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Predicting success of vagus nerve stimulation (VNS) from EEG symmetry

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ABSTRACT

Purpose: Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy, with achieving more than 50% seizure reduction in one third of the treated patients. In order to predict which patients will profit from VNS, we previously found that a low pairwise derived Brain Symmetry Index (pdBSI) could potentially predict good responders to VNS treatment. These findings however have to be validated before they can be generalized.
Methods: 39 patients (age 18–68 years) with medically intractable epilepsy who were referred for an implanted VNS system were included. Routine EEG registrations, recorded before implantation, were analyzed. Artefact-free epochs with eyes open and eyes closed were quantitatively analyzed. The pdBSI was tested for relation with VNS outcome one year after surgery.
Results: Twenty-three patients (59%) obtained a reduction in seizure frequency, of whom ten (26%) had a reduction of at least 50% (good responders) and thirteen (33%) a reduction of less than 50% (moderate responders). Sixteen patients without seizure reduction are defined as non-responders. No significant differences were found in the pdBSI of good responders (mean 0.27), moderate responders (mean 0.26) and non-responders (mean 0.25) ($p > 0.05$). Besides seizure reduction, many patients (56%) reported additional positive effects of VNS in terms of seizure duration, seizure intensity and/or postictal recovery.
Conclusion: EEG features that correlate with VNS therapy outcome may enable better patient selection and prevent unnecessary VNS surgery. Contrary to earlier findings, this validation study suggests that pdBSI might not be helpful to predict VNS therapy outcome.

1. Introduction

Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy in numerous patients. However, long-term studies showed that a good response (>50% seizure reduction) is only achieved in 20–55% of the patients [1–3], which means that a substantial number of patients only show moderate or even no response to VNS treatment. Determining the success of VNS is important to counsel patients and give them information about the expected seizure reduction. Potential responders might not need to try other kinds of therapy before they receive an effective VNS system and on the other hand, a low likelihood to respond could prevent someone from undergoing surgery and having an expensive VNS system implanted while only minimal effects will be obtained. Despite the growing application of VNS, it is still not possible to predict which patients respond to what extent to VNS therapy. Most studies that attempt to predict the success of VNS are based upon patient characteristics [4], epilepsy syndrome [5] or localization of the seizure focus [2,6,7]. A meta-analysis by Englot et al. on predictors of response to VNS therapy, showed that young patients (<6 years) respond slightly better in terms of seizure reduction compared to adults [2]. However, good predictors of efficacy of VNS therapy for individual patients are still elusive.

We previously showed that quantifying EEG asymmetry using the pairwise derived Brain Symmetry Index (pdBSI) could potentially predict which patients will benefit from VNS treatment. It was observed that non-responders show significantly higher EEG

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asymmetry, reflected in higher pdBSI values, as compared with responders [9]. These findings however require validation in new patient groups before they can be generalized. We have therefore conducted this prospective study in adult epilepsy patients without cognitive impairment; expecting to confirm the predictive value of EEG symmetry, as defined by pdBSI.

2. Materials/methods

2.1. Patients

We have included otherwise healthy epilepsy patients (age > 18 years) who were referred by SEIN Centre of Excellence for Epilepsy and Sleep Medicine (Epilepsy Centre) to Medisch Spectrum Twente hospital for implantation of a VNS system. All patients suffered from medically intractable (generalized or localized) epilepsy with varying focus locations. Patients had to keep seizure diaries for at least six months prior to implantation and during the one year follow up period of the study.

2.2. VNS outcome

After implantation, patients have regular follow up visits at their Epilepsy Centre. During these visits, stimulation parameters are optimized for the individual patient and the effect of VNS therapy is monitored. The success of VNS was determined by the amount of seizure reduction due to the therapy. Patients were grouped as good (>50% reduction), moderate (<50% reduction) and non-responders (no reduction) based on seizure diary data provided by the treating nurse practitioner from the Epilepsy Centre.

In addition, patients are asked to fill in a questionnaire about the effects of VNS and their satisfaction with the device approximately one year after implantation. The questionnaire addresses various parameters such as seizure frequency, duration and intensity, postictal recovery, patient satisfaction, and side-effects. Patients indicate how much various parameters have improved or worsened upon VNS therapy on a 7-point scale (Clinical Global Impression – Improvement scale, CGI-I), where 1 means very much improved and 7 means very much worsened. Data from questionnaires was used to compare patient's own perception with the data from the Epilepsy Centre and is used to make a second classification, where CGI-I scores 1–2 = good responder, score 3 = moderate responder, scores 4–7 = non-responder.

2.3. EEG analysis

Thirty-minute routine EEG registrations were made several weeks before VNS implantation. Electrodes were placed conform the international 10–20 system, using an electrocap and signal was recorded using a BrainLab EEG recording system (OSG BVBA, Belgium) with a sampling frequency of 250 Hz. During the registration, the patients were comfortably lying down in a quiet, shielded room. Artefact-free epochs with eyes open and eyes closed were selected for quantitative analysis. Selected epochs were filtered with a bandpass filter between 0.5 and 30 Hz. Epochs of 500 samples with 50% overlap were Fourier transformed with pwelch in MATLAB (The Mathworks, Inc., USA) using a Hamming window.

Brain symmetry was quantified using the pair-wise derived Brain Symmetry Index (pdBSI), which was described previously [9–11]. Briefly, the pdBSI evaluates asymmetry by calculating the power per frequency coefficient along homologous EEG channel pairs. Low pdBSI values represent symmetric EEG activity, whereas higher pdBSI values indicate higher asymmetry of the EEG. For each patient, pdBSI values were determined for four different frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). EEG symmetry, defined by pdBSI, was tested for relation with effect of VNS therapy after one year.

2.4. Statistics

Statistical analyses were performed using *t*-tests when (normal distribution) and Mann–Whitney *U* tests (non-normal distribution) with a confidence interval of 95%.

3. Results

3.1. Patient characteristics

Between March 2011 and January 2015, 39 patients had a routine EEG recorded a few weeks prior to implantation of a VNS system and gave informed consent to analyze EEG characteristics and look for relation with VNS effects. Patient characteristics are summarized in Table 1. Patients were not considered surgical candidates and their intellectual ability varied, however none of the patients was severely cognitively impaired. For all 39 patients, data provided by the nurse practitioner (follow-up time on average 14 months, range 8–24 months) and pdBSI values are available. Five out of 39 patients did not send back the questionnaire about their perception of effects and satisfaction with the VNS therapy so this information is only available for 34 patients (follow-up time on average 14 months, range 6–36 months).

3.2. Effects of VNS

3.2.1. Seizure reduction

Based on data provided by the nurse practitioner, twenty-three patients obtained a reduction in seizure frequency, of whom ten had a reduction of at least 50% (good responders) and thirteen a reduction of less than 50% (moderate responders). The other sixteen patients did not show any reduction in seizure frequency and were defined as non-responders to VNS therapy. Neither the patient's age nor the type of epilepsy correlated with the seizure reduction obtained with VNS and therefore these parameters could not predict the effect of VNS (Table 1).

Besides seizure reduction, other positive effects of VNS treatment were reported by the nurse practitioner. Out of sixteen patients who were defined as non-responders, seven patients still experienced other positive effects of VNS. Also, the majority of the good responders (7 out of 10) and moderate responders (8 out of 13) showed additional positive effects in terms of seizure duration, seizure intensity and/or postictal recovery.

3.2.2. Patient perception

In addition to the data provided by the nurse practitioner, VNS outcome was determined using patient questionnaires. Ten patients indicated that their seizure frequency has improved very much or much (CGI-I score 1 or 2). Fourteen patients mentioned a small improvement in seizure frequency (score 3) and ten patients indicated that the seizure frequency had not changed (score 4). No patient indicated worsening of seizure frequency. The patient's general impression regarding seizure frequency only partly corresponded with the percentages of seizure reduction that were provided by the nurse practitioner (Table 1).

All patients who indicated that their seizure frequency has (very) much improved also experienced (some) improvement in seizure intensity and/or postictal recovery. Majority of the fourteen patients who reported minimal improvement in seizure frequency also report little or no improvement in seizure intensity and