What can We Learn from the First Cohort of Vagus Nerve Stimulation-Treated Epilepsy Patients in Israel?

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Epilepsy affects about 1% of the population worldwide, and about 30% of patients continue to have seizures while under treatment with anti-epileptic drugs [1]. Electrical stimulation of the vagus is used mainly for the treatment of drug-resistant epilepsy, but also for depression, and it has also been suggested as a potential agent for treating obesity and memory deficit [2]. Electrodes are implanted on the left vagus nerve in the neck and are connected to a generator implanted subcutaneously or subpectorally in the left subclavian area. A hand-held wand directed to the generator is then used intermittently for programming the stimulation parameters of the device. The potential of vagal nerve stimulation to prevent epileptic seizures was first reported by Zabara in 1985 [3]. This technique (VNS Therapy System, Cyberonics, Inc., Houston, TX, USA) was used in humans for the first time 3 years later [4], followed by several controlled studies, culminating in FDA approval of VNS in 1997 for the treatment of focal epilepsy in adults and children over age 12 years. VNS was approved in Israel in 2006 for the treatment of patients with drug-resistant epilepsy who cannot undergo epilepsy surgery.

In this issue of *IMAJ* Menascu et al. [5] report on the first experience with VNS in Israel. They bring efficacy and safety data of 42 pediatric and adult patients with drug-resistant epilepsy who were implanted during an 18 month period and had at least 18 months of follow-up each. Overall, 43.3% of patients reported a reduction in seizure frequency of more than 50% and 10.8% of patients reported a 25–50% reduction. In a meta-analysis [6] of 3321 patients with VNS treatment it was found that 50.6% of 2634 patients attained a ≥ 50% reduction in seizure frequency, 12.2% benefited from a ≥ 90% decrease, and 4.6% attained seizure freedom. Among 1513 patients, 25.4% experienced no measurable benefit from treatment. A recent single-center experience with more than 400 VNS-implanted pediatric and adult patients [7] reported even better outcomes: 63.75% had a ≥ 50% improvement, 8.25% remained seizure-free for at least 6 months prior to the last follow-up, 12.25% experienced no reduction in seizure burden, and 2.75% had an increase in seizure activity from their baseline. The figures in both articles are more favorable than the results reported by Menascu et al. [5], especially when the relatively long period of follow-up in the Israeli study is taken into consideration. A delayed benefit of VNS therapy has been repeatedly suggested, as reflected by the meta-analysis findings of a significant difference in mean seizure reduction between patients seen ≤ 1 year after implantation (36.2% in 1178 patients) and those seen > 1 year postoperatively (51.0% in 1247 patients) [6]. In any case, the results of most studies, including those of Menascu and colleagues, are similar to the benefit expected when adding a new anti-epileptic drug after failure of two to five drugs and superior to adding a new anti-epileptic drug after failure of six or more medications [8]. Only very recently was the role of VNS as adjunctive therapy in drug-resistant epilepsy patients challenged [9].

What is the reason for the relatively less favorable results of VNS treatment in this first Israeli cohort? One cause could be the use of suboptimal stimulation parameters, possibly due to side effects experienced by the patients. However, although cough (experienced by less than 10% of patients) and vocal alteration, hoarseness or tingling (reported by about 26%) were described more frequently in the Israeli patients than reported by Elliott et al. [5,7], they were less prevalent than in other studies [6]. Stimulation parameters are only barely reported in the clinical VNS experience literature. For example, the mean stimulation current was 1.6 mAmp in 189 patients followed for more than one year after VNS implantation, and a significant difference was found in this study between the group with a very favorable outcome (mean 1.2 mAmp, range 0.25–2.5) and a less favorable one (mean 1.75 mAmp, range 0–3.5) [10]. A recent computation study concluded that a range of output current settings between 0.75 and 1.75 mAmp, with pulse width settings of 250 or 500 μsec, may result in optimal stimulation [11]. In contrast, in most of the cases reported by Menascu et al., the pulse width of the stimulation was 500 μsec, the median output current 1 mAmp, the mean 1.13 and the range 0.25–2 mAmp, suggesting lower than optimal settings in part of the cohort [5]. It would be interesting to analyze whether a further increase in stimulation parameters after completion of this study resulted in an additional improvement in outcomes.

FDA = Food and Drug Administrtion
VNS = vagal nerve stimulation

Another reason for the relatively less favorable response of the Israeli patients to VNS therapy could be the basic characteristics of the individuals included in this cohort. Several factors have been studied as possible predictors of better outcome. The patients in the Israeli cohort had a relatively longer course of intractable disease, as suggested by an average of 29.2 years of epilepsy prior to VNS implantation and failure of treatment with a mean of 6.8 anti-epileptic drugs. For comparison, in the study by Elliott et al. [7], the presurgical duration of disease was 19.2 years, and the patients failed 5.6 medications before VNS implantation. In addition, in the study by Menascu and co-researchers [5], resective surgery had been attempted in 7 of the 42 patients and 15 had tried a ketogenic diet [5]. Some studies pointed to less than 15 years to the time to implantation as a good prognostic factor [12], although others did not find that this influenced seizure control after implantation [7,10]. There were more children than adults who underwent VNS implantation in this first Israeli experience, while other series of combined patients included more adults [5,7,10]. However, although Menascu et al. reported a less favorable response to treatment among children in comparison to adults, others concluded that children have a better prognosis [5,6,12] or did not find age at implantation to be a significant predictor of improvement with VNS therapy [7,10]. Developmental delay has been reported to negatively affect improvement [10]. The Israeli cohort included 60% developmentally delayed patients [5], but this figure is not markedly different when compared to the 56.4% in the study of Elliott et al. [7] which reported a much more favorable outcome of VNS. Finally, the type of epilepsy and its etiology have been proposed as predictors of response to VNS therapy but with contradictory findings. While some studies reported that patients with focal epilepsy improved more than those with generalized or multifocal epilepsy [7,12] similar to the findings of Menascu et al. [5], others found that patients with generalized epilepsy had a better prognosis [6]. Analysis of the VNS therapy results in a larger population of Israeli patients will be able to better predict who would be the best candidates for this treatment.

To date, by the middle of 2013, close to 400 epilepsy patients have been implanted with VNS in Israel. Given the estimation of more than 20,000 people having drug-resistant epilepsy in the country, there is no doubt that too few of the eligible patients are offered this means of treatment. Is this therapy underused because of the not very favorable results of the first patients who underwent VNS implantation? Probably not, since this figure is similar to only a small proportion of potentially eligible patients undergoing brain surgery for epilepsy. During 10 years, between 1997 and 2006, only about 200 patients had epilepsy surgery in Israel [13]. The data from other Western countries are very similar, despite evidence on the efficacy and safety of this procedure [14,15], positioning it among the most underused of all effective therapeutic interventions [16]. In contrast to less developed countries where a large treatment gap in epilepsy is caused by a paucity of resources for prevention, diagnosis and basic treatment [17], the treatment gap still existing in the developed world, including Israel, is primarily caused by under-utilization of the available resources. Drug resistance can be identified early in the course of epilepsy after failure of two adequate anti-epileptic drugs to achieve freedom of seizures [18]. Therefore, primary care physicians and general neurologists should timely refer these patients, whose chances of responding to trials of additional anti-epileptic medications are low, to tertiary epilepsy centers for more thorough investigations and consideration of other means of treatment, such as epilepsy surgery or VNS implantation.

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