



Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood

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Received 10 November 2004

KEYWORDS

Epilepsy;
Vagus nerve
stimulation;
Cognitive
development;
Quality of life;
Mood;
Children

Summary

Purpose: Vagus nerve stimulation (VNS) is a neurophysiologic treatment for patients with refractory epilepsy. There is growing evidence of additional quality of life (QOL) benefits of VNS. We report the effects of VNS on seizure frequency and severity and how these changes are related to cognitive abilities, QOL, behaviour and mood in 15 children with medically refractory and for surgery not eligible epilepsy.

Methods: Initially, and after 3 and 9 months of VNS-treatment, 15 children were investigated with Bayley Scales of Infant Development (BSID), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R), Wechsler Intelligence Scales for Children (WISC-III) depending on the child's level of functioning, a Visual Analogue Scale for validating QOL, Child Behaviour Checklist (CBCL) for quantifying behaviour problems, DODRILL Mood Analogue Scale and BIRLESON Depression Self-Rating Scale, and the National Hospital Seizure Severity Scale (NHS3). A diary of seizure frequency was collected.

Results: Six of 15 children showed a 50% or more reduction in seizure frequency; one of these became seizure-free. Two children had a 25–50% seizure reduction. Two children showed increased seizure frequency. In 13 of 15 children there was an improvement in NHS3. The parents reported shorter duration of seizure and recovery phase. There were no changes in cognitive functioning. Twelve children showed an improvement in QOL. Eleven of these also improved in seizure severity and mood and five also in depressive parameters.

Conclusion: This study has shown a good anti-seizure effect of VNS, an improvement in seizure severity and in QOL and a tendency to improvement over time regarding

DOI of original article: 10.1016/j.seizure.2005.07.004.

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behaviour, mood and depressive parameters. The improvement in seizure severity, QOL, behaviour, mood and depressive parameters was not related to the anti-seizure effect.

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Introduction

When anti-epileptic drugs fail, and epilepsy surgery is found unfeasible or ineffective, there remains a group of at least 10% of adults and 25% of children with epilepsy in whom seizure control cannot be achieved.

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 an 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 wellbeing and quality of life (QOL). Parents or caregivers reported an increase in alertness, memory-, motor-, verbal- and cognitive-function that in part was unrelated to the anti-seizure effect.^{3–6}

More directed adult studies have revealed improvement in mood, depression and memory function.^{7–12} No VNS studies have revealed negative effects on cognition in adults or in children.^{7–9} The effects were independent of seizure control.

A few paediatric studies have indicated only moderate improvement in these qualities.^{13,14}

In this article we report the effects of VNS on cognition, behaviour, mood and QOL in 15 children with refractory epilepsy and how these changes are related to seizure frequency and severity.

We also elucidate the difficulties in assessing and in interpreting the results in a poorly investigated but needful group of children with therapy-resistant epilepsy and developmental impairment.

Effects on sleep quality and epileptiform EEG abnormalities will be reported separately.

Methods

Subjects

The study group comprises 15 children (10 boys and 5 girls) aged 4–17 years (median 11 years) with the diagnosis of epilepsy and absence of non-epileptic seizures (Table 1). Epilepsy surgery has been performed in four patients and found not applicable in the others. Age of epilepsy onset was between 4

months and 9 years (median three years). Duration of epilepsy was 4–12 years (median 8.5 years). The aetiology was unknown in three subjects. These three had normal MRI-scans. All patients had been on stable anti-epileptic drug medication for at least 3 months prior to the VNS implantation and during the 9 months 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 and VNS stimulation parameters

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 for the purpose of suppressing and reducing the frequency and/or severity of epileptic seizures. The VNS can be programmed externally with stimulation parameters appropriate to individual patients. 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 0.25 mA; signal frequency 30 Hz; pulse-width 500 μ s; stimulation on-time 30 s; stimulation off-time 5 min. During 4 weeks the output current is increased in steps of 0.25 mA to 1–1.5 mA and is then kept stable during the 9 months follow up. Patient number 12 was changed to rapid stimulation (stimulation on-time 7 s; stimulation off-time 12 s) after 6 months.

Clinical outcome measures/seizures

During 3 months before initiation a diary of seizure frequency and severity was collected together with clinical data. These data serve as a baseline. Follow-up assessments were performed at 3 and 9 months after VNS-initiation. Each patient serves as his own control.

The parents or caregiver filled in a protocol over seizure frequency and was questioned about the nature and timing of any seizures occurring during the previous 3 months. Information about adverse effects, compliance with medication over the same

period was asked for and plasma concentrations of anti-epileptic drugs were measured.

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.^{15,16}

The following seizure types were recorded. Simple partial seizures, complex partial seizures, partial seizures evolving to secondary generalized tonic-clonic seizures, generalized tonic-clonic seizures, atonic seizures (drop attacks with complete relaxation of the body), atypical absences (moments of decreased consciousness with minor accompanying symptoms) and myoclonic seizures (short contractions of the face or limb). The myoclonic seizures were not scored. The Seizure Severity was scored with the National Hospital Seizure Severity Scale, a further development of the Chalfont Seizure Severity Scale described by O'Donoghue et al.¹⁷

Cognitive functioning, QOL and behaviour

For assessment of cognitive abilities three different tests were used depending on the child's level of functioning: BSID, Bayley Scales of Infant Development, American version,¹⁸ WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence, Swedish version¹⁹ and WISC-III, Wechsler Intelligence Scales for Children, Swedish version.²⁰ For children assessed with BSID the Mental Developmental Index (MDI) was used to express the cognitive functioning and for children assessed with WPPSI-R and WISC-III Full Scale IQ (IQ) was used. Fourteen children were assessed before onset of VNS and 3 and 9 months after. In one child the parents only wanted to perform the assessment of cognitive functioning before onset of VNS and after 3 months and not after 9 months.

QOL, behaviour, mood and depression were assessed by questionnaires and visual analogue scales filled in by the parents, usually the mother. Questionnaires were filled in immediately before VNS-initiation and 3 and 9 months after.

To describe QOL a visual analogue scale (VAS) was used with scores between -10 and +10. Zero in the middle is the parent's conception of the child's QOL immediately before VNS-initiation, -10 is 100% reduction and +10 is 100% improvement of quality of life.

Parent's perceptions of the children's general behavioural problems were quantified by using the total score of the Child Behaviour Checklist (CBCL).²¹ The questionnaire comprises 115 items and the parent was asked to rate, on a three point scale, whether a behaviour problem was present or not in the child and to what degree. The cut-off

score for manifest behaviour problems is 30 according to Swedish norms for the scale.²²

Mood was assessed by using a visual analogue scale, which consists of 100 mm scales for 18 dimensions (e.g. alert-drowsy; tense-relaxed), commonly reported in the literature to be sensitive to drug effects.²³ The scale was translated and retranslated into Swedish.

For measuring depression Birlson Depression Self-Rating Scale (DSRS) was used. The scale has been translated into Swedish and the wording of the translation has made it acceptable both to children²⁴ and adolescents.²⁵ It is an 18-item self-report questionnaire in which the child is asked to estimate his/her own situation during the last week on a three-point scale. Scores of two, one or zero, respectively, in the direction of disturbance, refer to "most of the time", "sometimes" or "never".

Statistical evaluation

Wilcoxon signed rank test was used for comparisons of the patient's response before VNS initiation and 3 and 9 months after. Kruskal-Wallis test was used for comparison between the three subgroups based on treatment effect, before VNS initiation and 3 and 9 months after. Spearman rank correlation test was used to calculate the correlation in degree of improvement between QOL and NHS3 and QOL and seizure reduction. The level of significance was set at $p < 0.05$.

Results

This prospective longitudinal study, presents the response of VNS after 3 and 9 months in 15 children with refractory epilepsy and in particular the effects on seizure frequency and seizure severity in relation to the effect on cognition, QOL, behaviour and mood.

Seizure frequency and severity

The seizure frequency decreased 50% or more in six children; one of these became seizure-free. The number of seizures decreased between 25 and 50% in two and decreased less than 25% in four. It increased in two patients and was unchanged in one.

Without considering seizure type, 3 and 9 months of VNS reduced the median seizure number from pre-implantation 51 (range 2–200) to post-implantation 18 (range 2–141) and 19 (range 0–112), respectively. Thus the median seizure reduction was 65% ($p = 0.02$) at 3 and 63% ($p = 0.04$) at 9 months.

Table 1 Demographics and clinical characteristics of the study group.

Patient no.	Age at study onset (year)	Sex	Age at epilepsy onset (year)	Epilepsy type/syndrome	Seizure type	Etiology	Previous epilepsy surgery	MRI	Changes in seizure frequency at 9 months (%)
1	10	M	0.25	Lennox-Gastaut	GTCS	Unknown	No	No	Increase (33%)
2	9	M	2.5	Partial, Symt.	CPS	CD	Yes	L.TL res., MD	Seizure free (100%)
3	15	F	3	Partial, Symt.	CPS	Encephalitis	No	No	Reduction (<25%)
4	4	M	1	Partial, Symt.	CPS	CD	Yes	R.TL res., MD	Reduction (<25%)
5	13	M	5	Lennox-Gastaut	2°GTCS, AAbS	HIE	No	R. occ. lesion, focal atrophy	No change (0%)
6	11	M	4.5	CSWS	SPS, 2°GTCS	HIE	No	L. lesion, atrophy	Reduction (>50%)
7	15	M	5	Partial, Symt.	SPS	HIE	No	L. parietal lesion	Reduction (50%)
8	9	F	0.5	Lennox-Gastaut	2°GTCS	HIE	No	R. Schiz., L.CD, CCA	Reduction (50%)
9	17	M	9	Partial, Symt.	CPS	CD	No	Multiple prenatal lesions	Increase (16%)
10	6	M	0.75	Partial, Symt.	CPS, MS	Unknown	No	No	Reduction (<50%)
11	10	F	2	Partial, Symt.	2°GTCS	CD	Yes	L. parieto-occ. res., MD	Reduction (<25%)
12	11	M	0.25	Lennox-Gastaut	GTCS, AS, MS	CD	Yes	R. frontal and occ. res., MD	Reduction (25%)
13	16	M	7	Partial, Symt.	CPS	HIE	No	L. PVL, BG lesion	Reduction (>50%)
14	12	F	3	Partial, Symt.	CPS	Unknown	No	No	Reduction (>50%)
15	12	F	5	CSWS	CPS	Unknown	No	R. anterior hipp. atrophy	Reduction (<25%)

Epilepsy and seizure types according to the International Classification of the International League Against Epilepsy. Abbreviations—AS: atonic seizure; AAbS: atypical absence seizure; BG: basal ganglia; CCA: corpus callosum agenesis; CD: cortical dysplasia; CPS: complex partial seizure; CSWS: continuous spike-wave during slow sleep; F: female; GTCS: generalized tonic-clonic seizure; 2°GTCS: secondary generalized tonic-clonic seizure; HIE: hypoxic-ischemic encephalopathy; hipp.: hippocampus; L.: left; M: male; MD: multiple dysplasia; MS: myoclonic seizure; occ.: occipital; PVL: periventricular leukomalacia; R.: right; Res.: resection; Schiz.: schizencephaly; Symt.: symptomatic; TL: temporal lobe.

Table 2 Reduction of seizure frequency according to seizure type initially and after 3 and 9 months of VNS-treatment.

Patient no.	Number of patients	Before initiation total number of seizure	3 months after initiation total number of seizure (% reduction)	9 months after initiation total number of seizure (% reduction)
Complex partial seizures	8	325	207 (36%)	202 (37%)
2		53	5	0
3		19	18	18
4		78	63	75
9		6	7	7
10 ^a		14	9	9
13		9	2	2
14		72	40	31
15		74	63	60
Generalized	2	131	130 (0%)	163 (24% increase)
1		75	91	100
12 ^a		56	39	63
Secondary generalized	4	258	198 (23%)	163 (37%)
5 ^a		5	6	10
6 ^a		2	1	2
8		200	141	100
11		51	49	48
Simple partial seizures	2	13	11 (15%)	6 (54%)
6		11	9	5
7		2	2	1
Atonic drop attacks	1	76	37 (51%)	36 (53%)
12		76	37	36
Atypical absences	1	9	9 (0%)	4 (56%)
5		9	9	4
Myoclonic seizures	2	Yes	No	No
10		Yes	No	No
12		Yes	No	No

Seizure types according to the International Classification of the International League Against Epilepsy. The number of seizure was collected from seizure diary and counted as the mean value of the last 3 months.

^a Four patients had more than one seizure type.

The results on different seizure types are presented in Table 2. Simple partial, complex partial and atonic seizures seemed to decrease more than other seizure types scored. Two children had myoclonic seizures that were not scored. In both cases the myoclonic seizures ceased after 3 months.

Seizure severity, measured as NHS3, showed an improvement both at 3 and 9 months ($p < 0.001$). The median score at baseline, 3 and 9 months of treatment were 12 (range 4–19), 9 (range 1–19) and 9 (range 1–16), respectively. The parents reported shorter seizure duration and shorter recovery phase after a seizure.

Cognition

Six children were tested with BSID, one with WPPSI-R, seven with WISC-III Full Scale and one

with WISC-III Verbal Scale. This child has a cerebral palsy and was not able to fulfil the performance test. All, but one child, were mentally retarded ($IQ < 70$) at the assessment before onset of treatment. In one child (12) the parents only wanted to perform the assessment of cognitive functioning before onset of VNS and after 3 months and not after 9 months.

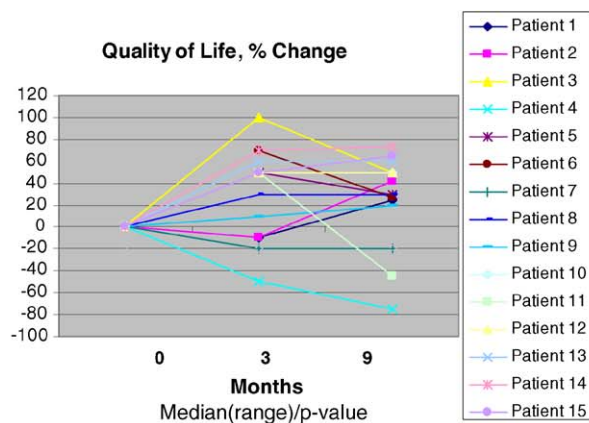
The results of the baseline to treatment and the follow-up 3 and 9 months after VNS implantation are shown in Table 3. For most children there are no differences in cognitive functioning before and after VNS. Two children (6 and 7) improved their IQ and one (11) child deteriorated. Four children were severely mentally retarded with $IQ < 30$. For them also mental age was calculated at the three assessments but they showed no improvement over time.

Table 3 Results of assessments of cognitive abilities initially (baseline), and after 3 and 9 months of VNS-treatment.

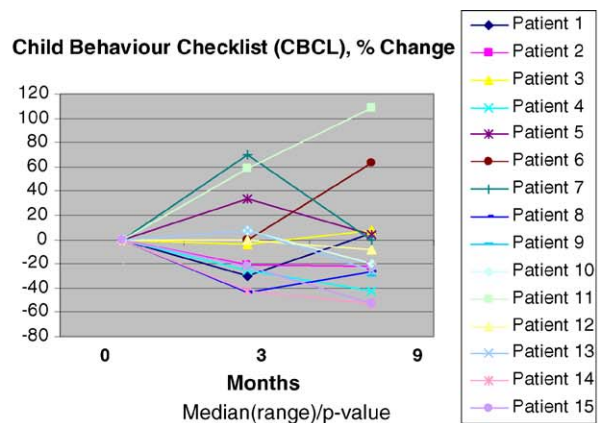
Patient no.	Age (year:month)	Method	Baseline MDI ^a /IQ	3 months MDI ^a /IQ	9 months MDI ^a /IQ
1	10:3	BSID	<30	<30	<30
2	9:10	WISC	39	37	42
3	15:3	WISC	45	42	41
4	5:3	BSID	48	48	49
5	13:5	WPPSI	40	40	40
6	11:1	WISC	56	69	68
7	15:6	WISC	61	65	76
8	8:9	BSID	<30	<30	<30
9	17:11	WISC	37	37	37
10	5:9	BSID	49	47	47
11	10:6	WISC	74	60	54
12	11:1	BSID	<30	<30	<30
13	16:6	WISC	42	42	42
14	11:2	BSID	<30	<30	<30
15	12:0	WISC	37	37	37

BSID: Bayley Scales of Infant Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scales for Children; MDI: Mental Developmental Index.

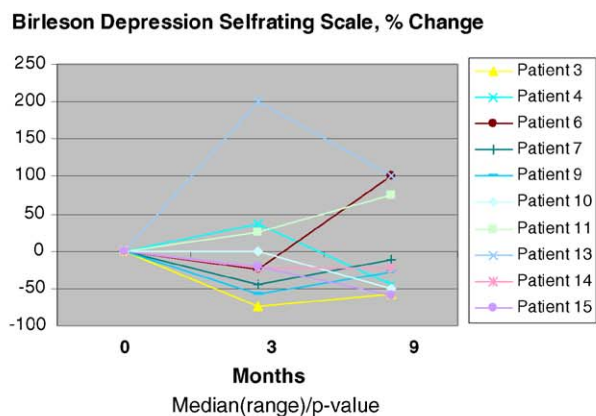
^a MDI was used for children assessed with BSID.



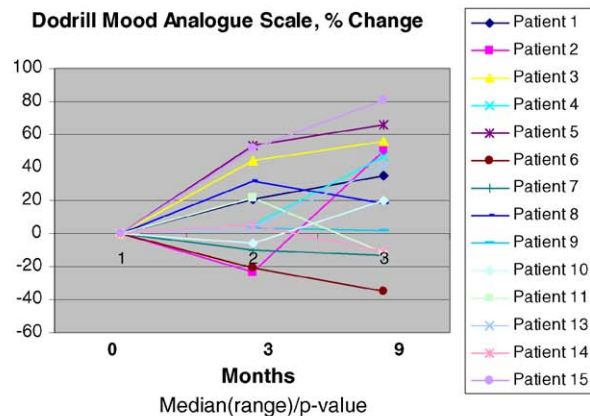
(A) 10(10-10) 15(5-20)/0.04 13(2.5-17.4)/0.04



(B) 49(19-94) 50(19-102)/0.69 43(18-92)/0.10



(C) 925(604-1502) 1022(672-1464)/0.17 1131(818-1364)/0.06



(D) 9(1-4) 5(3-15)/0.21 6.5(2-10)/0.1

Figure 1 (A) Percentage change of quality of life scores in 15 children initially, and after 3 and 9 months of vagus nerve stimulation. (B) Percentage change of Child Behaviour Checklist (CBCL) scores in 15 children initially, and after 3 and 9 months of vagus nerve stimulation. (C) Percentage change of depression scores in 10 of the 15 children initially, and after 3 and 9 months of vagus nerve stimulation. (D) Percentage change of Dodrill Mood Analogue Scale scores in 14 children initially, and after 3 and 9 months of vagus nerve stimulation.

Quality of life and behaviour

The results of QOL and the behaviour scales are presented in Fig. 1. Analysis of the estimation of the parent's conception of the child's QOL reveals significant improvement both after 3 and 9 months of VNS treatment.

In CBCL higher scores indicate more problems. In Dodrill Mood Analogue Scale higher scores indicate improvement in mood and in DRSRS higher scores indicate more depressive symptoms. There seems to be a tendency to an improvement in behaviour, mood and depression parameters when using these questionnaires although the changes are not significant. The behaviour score was over the cut off score for manifest behaviour problems in 11/15 children. Seven of these improved. The four children with behaviour score under the cut off score did not change their score. One child with CSWS and episodes of "zombie-like" behaviour lasting for days besides overt CPS had only a slight reduction in the frequency of the CPS (16% and 17% at 3 and 9 months, respectively) but recovered considerably in QOL and behaviour score, and from the "zombie-like" episodes. CSWS is a therapy resistant, neuro-physiologic and clinical entity with epileptiform activity in >85% of non-REM sleep.²⁶

When comparing the results of QOL and behaviour between three subgroups based on seizure reduction, no difference was discerned ($p = 0.6$ in QOL, $p = 0.6$ in CBCL, $p = 0.5$ in Dodrill and $p = 0.2$ in DRSRS when comparing 9 months against baseline in the three subgroups) (Table 4). However, there seemed to be a correlation between improvement in QOL, mood and seizure severity. In 13 of the 15 children there was an improvement in NHS3. Twelve children showed an improvement in QOL. Eleven also improved in seizure severity and mood and 5 also in depressive parameters. The number of children with improvement in both QOL and NHS3 was higher than QOL combined with seizure reduction. No correlations in degree of improvement were found (Fig. 2). (Spearman correlation coefficient was 0.32 and 0.40, respectively.) In general there was a tendency of improvement over time in median scores regarding behaviour, mood and depressive parameters.

Side effects

No severe side effects were seen either from the surgical procedure or from VNS itself.

Transient coughing and hoarseness for 1 or 2 days after increasing the current was reported in four patients. Weight loss was seen in one adolescent. One had a non-transient pain and paresthesia in the

Table 4 Results of behaviour and quality of life scores in three subgroups based on anti-epileptic effect, initially and after 3 and 9 months of VNS-treatment.

	No seizure reduction (n = 3)			<50% seizure reduction (n = 6)			>50% seizure reduction (n = 6)		
	Baseline Median (range)	3 months Median (range)	9 months Median (range)	Baseline Median (range)	3 months Median (range)	9 months Median (range)	Baseline Median (range)	3 months Median (range)	9 months Median (range)
CBCL	61 (37–76)	69 (36–102)	43 (39–79)	47 (28–77)	53 (27–70)	41 (23–92)	59 (19–94)	50 (19–74)	38 (18–73)
Dodrill	680 (604–970)	1000 (732–1038)	985 (818–1364)	782 (637–1203)	1125 (672–1464)	1217 (939–1364)	1050 (736–1502)	1084 (719–1331)	1163 (865–1392)
DRSRS	14 (14–14)	6 (6–6)	10 (10–10)	10 (4–12)	5 (3–15)	5 (2–7)	7 (1–9)	4 (3–7)	8 (2–8)
QOL	10 (10–10)	11 (9–15)	12.5 (12–13)	10 (10–10)	15 (5–20)	15 (2.5–16.5)	10 (10–10)	14 (8–17)	13.6 (8–17.4)

Abbreviations—CBCL: Child Behaviour Checklist; Dodrill: Dodrill Mood Analogue Scale; DRSRS: Birtleson Depression Self-Rating Scale; QOL: quality of life.

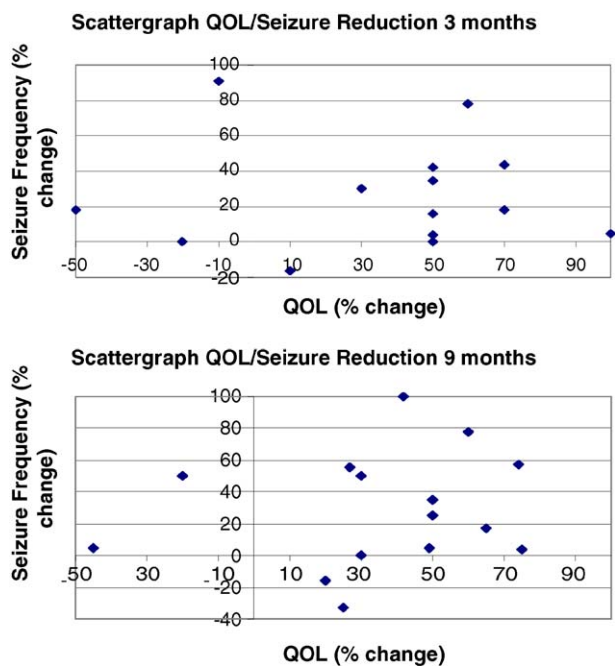


Figure 2 Correlation between the percentage changes in QOL and seizure frequency at 3 and 9 months after initiation of vagus nerve stimulation. No correlation in degree of improvement was found ($p = 0.25$ and 0.40 ; Spearman correlation coefficient).

neck that was so disabling that QOL, behaviour score and mood were affected and the stimulator was withdrawn after the study was finished. One child was complaining from breath shortness that did not improve completely until we reduced the pulse width from 500 to 250 ms after 9 months.

Discussion

This study confirms previous studies of vagus nerve stimulation indicating better anti-seizure effect in children compared to adults with $>50\%$ seizure reduction in 40% of children. In addition our results show improvement in QOL and indicate better behaviour-, mood- and depressive parameters after VNS.

Parker et al.⁵ and Majoie et al.¹⁴ reported less good effect in children with severe encephalopathy. Aldenkamp et al.¹³ suggested that the treatment effect of VNS is related to the severity of the mental impairment, with the most positive effects in patients with less severe disabilities. In this study there are fewer patients suffering from severe epileptic encephalopathy and better anti-epileptic effect in those with less mental retardation. This supports the suggestions of better anti-seizure effect in children with less severe impairment.

In this study 80% of the children had an improvement in parent's conception of the child's QOL, but

the effect seemed not related to the anti-seizure effects. One of the three patients with a worsening in QOL had unchanged seizure frequency and two patients with improved QOL had increased seizure frequency. However, there seemed to be a correlation between improvement in QOL, mood and seizure severity. Eleven of the 12 children with improvement in QOL also improved in seizure severity and mood and 5 also in depressive parameters. The number of children with improvement in both QOL and NHS3 was higher than QOL combined with seizure reduction. No correlations in degree of improvement were found (Fig. 2). Our results are in accordance with previous reports with epilepsy surgery. Reduction in seizure severity is significantly correlated with improvement in QOL after corpus callosotomy.²⁷ Low seizure severity correlated with higher health-related quality of life (HRQOL) ratings for scales measuring social function, vitality, and mental health after epilepsy surgery in a Swedish multicenter study in patients from 16 years of age and a $>75\%$ reduction of seizure frequency.²⁸

We used parent's conception of the child's QOL even though major concerns have been raised regarding the accuracy and acceptability of parent rating of children's QOL. Ronen et al.²⁹ showed that there is a tendency for parents to score lower than the child in QOL and performance status. In very young children and in severely handicapped children measurements can be based only on parent reports. Parent reports may prove to be more reliable and valid in long-term investigations because of the rapid changes in children's attitudes, abilities and priorities as part of the developmental processes.

Our results suggest an improvement in mood and some antidepressant effect. Studies in adults show a marked antidepressant effect in patients suffering from major depression.¹¹ In our study no child had depressive scores below the cut off for manifest depression. True changes in depression parameters might be difficult to determine in patients not suffering from major depression.¹³ Scoring tests better elucidating mood changes in children not suffering a depressive disorder might have given more truthfully results.

Our results in behavioural changes as a result of VNS stimulation at 3 and 9 months did not show any significant improvement. However, there seemed to be an improvement over time. One could speculate that the improvement in behaviour had not yet occurred to its full extent after 9 months. A longer follow up might show additional improvement. Although caution must be taken when expressing absence of differences in a small group, we cannot find an association between anti-seizure effect and improvement in QOL and behaviour, not even when

comparing between the subgroups based on seizure reduction (Table 4).

We did not see any differences in cognitive functioning before and after VNS. The two children that improved their IQ had the highest baseline IQ. This could support previous findings of VNS on epileptiform activity that the treatment effect is related to the severity of the mental impairment, with the most positive effects in patients with less severe disabilities. Aldenkamp et al.¹³ described that cognitive and behavioural assessments are difficult to use in this type of patients with epilepsy and developmental impairment. Both testing and interpretation of test results are challenging. There is also a possibility that VNS does not affect cognitive functioning in this type of patients. Ott et al.³⁰ discussed limitations in the CBCL behaviour scores in identifying psychopathology in children with epilepsy who clearly warrant mental health interventions. They demonstrated a discrepancy between high rate of psychiatric diagnosis and low rate of mental health service. This shows that cognitive functioning has an important impact on behaviour and the importance of finding accurate assessments and to learn and understand the needs of this group of patients.

Despite the small number of included children, this study has shown a good anti-seizure effect of VNS, an improvement in seizure severity and in QOL and a tendency to improvement over time regarding behaviour, mood and depressive parameters. The improvement in seizure severity, QOL, behaviour, mood and depressive parameters was not related to the anti-seizure effect.

Acknowledgments

This research was supported by Orion-Pharma, the Linnéa and Josef Carlsson Foundation, the Margaretahemmetts Foundation, the Stiftelsen Samaritens Foundation, the Segerfalks Foundation and SRC 084. We are grateful to technicians Inger Nordlund and Eva-Karin Olsson and neuropsychologists Katarina Dykes and Kajsa Lönn for assessing many of the children in this study. We thank statistical consultant Jonas Björk.

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