Potential Predictors of Response to Vagus Nerve Stimulation in Refractory Epilepsy

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Introduction

Vagus nerve stimulation (VNS) has steadily grown as an option for treating refractory epilepsy. Unfortunately, considerable variability remains in the success of VNS in patients. Therefore, it is necessary to identify which characteristics increase or decrease the likelihood of successful VNS treatments to mitigate potential complications by performing unnecessary procedures. We examine available literature to determine the known predictors and characteristics of patients in relation to VNS performance.

Methods

PubMed was queried for articles pertaining to vagus nerve stimulation and predictive variables. Articles included in the review met the following inclusion criteria: clinical data on human subjects in English, articles reporting treatment of seizure disorder with VNS, data that was supported with multivariate analysis. No limit was placed on publication date.

Characteristics of Included Studies

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Study	No. of Patients	Male/Female	Age <18	Age >18	≥ 50% Seizure† Reduction
Janszky et al., 2005	47	22/25	-- †	--	--*
Ghaemi et al., 2010	144	67/77	63	18	87.8 (61.8%)
Montavont et al., 2007	50	--/-- †	--	--	29 (58%)
Englot et al., 2011	3321	--/--	--	--	1333 (50.6%)
Englot et al., 2015	5554	2888/2665	2999	2554	3332.4 (60.1%)
Arcos et al., 2014	36	16/20	3	33	29 (51.4%)
Elliott et al., 2011	436	216/220	129	307	225 (63.75%)
Kim et al., 2017	58	41/17	48	10	25 (58.1%)
Shahwan et al., 2008	26	--/--	26	0	14 (54 %)
De Vos et al., 2011	19	11/8	2	17	7 (36.9%)
Arya et al., 2013	43	23/20	--	--	27.52 (64%)
Lagae et al., 2015	70	--/--	54	16	38 (54%)
Hilderink et al., 2017	34	15/19	0	34	10 (26%)
Liu et al., 2017	32	21/11	12	20	17 (53%)

† Response rate at time of last follow up. 3mo-10yrs
† Not specified or unable to be determined based on data given
* Study did not give response data, only seizure freedom rate

Results

Younger age at implantation, later onset of epilepsy, and generalized over partial seizures were most strongly supported as predictive of successful therapy.

Study Focus: Age, Duration, Frequency

	Study Type	n	P
Younger age of implantation			
Ghaemi et al., 2010	Retrospective	144	0.026
Englot et al., 2011	Retrospective	1489	< 0.001
Lagae et al., 2015	Retrospective	70	< 0.006
Lower seizure frequency (<20 seizures/month)			
Arcos et al., 2014	Retrospective	36	0.024
Duration of epilepsy before implantation			
Arya et al., 2014	Retrospective	43	0.038
Later Epilepsy Onset (>12 years old)			
Englot et al., 2015	Retrospective	5554	< 0.05

a. The 10 seizure free patients had a significantly lower average age at 16.2 +- 10.8 relative to the 134 non-seizure free patients of average age 24.3 +-13.5. b. Disaggregated from 3321 patients to 1489 patients and separated to <18 years or >18 years of age. Patients <18 years of age had significantly greater seizure reduction. c. The 9 patients below the age of 5 of the 70 pediatric patients were significantly more likely to achieve seizure freedom. d. 10-month response time in patients with fewer than 20 seizures per month, significantly lower than 25 months in patients with more than 20 seizures per month. e. The 30 patients with ILAE (International League Against Epilepsy) score <_4 at 7.93 +-5.56 years versus the 13 patients with ILAE score >4 at 4.74+-2.18 years had significantly better outcomes. f. Patients with seizure freedom had significantly later onsets at $p < 0.001$ at 0 to 4 months, 4 to 12 months, and at 12 to 24 month follow-up visits. At 24 to 48 months, $p < 0.005$.

Study Focus: Localization of Epileptic Disorder

	Study type	n	P
Absence of bilateral IED or Unilateral IED			
Janszky et al., 2005	Retrospective	60	0.004
Ghaemi et al., 2010	Retrospective	144	0.005
Generalized seizures over partial seizures			
Montavont et al., 2007	Retrospective	50	0.03
Englot et al., 2011	Retrospective	618	<0.001
Englot et al., 2015	Retrospective	5554	<0.01
Focal Epilepsy			
Elliott et al., 2011	Retrospective	436	0.016
Kim et al., 2017	Retrospective	58	0.021
Temporal Discharges			
Arcos et al., 2014	Retrospective	36	0.037

a. 13 of 47 patients lacked bilateral IEDs (interictal epileptiform discharges) of which 5 became seizure free. b. 55 of 144 patients had unilateral IEDs of which 8 became seizure free. c. The 111 patients with generalized epilepsy had 57.5% +- 1.9% reduction in seizure, significantly greater than the 507 patients with partial epilepsy at 42.5% +- 0.9%. It was not significantly greater than other/mixed seizure types at 53.7% +- 1.9% seizure reduction. d. Significantly greater seizure freedom rates in the first 0 to 4 month and 4 to 12 month follow-up periods for patients with generalized epilepsy versus partial epilepsy. e. Mean seizure reduction of 74.6% in the 34 patients with focal/eloquent or temporal epilepsy of 436 total patients with VNS. f. Of 58 total patients, 28 patients demonstrated focal or multifocal epileptiform discharges on interictal EEG and were significantly associated to good VNS response of >50% seizure reduction. g. The 18 patients with temporal discharges and 3 patients with combined discharges based on video-EEG had a significantly shorter response time of 11 months than those with no temporal discharges with response time of 26 months.

Results (cont.)

Other potential positive predictors supported by smaller data sets include: lower seizure frequency, duration of epilepsy prior to implantation, unilateral IED or absence of bilateral IED, focal epilepsy, presence of temporal discharges, cortical dysgenesis, Lennox-Gastaut syndrome, post-traumatic epilepsy, and tuberous sclerosis. There are conflicting results regarding the prognostic value of pairwise derived brain symmetry index and the presence of MRI lesions. Indices of heart rate variability are a new and potentially useful predictor of response.

Conclusions

VNS remains a safe, efficacious means of treating refractory epilepsy. However, due to the highly variable response, there is a need for better understanding of its mechanisms and predictive variables to reduce unnecessary procedures. Though there are many potential VNS predictors, additional corroborative data is needed before these may guide decision making. Thus far, younger age of implantation, later onset of epilepsy, and generalized seizures are the factors most strongly associated with successful VNS therapy.

Learning Objectives

By the conclusion of this session, participants should understand: 1) VNS can be a safe and efficacious treatment for refractory epilepsy but the response is highly variable, 2) the current state of the research on predictors of response to VNS for refractory epilepsy, and 3) there is conflicting or insufficient data about many potential predictors of response to VNS.

References

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*contact authors for full list of references