in our study, indicate that VNS influences the epileptic process at different functional levels.

The persistence of the anticonvulsant effects and the gradual decrease in epileptiform discharges and electrographic seizure number in our study could suggest that VNS induces long-term neuron-modulating effects. Marrosu et al. recently described, in an Iomazenil



SPECT study on 10 subjects, that the anti-epileptic action of VNS, although probably multifactorial, might be an increase in GABA-mediated cortical inhibition. They showed a significant correlation between VNS seizure reduction and normalization of GABA receptor density [38]. Besides this long-term effect, the possible favorable direct VNS effects that might suppress both spikes and seizures could be mediated through different mechanisms, such as arousal-like effects via the reticular activating system [39-41] or sleep mechanisms and altered background activity of EEG with arousals or direct mood-elevating effects of VNS. The data from Binnie et al. [22], that interictal epileptiform activity without any clinical signs is associated with transitory cognitive disturbances, might suggest that a suppression of IED in VNS is related to an improvement in QOL. Further analyses of our recordings focusing on sleep and background frequency and arousal effects of VNS will be reported separately.

The high standard deviation in comparison with the median ISI indicates large variation in ISI length. This complicates the analysis of the VNS on ISI.

In conclusion we see a reduction in epileptiform activity particularly in REM and delta sleep and a reduction in the number of electrographic seizures. In the 12 children with epileptiform activity and electrographic seizures, we show a concordance between reduction in IEDs and electrographic seizures. The VNS effects on IEDs as well as on seizures indicate that VNS affects the epileptic pathophysiological process on different functional levels.

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**TABLE 1.**

Descriptive Statistics of the Pilot Study Between Visual Inspection and Persyst Spike Detector System

	Visual spike detection (spikes/h)	Persyst spike detection (spikes/h)	Difference between Visual and Persyst spike detection (spikes/h)
Range (min-max)	0 - 1856	0 - 1885	-29 - 78
Median	61	58	3
Quartiles (25 <sup>th</sup> 75 <sup>th</sup> )	7.5 , 91.5	7 , 84	0 , 14



**TABLE 2.**

Results of Spike Detection in One Hour of Wake, REM- Spindle- and Delta- Sleep, Before VNS-initiation (Baseline), 3 and 9 Months after Initiation. 13 Children, Excluding Two with CSWS.

Activity stage	Before initiation (baseline)	3 months after initiation	9 months after initiation
	Median (range)	Median (range) / p-value	Median (range) / p-value
wake	50.5 (0-2115)	49 (0-1999) / 0.64	39 (0-2182) / 0.67
ss	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
delta	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

15 Children, Including two with CSWS.

Activity stage	Before initiation (baseline)	3 months after initiation	9 months after initiation
	Median (range)	Median (range) / p-value	Median (range) / p-value
wake	91 (0-2115)	87 (0-1999) / 0.68	44 (0-2182) / 0.79
ss	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
delta	599 (0-5634)	264 (3-5678) / 0.08	269 (2-4819) / 0.008
total	989 (2-10430)	643 (8-12795) / 0.23	809 (9-11923) / 0.04

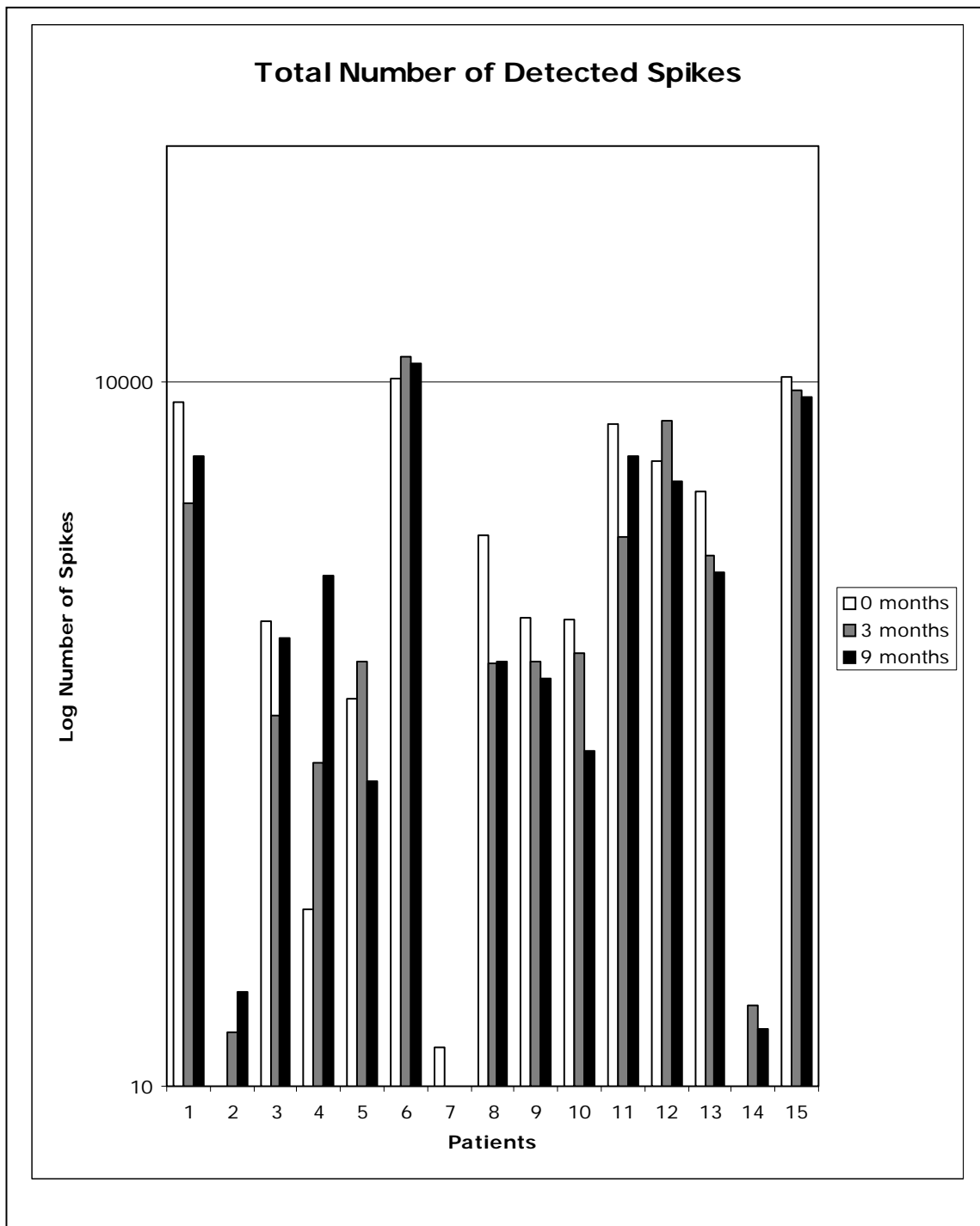
CSWS=continuous spike-wave discharges during slow sleep

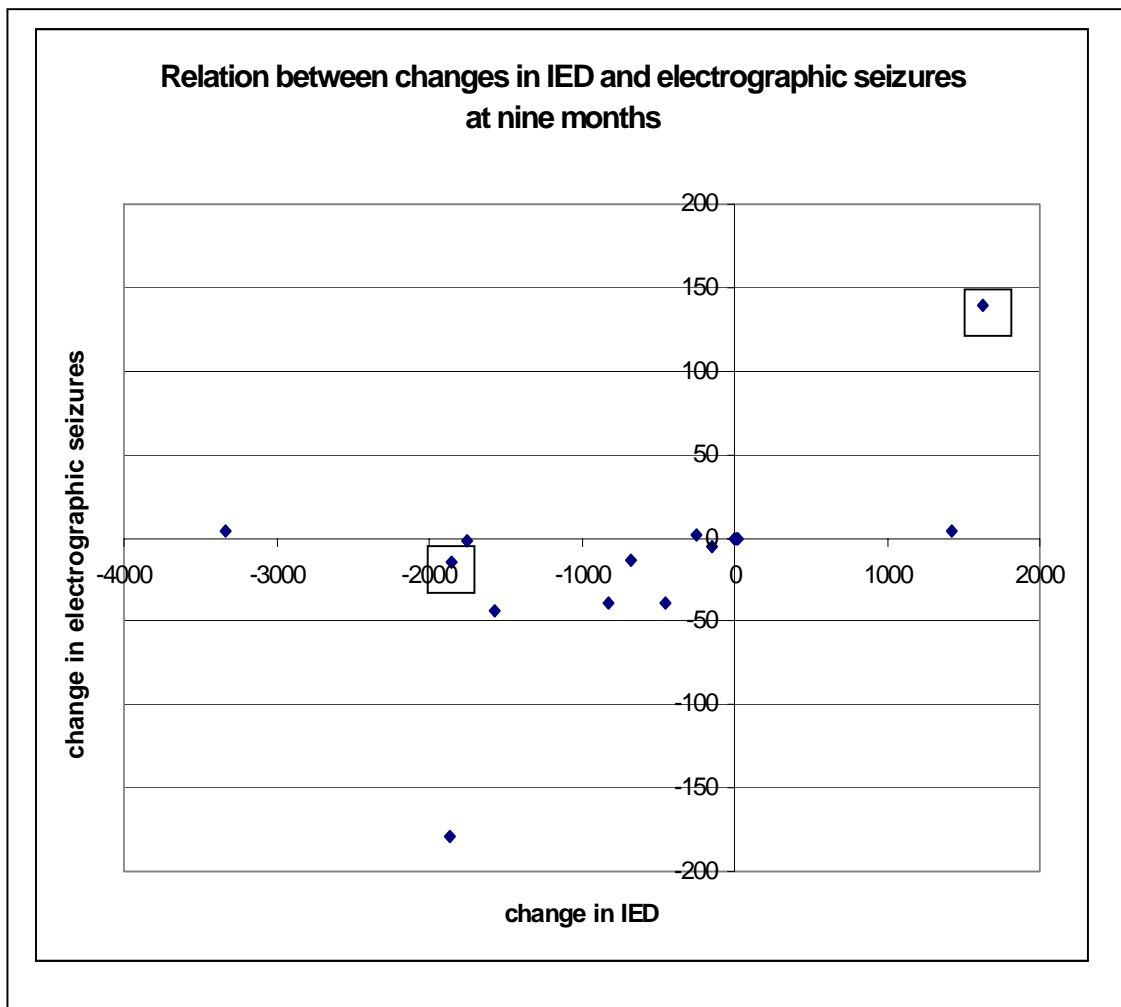
**FIGURE LEGENDS****FIGURE 1**

Total number of detected spikes in 15 children initially, and after three and nine months of vagus nerve stimulation ( $p=0.03$  at nine months). Patients number 6 and 15 with CSWS, a therapy resistant, neurophysiologic, and clinical entity with epileptiform activity in  $>85\%$  of non-REM sleep, are marked in the figure. They did not influence the comprehensive results of the group.

**FIGURE 2**

Concordance between changes in interictal epileptiform discharges (IED) and electrographic seizures during the 24 hours monitoring at nine months ( $p=0.04$ ).

**FIGURE 1**

**FIGURE 2**

IED=interictal epileptiform discharges

The two patients with CSWS are marked with a box