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Short communication

Effects of vagus nerve stimulation on symptoms of depression in patients with difficult-to-treat epilepsy

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A B S T R A C T

Purpose: Vagus nerve stimulation (VNS) is well established in the treatment of epilepsy and disorders of depression. The prevalence of depression is high in patients with epilepsy, but still it remains unclear how patients with a comorbidity of epilepsy and symptoms of depression respond to VNS.
Methods: We investigated 59 patients with different subtypes of disorders of depression as a comorbidity of epilepsy, who underwent VNS-surgery. Before and one year after VNS surgery, the severity of symptoms of depression was evaluated by a psychiatrist using Montgomery–Åsberg Depression Rating Scale (MADRS) and Beck-Depressions-Inventory (BDI). Response towards epilepsy was measured by a seizure reduction of at least 50%.
Results: Symptoms of depression ameliorated in response to VNS in the overall of all patients MADRS 29 to 18 ($p < 0{,}001$) and BDI 24 to 14 ($p < 0{,}001$) and all subtypes of disorders of depression. Seizure reduction of at least 50% was achieved in two out of three of all patients two years after VNS.
Conclusion: We were able to show the beneficial effect of VNS in the treatment of patients with pharmacoresistant epilepsy and a comorbidity of symptoms of depression.

1. Introduction

Vagus nerve stimulation (VNS) has been shown to be a useful therapy for pharmacoresistant epilepsy [1] and treatment-resistant depression alike [2]. In the treatment of pharmacoresistant epilepsy, VNS leads to a 50% reduction in seizure frequency in 43% of patients three years after a VNS device was implanted [1]. In the treatment of depression, combining VNS with treatment-as-usual has a significantly higher cumulative response and higher remission rate [3]. Depression is the most common psychiatric disorder in epilepsy patients [4] with a prevalence of 36% compared to 12% in patients without chronic disease [5]. Boylan reported that up to 63% of patients with pharmacoresistant epilepsy had undiagnosed depression, which is a powerful predictor of quality of life in patients with pharmacoresistant epilepsy [6]. In older patients, major depression has been shown as a risk factor for seizures [7]. A recent study has shown an antidepressant effect of VNS in the kainic acid mouse model for temporal lobe epilepsy [8]. Still, the effect of VNS in patients with difficult-to-treat epilepsy and a comorbidity of depressive symptoms remains unclarified. In our study, we investigated 59 patients with pharmacoresistant epilepsy and a comorbidity of symptoms of depression who have been treated with VNS.

2. Methods

During 2003–2014, 59 patients (38 female, 21 male) with a mean age of 38 years (range from 14 to 59) with epilepsy and a history of different types of symptoms of depression were treated with VNS. During that period a total of 80 patients has been treated with VNS for epilepsy, so the percentage of patients that were diagnose with symptoms of depression as a comorbidity in our cohort was 74%. Among those patients were 18 patients with focal-frontal, 18 with focal-temporal, five with multifocal, two with idiopathic generalized, seven with symptomatically generalized, and nine with cryptogenic epilepsy (Fig. 1A) All patients had a comorbidity of depressive disorders.

Within the depressive disorders, four different subtypes have been distinguished (Fig. 1B):

1) 33 cases of Interictal Dysphoric Disorder (IDD), an atypical depression determined by eight key symptoms divided into three dimensions: depressive symptoms (depressed mood, anger, pain, insomnia), affective symptoms (fear/panic, anxiety), and so-called “specific” symptoms (irritability and euphoria). At least three of the key symptoms producing considerable social and occupational dysfunction are sufficient to determine the diagnosis [9].

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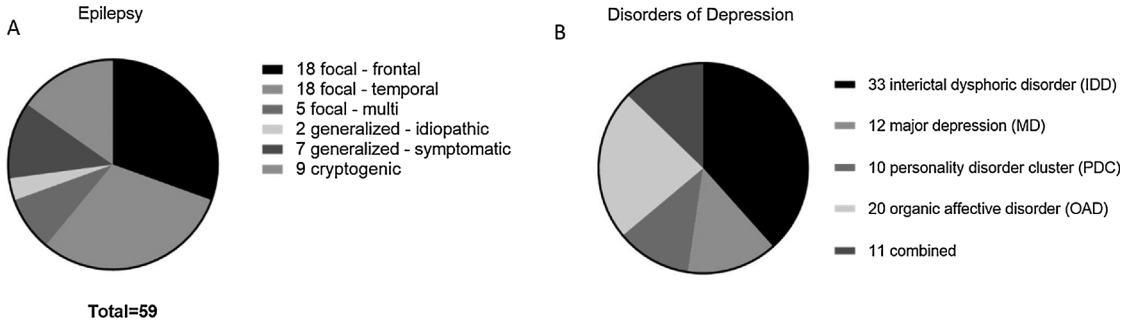

Fig. 1. 59 patients with A) pharmacoresistant epilepsy: 18 patients with focal-frontal, 18 focal-temporal, five multifocal, two idiopathic generalized, seven symptomatically generalized and nine with cryptogenic epilepsy B) disorders of depression as comorbidity to epilepsy: 33 patients with interictal dysphoric disorder (IDD), twelve major depression (MD), 10 personality disorder cluster (PDC), 20 organic affective disorder (OAD) and 11 combined disorders.

2) 12 cases of Major Depression (MD). Five or more symptoms of depression, of which at least one is depressed mood or diminished interest, should be present from the following list of the criteria: depressive mood; diminished pleasure or interest; weight loss or gain (decrease or increase of appetite); insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive guilt; diminished ability to concentrate or indecisiveness; and recurrent thought-of-death or recurrent suicidal ideation (ICD 10: F32.2).
3) Ten cases of Personality Disorder Cluster (PDC), an emotional instable personality disorder with a tendency for patients to act out impulses without consideration of consequences, accompanied by an unpredictable mood and a tendency to emotional outbursts and symptoms of depressions (ICD 10: F60.3)
4) 20 cases of Organic Affective Disorder (OAD), i.e. disorders characterized by changes of mood and affect accompanied by a change of overall activity caused by an organic disorder (e.g. encephalitis) (ICD 10: F06.3).

Eleven patients had a comorbidity of two or more of these subtypes (IDD + MD 1 patient, IDD + OAD 4 patients, IDD + PDC 2 patients, OAD + MD 1 patient, IDD + PDC + OAD 2 patients, IDD + MD + OAD 1 patient). The diagnoses were established by an independent psychiatrist who also performed Montgomery–Åsberg Depression Rating Scale (MADRS) and Beck-Depressions-Inventory (BDI) before VNS surgery to establish a baseline. As follow up one year after VNS-surgery patients were reevaluated with MADRS and BDI by the same psychiatrist to determine the progress of symptoms of depression. Indication for VNS surgery was felt by an interdisciplinary conference with respect to the etiology and severity of epilepsy. Former treatment of symptoms of depression was variable among patients and so not decisive for indication for surgery. The VNS stimulators were implanted on the left side to avoid cardiac side effects through the classic approach for anterior cervical discectomy. The actual device is composed of a wire with three helical contacts (two active contacts, one anchoring) secured around the vagus nerve, and a one-pin battery [10].

GraphPad Prism software was used for data analysis with multiple t-test. Statistical significance was determined using the Holm-Sidak method, with alpha = 0.05.

3. Results

VNS has a beneficial effect on symptoms of depression in patients with difficult-to-treat epilepsy. The totality of patients investigated had a reduction of MADRS and BDI scores from 29 to 18 ($p < 0{,}001$) and 24 to 14 ($p < 0{,}001$) respectively (Fig. 2A). All subtypes of patients with symptoms of depression improved from VNS as well: For IDD, the reductions in MADRS and BDI were 28 to 18 ($p < 0{,}001$) and 23 to 14 ($p < 0{,}001$). The most impressive effect was observed in patients with MD as they ameliorated MADRS 32 to 16 ($p < 0{,}001$) and BDI 26 to 13 ($p < 0{,}001$). Patients with PDC improved from a mean MADRS 32 to 20 ($p < 0{,}001$) and BDI 26 to 16 ($p < 0{,}001$). Even the OAD subgroup, which showed the lowest response towards VNS, achieved a reduction of MADRS 24 to 20 ($p = 0{,}016$) and BDI 23 to 16 ($p < 0{,}001$) (Fig. 2B and C). Patients with a comorbidity of two or more subtypes did not show such an improvement from VNS. The MADRS score showed a reduction from 29 to 17 ($p < 0{,}001$), but in the BDI no significant difference before and after VNS was noted (24 to 22 p = n.s.) (Fig. 2D)

VNS has a beneficial effect on epilepsy as well. Three follow-up investigations were performed independently from the psychiatric examination by a neurologist. After six months, 59% of the patients had a reduction of seizure frequency > 50% or reported a huge improvement in quality of life due to a reduction in the severity of their seizures. The number of positive responses towards VNS increased to 64% after twelve months and to 66% two years after VNS implantation. All subgroups of epilepsy ameliorated in response to VNS. Especially multifocal (4 of 5 patients) and generalised idiopathic and symptomatic (2 of 2 patients and 4 of 6 respectively) improved.

It is assumption here that an improvement in depression-scores correlates with a reduction of seizure frequency. Determining a reduction of seizure frequency of > 50% as an improvement and a lower or no reduction as a no-improvement significant amelioration in MADRS and BDI correlate with seizure-improvement. We performed Spearman nonparametric correlation with r = 0.56. 95% confidence interval of 0,34 – 0,72 and $r^2 = 0.31$ for seizure reduction and MADRS and r = 0.3.95% confidence interval of 0,03 – 0,53 and $r^2 = 0.09$ for BDI respectively.

4. Discussion

Since VNS was proven to be a sufficient tool in the treatment of depression [2] and epilepsy [1], we investigated the effect of VNS in patients with comorbidity of epilepsy and depression. In our trial, we confirmed the former results for depression and epilepsy and expanded it on the positive effect of VNS on their comorbidity to each other. Both morbidities ameliorated after VNS. Two years after VNS, two thirds of all patients had a reduction of their seizure frequency of more than 50%. Severity of symptoms of depression improved from a mean MADRS of 29 to 18 and BDI 24 to 14. We differentiated four different subtypes of symptoms of depression (IDD, MD, PDC, OAD). All subtypes improved, especially IDD and MD patients. Patients with a comorbidity of two or more subtypes of symptoms of depression show a significant amelioration in MADRS but no relevant improvement in BDI. A possible reason for that difference could be the structure of the tests: in BDI patients performed a self-assessment while in MADRS the patients have been assessed by a psychiatrist. Retrospectively we noticed a strong correlation between improvement of seizure frequency and reduction of symptoms of depression. One could argue that the amelioration of depression is due to seizure improvement and therefore an indirect

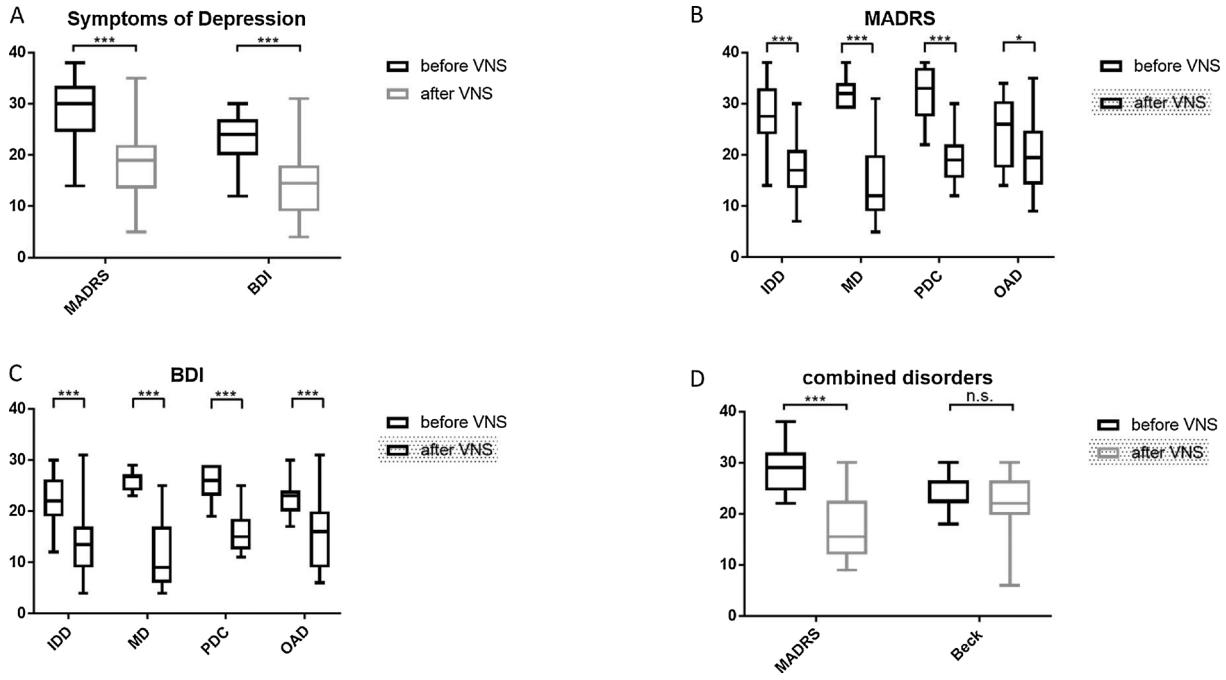

Fig. 2. A) Reduction of MADRS and BDI scores from 29 to 18 ($p < 0{,}001$) and 24 to 14 ($p < 0{,}001$) one year after VNS-surgery in the overall of patient. B) Reduction of MADRS one year after VNS-surgery for subtypes of patients with symptoms of depression: IDD 28 to 18 ($p < 0{,}001$), MD 32 to 16 ($p < 0{,}001$), PDC 32 to 20 ($p < 0{,}001$) OAD 24 to 20 ($p = 0{,}016$). C) Reduction of BDI one year after VNS-surgery for subtypes of patients with symptoms of depression: IDD 23 to 14 ($p < 0{,}001$), MD 26 to 13 ($p < 0{,}001$), PDC 26 to 16 ($p < 0{,}001$) OAD 23 to 16 ($p < 0{,}001$). D) Reduction of MADRS and BDI one year after VNS-surgery for comorbidity of two or more subtypes of disorders of depression. MADRS 29 to 17 ($p < 0{,}001$), BDI (24 to 22 p = n.s.).

improvement. In our trial we performed investigations for depression and seizure frequency separated from each other at different time points so a proposition about causality is limited. To explore whether the improvement in depressive symptoms remains significant if the improvement in seizures is controlled further prospective investigations to figure out a causality are required. All in all symptoms of depression as comorbidity of epilepsy have a major negative impact on the quality of patients' lives. Still, the diagnosis and treatment of depression does not belong to the clinical standard for patients with epilepsy. Against the backdrop of our results, VNS seems to be a very effective tool in the treatment of patients suffering from both diseases as a comorbidity and should receive more consideration in clinical standard and treatment.

Declaration of interest

None.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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MADRS and BDI have been performed by Katja Bohlmann. VNS surgery has been performed by Ulf Christoph Schneider.

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