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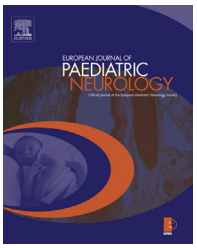

Original Article

Vagus nerve stimulation in the treatment of drug-resistant epilepsy in 29 children

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ABSTRACT

Background/purpose: Vagus nerve stimulation (VNS) has been demonstrated to be safe and effective for adults and children with drug-resistant epilepsy and is able to improve most types of epilepsy. The aim of this study, in a paediatric population, was to assess the overall efficacy of vagus nerve stimulation on seizures, to assess tolerability and quality of life.

Methods: This single-centre, retrospective study reviewed the files of 29 children in whom a vagus nerve stimulator was implanted between 1995 and 2012. The response rate (greater than 50% reduction of the seizure frequency), antiepileptic efficacy according to the type of epilepsy or age at implantation or age at onset of epilepsy, the time-course of seizures, adverse effects, overall quality of life and number of hospitalisations were studied.

Results: In our population, vagus nerve stimulation achieved a significant reduction in the seizure frequency throughout follow-up ($p = 0.015$). Response rates were 59% at 3 months, and 66% at 6 months, and the response rate then remained stable at about 70%. Stimulation tended to be more effective in patients with non-idiopathic partial epilepsy than in patients with non-idiopathic and idiopathic generalised epilepsy ($0.01 < p < 0.11$). No other predictive factors of efficacy were identified. Patients, parents, caregivers reported improvement in overall quality of life in 38% of patients during clinical interviews. A significant reduction in the number of hospitalisations due to a reduction of seizure frequency was observed after implantation ($p = 0.03$). VNS was stopped because of complications or insufficient efficacy in 9 cases.

Conclusion: Vagus nerve stimulation is a safe and effective treatment option in children with drug-resistant epilepsy who are not candidates for surgery.

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1. Introduction

Epilepsy is one of the most common neurological conditions, affecting approximately 100–200 per 100,000 children per year. Ten to 30% of these epileptic children are drug-resistant,[1,2] which means that they continue to have seizures after two years of treatment with at least two antiepileptics at effective doses.[3]

Vagus nerve stimulation (VNS) is indicated as an adjuvant to antiepileptic drugs in patients with drug-resistant epilepsy not amenable to surgical resection[4] and only 10–30% of patients are suitable candidates for surgical procedures.[5]

VNS was approved by European authorities in 1994 for all patients with inoperable drug-resistant partial epilepsy and by the *United States Food and Drug Administration* in 1997 only for adults or children over the age of 12 years with drug-resistant partial epilepsy. Nevertheless, about 20,000 children, many under the age of 12 years, have currently been implanted throughout the world.

This neurostimulation technique consists of delivering intermittent electrical stimulation continuously to the left vagus nerve by means of two electrodes implanted on the nerve and connected to a subcutaneously implanted pulse generator.[6]

The mechanism of action has not been fully elucidated, but vagus nerve stimulation appears to actvia projections of the vagus nerve onto nucleus tractus solitarius neurons, locus coeruleus, raphe nuclei, thalamus and cortex.[7] This stimulation appears to induce immediate changes by its action on the nucleus tractus solitarius by inducing synchronisation/desynchronisation of cerebral electrical activity and long-term changes by modification of neurotransmitter concentrations (reduction of excitatory neurotransmitters and increase of inhibitory neurotransmitters) and by modification of the distribution of cerebral blood flow[8] (particularly by an increase in blood flow in the thalamus).

Of the 440 patients included in the first controlled studies, on average, 37% of patients saw a decrease of over 50% in the seizure frequency at 12 months and 43% at 24 months.[9,10] In the largest cohort of paediatric patients treated with VNS,[2] the 12-month response rate was 38%. In a pooled analysis of 481 children,[11] the response rate was 55%.

The efficacy of VNS compared to antiepileptic drugs was assessed in a prospective case–control study.[5] A statistically significant reduction of the number of seizures and decreased morbidity were observed in the VNS group, but not in the group treated with antiepileptic drugs. The overall results appeared to be better in children than in adults, particularly with a higher rate of ≥90% seizure control.[4]

VNS appears to be effective in patients with high baseline seizure frequencies (>45 seizures/month), but may lack long-term efficacy in patients with lower baseline seizure frequency.[12]

VNS appears to be effective on most types of epilepsy (partial or generalized), regardless of the aetiology, EEG anomalies or MRI abnormalities.[11–14] In this review[15] of the first 100 paediatric cases, no difference was observed in terms of response to VNS according to age of implantation, but in another study,[2] efficacy was significantly better in patients <12 years of age than in patients >12 years of age.

VNS is globally well tolerated. The adverse effects reported were mainly minor, such as cough, transient pharyngitis, hoarseness, paraesthesia of the larynx and dyspnoea.

Some studies have reported improvement of cognitive functions that may be due to reduction of the seizure frequency, but a direct effect of VNS has also been suggested.[16] Most studies have also reported improvement of overall quality of life, especially related to improved vigilance, verbal communication, behaviour, memory, attention and concentration.[2–11]

Analysis of stimulation parameters shows that a higher total daily charge of VNS is associated with significantly higher response rates.[2]

Several studies have shown that VNS is associated with a significant reduction of medical costs (decreased number of consultations, emergency room (ER) visits, and hospitalisations).[8]

In this study, we report the results for the overall efficacy of vagus nerve stimulation in 29 paediatric patients. The primary objectives of this study were to evaluate VNS efficacy on seizures during a long observation period and the course of seizures after stopping VNS. The secondary objectives were to assess tolerability and quality of life of VNS in this population.

2. Material and methods

This was a single-centre, retrospective study which review the medical data for all children who were implanted with a Cyberonics® vagus nerve stimulator.

VNS implantations were performed under general anaesthesia in Amiens University Hospital by two neurosurgeons, according to standard procedures.

The following medical data were extracted from the files of these patients for analysis:

- Medical history.
- Data on epilepsy (age of onset, aetiology, type of seizures, seizure frequency (mean per month), seizure duration, number of episodes of status epilepticus, number of days of epilepsy-related hospitalisation). Baseline seizure frequency prior to VNS implantation was defined on the basis of the reported calendar provided by parents to the neurologist at the last visit prior to implantation.
- Treatment data (number of antiepileptic treatments tried before implantation and number of antiepileptic treatments taken).
- Operative data (date of implantation, date of stimulator removal, date and reason for a new operation).
- Data after VNS implantation included: seizure frequency (monthly mean) at regular intervals (3 months, 6 months, 12 months, 18 months, 24 months then yearly), seizure duration (increase, decrease or identical), overall quality of life (based on available patient records from the patients, parents, caregivers at follow-up visits, without a structured interview), adverse effects.

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