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VAGUS NERVE STIMULATION IN CHILDREN WITH REFRACTORY EPILEPSY: AGE AT IMPLANTATION AS A PREDICTOR OF BETTER EFFICACY

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In this study, the efficacy of vagus nerve stimulation treatment was analyzed in a cohort of 70 children with refractory epilepsy. Both children with partial (n=16) and generalized epilepsies (n=54) were included. Age at implantation varied between 19 months and 25 years. Overall, responder rate was 54% with 5.7% of the children becoming seizure free. The only factor in our analysis that could predict good outcome was age at implantation. In the youngest age group (<5 years), responder rate was 77% and this group also included 3 of the 4 seizure free children. These 3 seizure free children were known to suffer from tuberous sclerosis. There were no outcome differences comparing generalized with partial epilepsies.

Descriptors: VAGUS NERVE STIMULATION; EPILEPSY; CHILDREN

INTRODUCTION

Vagus nerve stimulation (VNS) is an approved therapy for refractory epilepsy since 1997 (FDA approval) (1). Although registration and reimbursement procedures substantially differ from country to country, VNS therapy is considered a possible treatment option only if one can show that the patient has refractory epilepsy and is not a candidate for resective surgery. In this sense, VNS therapy is still considered as a "last resort" or "palliative" therapy in refractory 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 (2-5).

In recent years, however, several studies have been published showing that the efficacy of VNS therapy is at least comparable to the efficacy after introducing a new antiepileptic drug (AED) in a patient with refractory epilepsy (6-8). Both responder rates and seizure freedom rates are very comparable. These better results can be explained by inclusion of less refractory patients and also younger patients with a shorter duration of refractory epilepsy. In the US, VNS therapy is approved only beyond the age of 14, whereas in Europe, for instance, VNS therapy can be considered at much younger ages and also for generalized epilepsies (9). In younger patients with epileptic encephalopathies such as the Lennox Gastaut syndrome, it is often performed early in the course of disease, when resective surgery is not an option. This emphasis on younger patients and 'non-surgical' cases implies that now more patients with generalized seizures are also included in more recent trials. Another factor that is important in judging the efficacy of VNS therapy is the notion that the efficacy of VNS can only be appreciated after several months of therapy (10). Many studies have demonstrated an increasing efficacy with time, which cannot be explained by changing the background AED treatment in these patients. In addition, although not the primary focus in the majority of available studies, a substantial benefit concerning the quality of life (QOL) and especially alertness, concentration and communication has often been reported (11-13).

Focusing on the existing data on VNS therapy in childhood epilepsy, the most recent study by Elliott et al. confirms that VNS therapy in refractory 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 (14). Also, in our multicenter Belgian study, we found equally good efficacy both in childhood and adult refractory epilepsy (15).

An 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 the use of 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.

METHODOLOGY

We reviewed the files of all our patients who had a VNS device implanted after the year 2000. Patient characteristics and epilepsy syndrome with type and frequency of seizures were prospectively

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collected in a database. This database also contained data on the settings of the VNS device, the AEDs used before and during the follow up and the efficacy of 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 QOL 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 was done only for those patients who had a minimum follow up of 6 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 2 months before the last assessment and compared with the same baseline period before implantation. Patients had to be at least 2 months seizure free at the last follow up visit to be considered 'seizure free'.

At our centre, we use a rather standardized protocol for the VNS device settings. We usually take 2 months to get a first final setting of 2.0 mA output current, 'classic duty cycle' with 5 minutes OFF and 30 sec ON (500 μsec pulse bandwidth and 25 Hz stimulation frequency). These settings are maintained for at least 2-3 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, i.e. shortening the OFF period to 3 minutes or less. Each new setting is maintained for at least 1 month. If the patient and/or parents are satisfied with the result, we keep the settings for longer periods. This means that in a very unresponsive patient, we gradually move to a stimulation frequency of >30% (for instance, 30 sec ON, 1.1 min OFF, 35% stimulation). Only occasionally we increase the output current to a maximum of 3.0 mA.

In all children, the epilepsy diagnosis was confirmed by history taking, documenting seizure type(s), MRI analysis and at least one 24-h 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 a presurgical work up was actually done, including at least 5-day video EEG monitoring and 3T MRI and ictal and interictal SPECT with SISCOM analysis. We considered VNS therapy in those patients who were not eligible for resection epilepsy surgery after rigorous pre-surgical work up, or in those patients with an epilepsy syndrome that was not suitable for epilepsy surgery and/or was refractory to at least 3 AEDs over a period of at least 6 months.

RESULTS

In total, 70 patients could be considered for this interim analysis. The follow up 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 breakdown in age groups is shown in Table 1. As can be seen, the majority of children were implanted between 5 and 10 years (n=26), but there was also a small 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, refractory epilepsy was classified as typical partial; the rest of 54 patients presented with a more generalized epilepsy syndrome or 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.

Table 1. *Number of vagus nerve stimulation implantations according to age groups*
Tablica 1. *Broj ugradnja stimulacije vagalnog živca prema dobnim skupinama*

0-5 years/godina	9
5-10 years/godina	26
10-15 years/godina	19
>15 years/godina	16

Table 2. *Epilepsy syndromes*
Tablica 2. *Sindromi epilepsije*

Lennox Gastaut Epilepsy	20
Myoclonic Astathic epilepsy	4
Dravet syndrome	5
Tuberous sclerosis syndrome	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 partial epilepsy	11
Epilepsia partialis continua	1
Total	70

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

In general, responder rate at the last follow up was 54%, which means that a seizure frequency decrease by >50% was observed in 38/70 children. Four (5.7%) children remained seizure free. Three of these children were known to have tuberous sclerosis and one seizure free child was a 12-year-old girl with refractory myoclonic absence epilepsy. The four seizure free children all became seizure free within the first 6 months after implantation and remained seizure free during the follow up (6 months to 1.2 years). The results in the largest subgroup, i.e. the Lennox Gastaut epilepsy children, were also studied in more detail. The responder rate in this group of patients with Lennox Gastaut epilepsy was 60% (12/20). There were no children who became seizure free, although 3 reported a >75% seizure frequency reduction.

Comparison of partial *versus* generalized epilepsies did not yield significantly different results either: eight of the 16 children (50%) in the partial group and 30 of the 54 children in the generalized group (55%) were responders.

The only factor that did make a difference in outcome was age at implantation (Figure 1). In the youngest group, 7/9 were responders (77%) and this group also included 3 of the 4 seizure free patients. The lowest number of responders was found in the >15-year-old patients with 37% (6/16) responder rate.

We also analyzed what happened with the AEDs during the follow up. We looked at the number of AEDs at implantation and after one year (only in those children with already one-year 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 the background AEDs was observed (n=43/60, 72%). To be noted is that we only analyzed the actual number of drugs and not dosage changes of these AEDs.

Side effects were mild in most cases. Only 4 patients in our cohort actually

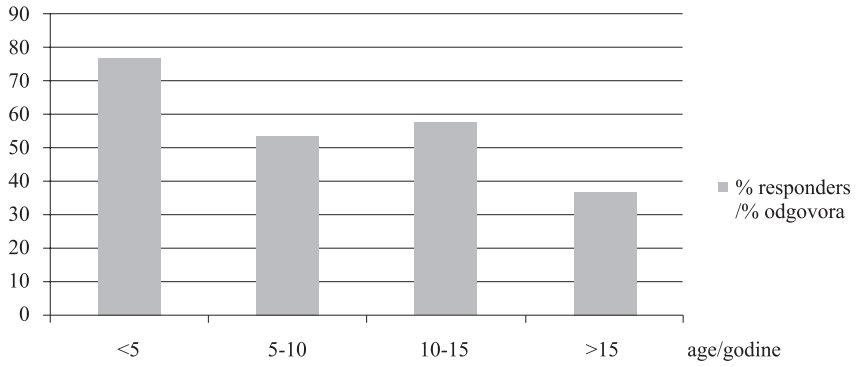

Figure 1. *Responder rate as a function of age (years)*
Slika 1. *Stopa odgovora na terapiju kao funkcija dobi (godine)*

complained of strange voice, tingling or hoarseness. In 2 of these patients, this adverse event could be minimized by reducing pulse width and/or stimulation frequency. There was one child with a wound infection 3 weeks after implantation, needing intravenous antibiotics and eventually replacement of the VNS device. In 3 patients, a lead break necessitated re-intervention. In one child, the parents decided to explant the device after 6 months because of the lack of efficacy (a 7-year-old boy with ESES).

Concerning QOL, we only collected qualitative data. At the last follow up visit, 48/70 (68%) patients indicated that their QOL had improved significantly compared to the pre-implantation period. We cannot specify this in more detail, but the large majority reported an increase of alertness and communication.

DISCUSSION

This study confirmed many other studies on VNS treatment in refractory childhood epilepsy (16-22). In more than 50% of our patients, a seizure reduction by more than 50% was obtained. In view of the fact that all children had refractory epilepsy, these results are very comparable to the results obtained when introducing a new AED in a patient with refractory epilepsy. Also, the percentage of seizure free patients is in line with these add-on trials of new AEDs in children with refractory epilepsy. We believe these results cannot be explained by the natural evolution of the epilepsy syndrome, or by changing/adding the 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 a follow up, which is considerably longer than in a typical 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 (23, 24). In children with tuberous sclerosis and refractory epilepsy, it is difficult to imagine sustained and complete seizure freedom within 6 months as the natural evolution of their epilepsy.

Apart from the TS group, we could not identify another epilepsy syndrome with a particular positive or negative predictability concerning VNS efficacy. In larger studies (25), it was shown that multifocal or focal epilepsy did somewhat better 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 3 of the 4 seizure free children. Again, several factors contribute to this high success rate: age *per se* can play a role, but it is clear that younger age also indicates a shorter time of epilepsy. Other studies also found better efficacy when VNS therapy was started earlier (26-28). 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 (29, 30).

The finding that VNS therapy at younger ages might be more effective than in older children and adults with refractory 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 (31-36). It can be hypothesized that after some time VNS clearly induces long lasting changes in the neuronal circuits involved in epilepsy and that the earlier this can be done, the better.

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 might be better when stimulation time (or percentage) is increased, more 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, dosage of the new add-on AED is kept within the 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 also VNS dosing is very variable throughout the published studies and that one cannot expect strict standard guidelines for VNS dosing. There is definitely a need for studying this in more detail, with percentage stimulation probably as a more important parameter than output current. Also, there might be an age dependent stimulation sensitivity, which could influence efficacy. Perhaps the good 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 gets after introducing a new AED. One might argue that introduction (and stopping) of a new drug is much easier than performing a surgical and less reversible procedure, but it has been clearly shown that chances for efficacy dramatically go down with the number of drugs used in the past. Throughout our follow up of children with epilepsy, we try to identify as early as possible those children with refractory epilepsy following the recent definition of the ILAE. This also implies that the chance that these children will ever become seizure free is very low

and we convey this message as early as possible to the parents. This does not indicate a fatalistic view on the treatment of refractory epilepsy: whenever possible, epilepsy surgery should be considered, ketogenic diet can be tried and/or the child can be identified for a trial of 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, positive and negative side effects, makes the decision of the parents to consent to 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 as the reported seizure reduction.

In conclusion, our study confirms that VNS therapy is a valid option in the treatment arsenal for children with refractory epilepsy and that it should be considered earlier in the course of the disease: chances for sustained efficacy are higher in younger children with refractory epilepsy.

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Authors declare no conflict of interest.

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S a ž e t a k

STIMULACIJA VAGALNOG ŽIVCA KOD DJECE S REFRAKTORNOM EPILEPSIJOM:
DOB U VRIJEME ZAHVATA KAO ČIMBENIK PROGNOZE BOLJE UČINKOVITOSTI

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U ovoj studiji analizirala se učinkovitost liječenja stimulacijom vagalnog živca u skupini od 70 djece s refraktornom epilepsijom. Uključena su djeca s parcijalnom (n=16) i ona s generaliziranom (m=54) epilepsijom. Dob djece u vrijeme ugradnje kretala se od 19 mjeseci do 25 godina. Sveukupna stopa odgovora na ovu terapiju bila je 54%, od čega 5,7% djece više nije imalo konvulzije. U našoj analizi je dob u vrijeme ugradnje bila jedini čimbenik koji je mogao predskazati dobar ishod. U najmlađoj dobnoj skupini (<5 godina) stopa odgovora na terapiju bila je 77% i u ovoj je skupini također bilo 3 od 4 djece bez konvulzija. Za ovo troje djece bez konvulzija znalo se da boluju od tuberozne skleroze. Usporedba generaliziranih i parcijalnih epilepsija nije pokazala nikakvih razlika u ishodu.

Deskriptori: STIMULACIJA VAGALNOG ŽIVCA; EPILEPSIJA; DJECA

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