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Efficacy and tolerability of long-term treatment with vagus nerve stimulation in adolescents and adults with refractory epilepsy and learning disabilities

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ABSTRACT

The long-term effects of vagus nerve stimulation (VNS) on seizure frequency were studied in 50 patients with epilepsy and learning disabilities. Mean observation time was 4.6 years. At follow-up, none of the patients was seizure-free, 25% had more than 50% seizure reduction, and 46% had some seizure reduction, but less than 50%. The discontinuation rate was 18%. Our results indicate that, like antiepileptic drugs, VNS does not have such a good seizure-reducing effect in patients with epilepsy and learning disabilities compared with the general epilepsy population.

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1. Introduction

Approximately 20% of the adult epilepsy population has learning disabilities (LD), and the occurrence of epilepsy increases with the severity of LD.[1] The chances of achieving seizure control in patients with epilepsy and LD is poorer than in those without LD, with 45% of epilepsy patients with LD being refractory to antiepileptic drugs (AEDs), as compared with approximately 30% of the total epilepsy population.[2,3]

The most difficult-to-control epilepsies are found in this subpopulation. For example, in epileptic encephalopathies, such as Lennox–Gastaut syndrome and Dravet syndrome, the seizures are mostly pharmacoresistant.[4,5] Nevertheless, many of these patients have a heavy drug burden despite the fact that individuals with LD appears to be more prone to central nervous side effects from AEDs than those without LD.[6,7] Patients with epilepsy and LD are a very heterogeneous patient group necessitating that the treatments are tailored to every individual patient, with the aim of obtaining an optimal balance between seizure reduction and side effects.

Vagus nerve stimulation (VNS) is an established treatment option that is offered to patients with drug-resistant seizures and who after evaluation are not candidates for epilepsy surgery. The seizure-reducing effect of VNS may increase gradually over 18–24 months of treatment.[8] In a prospective 3-year follow-up study of adult patients more than 50% seizure reduction was reported in 43% of the patients.[9] Additionally, other studies have described subjective improvements in various quality-of-life measurements during VNS treatment, independent of the effect on the seizure frequency.[10–12] Side-effects of VNS treatment are mainly stimulation-related and tend to decrease over time.

A non-pharmacological treatment like VNS is to be warmly welcomed in patients with severe epilepsy and LD. However, it is not evident that persons with LD obtain the same seizure-reducing effect from VNS treatment as persons without LD. Responder rates (i.e. those having more than 50% seizure reduction) varying from 28% to 68% have been reported.[13,14]

The purpose of this open, uncontrolled, retrospective study was to analyze the efficacy and tolerability of VNS treatment in Norwegian patients with drug-resistant epilepsy and LD. We also wanted to explore the efficacy of VNS in different sub-groups of these patients.

2. Materials and methods

All those patients aged 14 years or older, and with a combination of LD and epilepsy, who had had a VNS implantation at The National Hospital in Oslo in the period between October 1997–May 2008 were included in the study. All the patients had been followed up at The National Centre for Epilepsy, located just outside Oslo, and their demographic and electroclinical data were retrospectively obtained from the patients' medical records at the centre. Patients' epilepsies were classified according to the recommendations of the International League Against Epilepsy in 1989.[15] Each patient had been diagnosed with learning

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disability, graded as either mild (IQ 50–70), moderate (IQ 35–49), severe (IQ 20–34), or profound (IQ < 20).[16]

The patients and their caregivers were contacted and asked to complete a questionnaire. Two patients had died during the follow-up period, and their relatives were not contacted regarding the questionnaire. Based on the medical records, the patients' seizure diaries, and the information given by the caregivers, the patients' seizure types, frequencies, and durations, their postictal condition, and their overall well-being were assessed both over a 6-month baseline period prior to VNS implantation, and also in the follow-up period after the implantation.

3. VNS stimulation parameters

The VNS was started 1–2 days after the operation with quick ramp-up procedure. The standard initial parameters were: output current (OC) 0.25 mA, frequency 20 Hz, pulse width 250 μs, on-time 30 s, and off-time 5 min. The OC was increased by 0.25 mA every other day up to 1 mA, if the stimulation was well-tolerated. Follow-up visits were usually every three months. The parameters were adjusted individually according to the effect and tolerance, and changes in on–off parameters were attempted in those who experienced no reduction in seizure frequency.

4. Results

50 patients fulfilled the inclusion criteria. Due to local infection, in two patients the devices were explanted after 5 and 8 months, respectively. Excluding these two patients, the mean follow-up period was 4.6 years (range: 1.3–11.9 years). For five patients, the devices were explanted due to lack of efficacy. One patient died during the follow-up period from a disease unrelated to the epilepsy. Another patient died in sudden unexpected death in epilepsy (SUDEP). Thus, the discontinuation rate of the patient group was 18%.

The generator was replaced in eight patients due to end of battery life, and three of these patients have now received their third generator.

Out of 48 caregivers, 34 (71%) completed and returned the questionnaire.

Table 1 summarizes the demographic and clinical features of the patients.

4.1. Surgical complications

Two patients developed local infections necessitating device removal. In one patient with tuberous sclerosis complex (TSC) the operation was unusually prolonged, and the patient woke from anaesthesia with a unilateral central facial palsy. This could have been due to a thromboembolic episode, although a CT scan did not reveal a cerebral infarction. The facial palsy ameliorated after about 6 months.

4.2. AED treatment

Out of 48 patients, 29 (63%) changed their drug treatment (type of AED and/or dosage) during the follow-up period. Before implantation the patients were taking an average of 2.4 AEDs, and this number was unchanged at follow-up.

4.3. Effect on seizure frequency

At follow-up, none of the patients was seizure-free. Twelve patients (25%) had more than 50% reduction in seizure frequency, i.e. they were therapy responders, while 22 patients (46%) had a reduction in seizure frequency, but less than 50% compared with baseline frequency. In 14 patients (29%) the seizure frequency did not change. Table 2 shows the effects of VNS treatment on seizure frequency in different sub-groups of the patients. Unfortunately, these subgroups are too small to allow evaluation of which disorders benefited most from VNS treatment. However, there was a tendency for a better effect in patients with Lennox–Gastaut syndrome than in the rest of the population (38% responders in the Lennox–Gastaut syndrome group compared with 25% in the whole population). Likewise, it was not possible to draw firm conclusions about predictive factors regarding age at implantation, mental age, epilepsy syndrome, or epilepsy aetiology.

Table 1
Demographic and clinical features.

Clinical data	*N* = 48
Male/female	27/21
Mean age at onset of epilepsy (years)	3.5 (0–14)
Mean duration of epilepsy (years)	29 (10–55)
Number of previously tried AEDs	9 (4–15)
Learning disability, mild	21
Learning disability, moderate	16
Learning disability, severe	8
Learning disability, profound	1
Learning disability, degree not known	2
Mean age at VNS implant (years)	27 (14–53)
Epilepsy aetiology	*N* = 48
Unknown/known	25/23
Type of aetiology	
CNS infection	5
Cortical dysplasia	3
Traumatic brain injury	2
Birth-related asphyxia	5
Cerebrovascular insult	1
Encephalopathia induced by cytostatic agents	1
TSC	3
Rett syndrome	1
Dravet syndrome	1
Klinefelter syndrome	1
Epilepsy syndrome	
Focal	24
Focal symptomatic	15
Focal cryptogenic	9
Generalized	24
Generalized symptomatic	10 (LGS: 7)
Generalized cryptogenic	14 (LGS: 6)

AED: Antiepileptic Drugs; VNS: Vagus Nerve Stimulation; TSC: Tuberous Sclerosis Complex.

Table 2
Effects of VNS treatment.

	>50% seizure reduction	<50% seizure reduction	No seizure reduction
TSC (*n* = 3)		1	2
Dravet syndrome (*n* = 1)		1	
Rett syndrome (*n* = 1)	1		
LGS (*n* = 13)	5	5	3
LGS < 18 years (*n* = 4)	2	1	1
LGS > 18 years (*n* = 9)	3	4	2
Focal symptomatic epilepsy (*n* = 15)	4	6	5
Focal cryptogenic epilepsy (*n* = 9)	1	6	2
Focal epilepsy (all) (*n* = 24)	5	12	7
Generalized symptomatic epilepsy (*n* = 10)	3	4	3
Generalized cryptogenic epilepsy (*n* = 14)	4	7	3
Generalized epilepsy (all) (*n* = 24)	7	11	6
Symptomatic epilepsy (all) (25)	7	10	8
Cryptogenic epilepsy (all) (23)	5	13	5

TSC: Tuberous Sclerosis Complex; LGS: Lennox–Gastaut Syndrome.

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