Original article

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Vagus nerve stimulation in children with drug-resistant epilepsy: age at implantation and shorter duration of epilepsy as predictors of better efficacy?

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ABSTRACT – *Aim*. To study the efficacy of vagus nerve stimulation (VNS) therapy in a highly drug-resistant childhood epilepsy patient group and to investigate the effect of age at implantation on efficacy.
Methods. The efficacy of VNS treatment was analysed in a cohort of 70 patients with drug-resistant epilepsy. Both children with focal (*n*=16) and generalized epilepsies (*n*=54) were included. Age at implantation varied between 19 months and 25 years.
Results. Overall, responder rate was 54% with 5.7% children becoming seizure-free. The only factor in our analysis that could predict good outcome was age at implantation. In the youngest group (<5 years), the responder rate was 77% and this group also included three of the four seizure-free children. These three seizure-free children were known to have tuberous sclerosis. There were no outcome differences between generalized and focal epilepsies.
Conclusions. Our single centre study confirms previous studies on the efficacy of VNS in children. A larger study using multivariate analysis to disentangle the contribution of different factors (such as age at implantation, aetiology, and epilepsy duration) is necessary to confirm our preliminary finding that younger age at VNS implantation might result in a better outcome.

Key words: VNS, vagus nerve stimulation, drug-resistant epilepsy, children

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Vagus nerve stimulation (VNS) is an approved therapy for drug-resistant epilepsy since 1997 (FDA approved) (Ben-Menachem *et al.,* 1994). Although registration and reimbursement procedures may differ from country to country, VNS therapy is considered a possible treatment option only if one can show that the patient has drug-resistant epilepsy and is not a candidate for resective surgery. In this sense, VNS therapy is still considered a "last resort" or "palliative" therapy for drug-resistant epilepsy patients. Not surprisingly, therefore, this results in a patient selection bias and partly explains why the efficacy was reported to be lower in the earlier trials with this treatment option (Labar *et al.,* 1999; Murphy, 1999; Ben Menachem, 2002; Labar, 2004).

In recent years, however, several studies have been published showing that the efficacy of VNS therapy is at least comparable to the efficacy of a new antiepileptic drug in a patient with drug-resistant epilepsy (Elliott *et al.,* 2011; Englot *et al.,* 2011; Wheeler *et al.,* 2011). Both responder rates and seizure freedom rates are very comparable. These better results can be explained by inclusion of less drug-resistant patients, but also by inclusion of younger patients with a shorter duration of drug-resistant epilepsy. In the US, VNS therapy is approved only beyond the age of 12, whereas in Europe for instance, VNS therapy can be considered at much younger ages, and also for generalized epilepsies (Kostov *et al.,* 2007). In younger patients with epileptic encephalopathies, such as Lennox-Gastaut syndrome, it is often realized already early on in the course of the disease that resective epilepsy surgery will not be a valid treatment option, and that one does not need to go through a sometimes very long pre-surgical work-up. This emphasis on younger patients and on the "non-surgical" cases implies that now more and more patients with generalized seizures are included in the more recent trials. Another factor which is important in judging the efficacy of VNS therapy is the notion that the efficacy of VNS can only be appreciated after some months of therapy (Morris and Mueller, 1999). Many studies show an increasing efficacy with time, which cannot be explained by changing the background AED treatment in these patients. In addition, and although not the primary focus in the majority of the available studies, a substantial benefit concerning quality of life and especially alertness, concentration and communication has often been reported (Kossoff and Pyzik, 2004; Hallböök *et al.,* 2005a; Shahwan *et al.,* 2009).

Focusing on the existing data of VNS therapy in childhood epilepsy, the most recent studies of Elliott *et al.* confirm that VNS therapy in drug-resistant childhood epilepsy is an effective and well tolerated treatment option. Responder rate was about 65% in the paediatric series, with 7.8% achieving seizure freedom (Elliott *et al.,* 2011). Also in our multicentre Belgian study, we found equally good efficacy for both childhood and adult drug-resistant epilepsy (De Herdt *et al.,* 2007).

One issue that needs more study is the prediction of VNS efficacy in different childhood epilepsy syndromes, although one can argue that this is also badly needed for new AEDs. In this sense, we reviewed our experience with VNS. In particular, we studied the effect of age and onset of epilepsy on efficacy.

Aims and methods

We reviewed the files of all our patients who had a VNS device implanted after the year 2000. Patient characteristics and epilepsy syndrome, including type and frequency of seizures, were prospectively collected in a database. This database also contained data on the settings of the VNS device, on the AEDs used before and during the follow-up, and on the efficacy of the VNS treatment. For efficacy, we used the gold standard parameters: responder rate (50% decrease of seizure frequency) and seizure freedom rate. At each visit, we also qualitatively assessed quality of life items, by asking whether the patient or the caregiver(s) believed that overall QOL was significantly better, the same, or worse than during the baseline before VNS therapy.

Analysis for this study was performed only for those patients who had a minimum follow-up of six months after implantation. Responder rates and seizure freedom rates were calculated at the last visit during follow-up. Seizure frequency was calculated during the last two months before the last assessment and compared with the same baseline period before implantation. We evaluated "seizure freedom for the last three months" before the last visit, as a primary outcome measure. The exact number of seizure-free months was also calculated at the last visit.

In our centre, we use a rather standardized protocol for the settings of the VNS device. It usually takes two months to obtain a first final setting of 2.0-mA output current, "classic duty cycle" with five minutes "OFF" and 30 seconds "ON" (500-μsec pulse bandwidth and 25-Hz stimulation frequency). These settings are maintained for at least two to three months, before we consider other device settings. Depending on the reported efficacy and side effects, we then adjust the parameters first by increasing the stimulation time, by shortening the "OFF" period to three minutes or less. Each new setting is maintained for at least one month. If the patient and/or parents are satisfied with the result, the settings are kept for longer periods. This means that in the very un-responding patient, a stimulation frequency is gradually moved to >30% (for instance: 30 sec "ON"; 1.1 min "OFF"; 35% stimulation). Only occasionally is the output current increased to a maximum of 3.0 mA.

Table 1. Number of VNS implantations per age group.

Age at implantation	No. patients	Duration epilepsy (median)	
		Median (years)	Range (years)
0-5 years	9	3.5	(1-5 y)
5-10 years	26	4.5	(1,5-9,5 y)
10-15 years	19	8	(4-11 y)
>15 years	16	11.5	(3-20 y)

Table 2. Epilepsy types.

Lennox Gastaut syndrome	20
Myoclonic astatic epilepsy	4
Dravet syndrome	5
Tuberous sclerosis complex	4
West syndrome	1
(Myoclonic) absence epilepsy	4
Myoclonic epilepsy	5
Other generalized epilepsies	6
ESES/CSWSS	4
Ring chromosome 20	1
Frontal lobe epilepsy	4
Non frontal focal epilepsy	11
Epilepsia partialis continua	1
TOTAL	70

In all children, the epilepsy diagnosis was confirmed by history-taking, documenting seizure type(s), MRI analysis, and at least one 24-hour video-EEG. It is important to note that in all children, epilepsy surgery was considered at some point during the follow-up, but only in those children with clear-cut focal epilepsy or/and in children with a focal brain lesion was a pre-surgical work-up actually performed, including at least five days of video-EEG monitoring and 3T MRI, as well as ictal and interictal SPECT with SISCOM analysis. We considered VNS therapy in those patients who were not eligible for resective epilepsy surgery after rigorous pre-surgical work-up, or in those patients with an epilepsy syndrome which was not suitable for epilepsy surgery and/or which was resistant to at least three AEDs over a period of at least six months.

Results

In total, 70 patients could be considered for this analysis. The follow-up period varied between 6 months and 10 years (median: 1.6 years). The age at implantation varied between 19 months and 25 years (median: 8 years). The break-down in age groups is shown in *table 1*. As can be seen, the majority of children were implanted at between 5 and 10 years (*n*=26), but there was also a smaller group of children with implantation below the age of 5 years (*n*=9). *Table 2* shows the epilepsy syndromes or classification. Only in 16 children was the drug-resistant epilepsy classified as typical focal; the other 54 patients presented with a more generalized epilepsy syndrome or with multifocal epilepsy. Twenty children were known to have Lennox-Gastaut epilepsy. Other epileptic encephalopathies, such as myoclonic-astatic epilepsy (*n*=4), Dravet syndrome (*n*=5) and ring chromosome 20 syndrome, were also included in our series.

The settings of the VNS device at the last follow-up assessment were "standard" in 49/70 children, with a 2.0-mA output current and classic duty cycle (5 minutes "OFF"; 30 seconds "ON"; 10% stimulation). In the other 21 children, a higher output current (*n*=5) or another duty cycle with more percentage stimulation was used (typically 30 seconds "ON"; 1.1 min "OFF"; 35% stimulation).

In general, responder rate at the last follow-up visit was 54%, *i.e.* for 38/70 children, a seizure frequency decrease >50% was observed. Four children remained "seizure-free for the last three months" (5.7%). Three of these children were known to have tuberous sclerosis. The other seizure-free child was a 12-year-old girl with drug-resistant myoclonic absence epilepsy. The four seizure-free children all became seizure-free within the first six months after implantation and remained seizure-free during the follow-up (12 months to 1.8 years). We also studied in more detail the results from the largest subgroup, namely the children with Lennox-Gastaut epilepsy; the responder rate in this group of patients was 60% (12/20). There were no children who became seizure-free, although three reported a >75% reduction in seizure frequency.

Comparing focal versus generalized epilepsies also did not yield significantly different results: eight of the 16 children (50%) within the focal group, and 30 of the 54 in the generalized group (55%), were responders.

The only factors that apparently made a difference in outcome were age at implantation and duration of epilepsy (*figure 1*). In the youngest group, 7/9 were responders (77%) and this group also included three of the four seizure-free patients. The lowest number

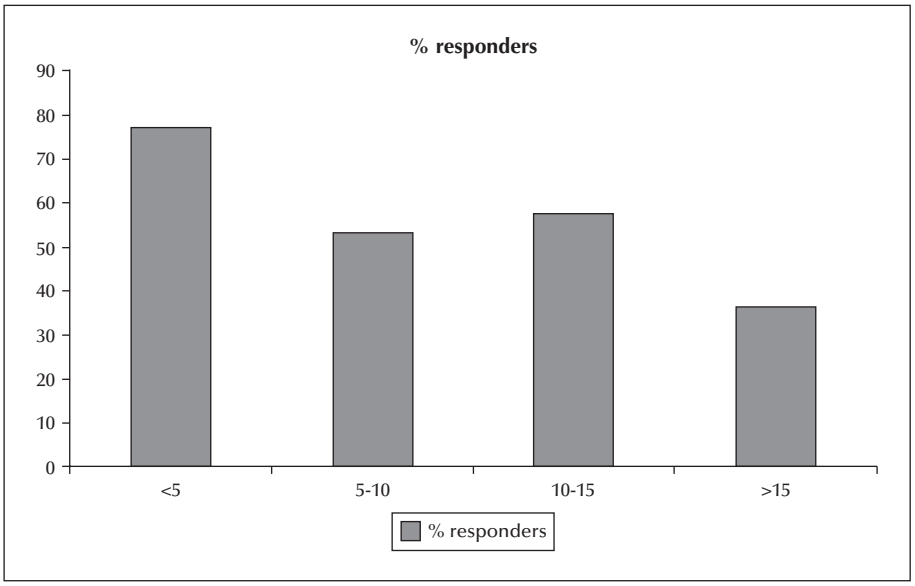

Figure 1. Responder rate as a function of age (years).

of responders was found in the >15-year-old patients with a responder rate of 37% (6/16). Statistically, there was a correlation between seizure freedom and younger age at implantation (<5 years compared to >5 years, $p<0.006$). Responder rate was not statistically correlated with age at implantation, however (Fisher-Freeman-Halton test: 0.29).

We studied in more detail the duration of epilepsy (*figure 1*). In all age groups, there was a large range of duration of epilepsy, with a median duration of 3.5 years in the youngest group and 11.5 years in the oldest group. No statistical differences were found by comparing the youngest groups with the older groups. However, in our study groups, younger age at implantation was also associated with shorter duration of epilepsy.

We also analysed AED treatment during follow-up. We investigated the number of AEDs at implantation and after one year (only in those children with already one year of follow-up; *n*=60). At implantation, the mean number of AEDs was 3 (range: 1-5) and after one year it was 2.5 (1-4). In the majority of these 60 children, however, no changes in background AEDs was observed (*n*=43/60; 72%). It should be noted that we only analysed the actual number of drugs and not dosage changes of these AEDs.

Side effects were mild in most cases. Only four patients in our cohort complained of hearing strange voices, tingling or hoarseness. In two of these patients, these adverse events could be minimized by reducing pulse width and/or stimulation frequency. One child had a wound infection three weeks after implantation, requiring intravenous antibiotics and eventually replacement of the VNS device. In three patients, a lead break necessitated re-intervention. In one child, the parents decided after six months to explant the device because of lack of efficacy (a 7-year-old boy with frontal lobe epilepsy).

Concerning quality of life, only qualitative data was collected. At the last follow-up visit, 48/70 (68%) indicated that QOL had significantly improved, compared to the pre-implantation period. Although we cannot specify in any further detail, the large majority reported an increase in alertness and communication.

Discussion

This observational study confirms many other studies on VNS treatment in drug-resistant childhood epilepsy (Majoie *et al.*, 2005; Alexopoulos *et al.*, 2006; Benifla *et al.*, 2006; Kabir *et al.*, 2009; Rossignol *et al.*, 2009; Cersósimo *et al.*, 2011; Zamponi *et al.*, 2011a; Orosz *et al.*, 2014). In more than 50% of the patients, a seizure reduction of more than 50% was obtained. In view of the fact that all children had drug-resistant epilepsy, these results are very comparable to the results obtained when introducing a new AED to a patient with drug-resistant epilepsy. Also, the percentage of seizure-free patients is in line with these add-on trials of new AEDs in children with drug-resistant epilepsy. We believe these results cannot be explained by the natural evolution of the epilepsy syndrome or by changing/adding background AEDs in these children. It has been argued that VNS results are sometimes difficult to interpret, because of the lack of a placebo

or control group. On the other hand, the sustained response after follow-up, which is considerably longer than in a typical randomised control trial (RCT), only supports the genuine efficacy of the VNS therapy. When looking at the results of the tuberous sclerosis children, these points are clearly illustrated (Major and Thiele, 2008; Elliott *et al.,* 2009). In children with tuberous sclerosis and drug-resistant epilepsy, it is difficult to imagine sustained and complete seizure freedom over six months as the natural evolution of their epilepsy.

Apart from the tuberous sclerosis group, we were unable to identify any particular positive or negative factors that correlated with VNS efficacy. In larger studies (Elliott *et al.,* 2011), such a correlation was more evident for multifocal or focal epilepsy rather than generalized epilepsy, but we did not observe this. Probably, the prediction of VNS response depends on multiple factors and not only on the type of epilepsy or seizures. One important factor, as clearly shown in our study, is the age of the patient at VNS implantation. In our group of children below the age of 5 years, responder rate was as high as 77%. This group also included three of the four seizure-free children. Again, several factors contribute to this high success rate; age *per se* can play a role, however, it is clear that younger age also indicates a shorter duration of epilepsy (*table 1*). In other studies, better efficacy was observed when VNS therapy was started earlier (Renfroe and Wheless, 2002; Helmers *et al.,* 2003; Zamponi *et al.,* 2011b). These findings could become important in selecting the right candidates for VNS therapy.

Several reports have shown that implantation at very young ages is practically feasible, especially with the newer smaller VNS devices (Farooqui *et al.,* 2001; Zamponi *et al.,* 2008).

The finding that VNS therapy at younger ages and/or with a shorter duration of epilepsy might be more effective than in older children and adults with drug-resistant epilepsy can perhaps be explained by the working mechanism of VNS. Although the exact working mechanism of VNS is not known yet, several lines of research have indicated profound changes in brain blood flow, brain neurotransmitter metabolism, and electro-physiological parameters; VNS has an effect on many brain circuits in the brain (Hallböök *et al.,* 2005b; Santiago-Rodríguez *et al.,* 2006; Barone *et al.,* 2007; Vonck *et al.,* 2008; Van Laere *et al.,* 2000; Majoie *et al.,* 2011). It can be hypothesized that VNS, after some time, clearly induces long-lasting changes in the neuronal network involved in epilepsy and that the earlier this is done, the better the outcome.

Although not the primary purpose of this study, we did not find a clear relationship between "dosing" of the VNS therapy and efficacy. In recent years, it has become clear that efficacy may be better when stimulation time (or percentage) is increased, rather than by increasing the output current. Changing the percentage of actual VNS stimulation time is somewhat comparable to changing the dosage of an AED. The optimal dosage of an AED is also very variable, depending on many factors, but especially on side effects and tolerability. Only in a typical RCT is dosage of a new add-on AED kept within very strict limits, but in clinical practice, optimal dosing sometimes varies between 50 and 150% of the advised standard dosage. In this respect, it is not surprising that VNS dosing is also very variable throughout all the published studies and that one cannot expect strict standard guidelines for VNS dosing. There is definitively a need for studying this in more detail, with percentage stimulation probably as a more important parameter than output current. Also, age-dependent stimulation sensitivity may play a role which could influence efficacy. Perhaps the positive results at younger ages can also be explained by higher sensitivity for the standard dosing at these ages. When looking at the results in older patients in our cohort, the results again are comparable to the efficacy one typically obtains after introducing a new AED. One might argue that introduction (and termination) of a new drug is much easier than performing a surgical and less reversible procedure, however, it has been clearly shown that the chance of efficacy dramatically decreases with the number of drugs used in the past. Throughout our follow-up of children with epilepsy, we have tried to identify as early as possible those children with drug-resistant epilepsy following the recent definition of the ILAE. This also implies that the chance of these children ever becoming seizure-free is very low and we convey this message as early as possible to the parents. This, however, does not indicate a fatalistic view on treatment of drug-resistant epilepsy; whenever possible, epilepsy surgery should be considered, the ketogenic diet can be tried, and/or the child can be identified for a trial with one of the newer AEDs. VNS is discussed early during the course of the disease and is not projected as the last possible treatment option. This more balanced way of discussing the outcome of VNS, both in terms of efficacy and positive and negative side effects, makes the decision of the parents to consent for a VNS device much easier. For many parents, the low incidence of side effects and the positive effect on alertness and concentration were equally important, relative to the reported seizure reduction.

In conclusion, our study confirms that VNS therapy is a valid option in the treatment arsenal for children with drug-resistant epilepsy and that it should be considered earlier in the course of the disease; the chance of sustained efficacy is higher in younger children or in children with a short duration of epilepsy. □

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