Seizure 42 (2016) 15–19

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Socioeconomic evaluation of vagus stimulation: A controlled national study

Poul Jennum [a,*], Anne Sabers [b], Jakob Christensen [c], Rikke Ibsen [d], Jakob Kjellberg [e]

[a] Danish Center for Sleep Medicine, Neurophysiology Clinic, Faculty of Health Sciences, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark
[b] Neurological Clinic, Faculty of Health Sciences, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark
[c] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[d] itracks, Klosterport 4E, 4, Aarhus, Denmark
[e] Danish National Institute for Local and Regional Government Research, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 8 May 2016
Received in revised form 28 August 2016
Accepted 30 August 2016

Keywords:
Epilepsy
Vagus
Treatment
Welfare costs
Prospective
Controlled

ABSTRACT

Purpose: We aimed to determine the health costs and social outcomes in terms of education, employment and income level after insertion of a vagus nerve stimulator (VNS) in patients with epilepsy.
Methods: This is a case–control study using Danish health care and socioeconomic register data. The analysis of the effect involved a comparison of the health care costs, occupation and income status of VNS-treated epilepsy patients with those of a control group of epilepsy patients who had a VNS implanted during the 12 months before the index date (pre-period) and during the two years after the index date (post-period).
Results: 101 patients who had undergone VNS implantation and 390 control patients were included. VNS implantation was associated with fewer inpatient admissions and emergency room visits and less frequent use of prescription medication compared with epilepsy patients without VNS implantation. VNS implantation was not associated with changes in occupational status (including employment and income). In fact, the number of people on disability pension increased during the period.
Conclusions: VNS implantation in people with epilepsy is associated with reduced health care use, but not with occupational or social status.

1. Introduction

Epilepsy is a serious and chronic neurological disorder that affects all ages from childhood to old age [1]. Epilepsy in adults, children and adolescents is strongly associated with significant morbidities, mortality, stigma and reduced quality of life. It is also associated with educational and professional problems and may therefore have a substantial socioeconomic impact [2,3]. Despite decades of research focusing on its medical or surgical treatment, a significant proportion of patients are left with medically intractable epilepsy and continued seizures. Vagus nerve stimulation (VNS) has been provided to some of these patients, particularly those with the most severe conditions. VNS is an additive treatment that may reduce seizure frequency and severity in patients with medically intractable epilepsy [4–6]. However, surgical implantation of VNS may cause complications and the VNS may cause side effects. The cost associated with its implantation may also limit the number of patients who are potentially treatable with the device. Little is known about the social outcomes of VNS implantation, but it is debatable whether VNS in general has an additive positive effect compared with the best available drug treatment [7]. Other studies have shown a positive effect, as determined by measures of pre- and post-VNS-implantation costs [8–13], although they did not compare these findings with a control group, or evaluate the social impacts of, for example, education and employment. Data on the consequences of VNS implantation are limited so we aimed to derive a national estimate of the effects of VNS implantation in persons with epilepsy on health care use and social outcomes compared with those in a control group who had not received a VNS implantation. We recently described the direct and indirect costs in children and adult patients diagnosed with epilepsy in Denmark [3]. These findings suggested that epilepsy causes a substantial health care

* Corresponding author at: Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Rigshospitalet, University of Copenhagen, DK 2600 Glostrup, Denmark.
E-mail addresses: poul.joergen.jennum@glo.regionh.dk (P. Jennum), anne.sabers@regionh.dk (A. Sabers), jakob@clin.au.dk (J. Christensen), rikke@itracks.dk (R. Ibsen), jakj@kora.dk (J. Kjellberg).

http://dx.doi.org/10.1016/j.seizure.2016.08.011
1059-1311/

burden not only at the time of diagnosis and after, but also before diagnosis. In this study, we focus on the health care costs and social outcomes for epilepsy patients undergoing VNS implantation based on a consideration of the national population.

2. Methods

In Denmark, it is possible to identify subjects with epilepsy, and to trace health, and educational, professional and income levels and thereby calculate direct and indirect costs related to diseases because information from general medical practice, and public and private hospitals, and the social and educational status of all Danes are registered in central databases that are linked by a unique identification number. We took advantage of historical medical archives of patients hospitalized with epilepsy in Denmark since 1997 [3], a randomly age- and gender-matched control group from the background population and several nationwide registers, including detailed information about education, employment, welfare benefits, family conditions, hospital contacts, visits to general practitioners and use of medication for the total Danish population. Using these data enabled us to identify long-term health and social effects before and after VNS implantation.

The study uses Danish health care and socioeconomic register data. The analysis of the effects involved comparing the health care costs, occupation and income status of VNS-treated epilepsy patients with those of a control group. We undertook a case–control study in which we compared the case study group (VNS implantation) and a control group (persons diagnosed with epilepsy who had no VNS implantation and no epilepsy surgery) during the 12 months before the index date (pre-period) and the two years following the index date (post-period).

We used the following national registers:

- The National Patient Registry (NPR) (Landspatientregisteret), which includes administrative information, diagnoses, and diagnostic and treatment procedures using several international classification systems, including the International Classification of Disorders (ICD-10). Since 1995, the NPR has also held information about outpatient costs.
- The Danish Prescription Register (Lægemiddelstatistik registeret), which includes information about usage and cost of medications.
- The National Health Insurance Register (Sygesikringsregisteret), which contains all contacts and costs in the primary sector (general practice and specialist care in the primary sector).
- The National Registers (Statistics Denmark), which include information about income from employment and public transfers.

2.1. Study population

The study examined only patients diagnosed with epilepsy (ICD-10: G40x; status epilepticus: G41x).

The follow-up population included VNS patients and their controls who were alive two years after VNS implantation (the index date).

2.2. Case group

The VNS case group consisted of all epilepsy patients receiving VNS who had not undergone an epilepsy surgery operation during the study period (i.e., between one year before and two years after the index date). A VNS patient was identified the first time the patient had a VNS procedure code registered in the NPR. Patients receiving both VNS and epilepsy surgery (KAAJ) in the period were excluded from the study.

2.3. Control group

The control group consisted of patients with a diagnosis of epilepsy or status epilepticus and who had not undergone epilepsy surgery or VNS implantation. We matched the control group with respect to gender, year of epilepsy diagnosis, year of VNS implantation (index year), and age at time of VNS implantation.

Matching for the VNS stimulation year and the year of epilepsy diagnosis ensures that the control patients were alive at the time of VNS implantation.

Patients or controls who immigrated into or emigrated out of the country during the study period were excluded.

2.4. Health care costs

Health care costs were calculated as annual costs over the 12 months before the index date and during the two years after the index date.

Health care costs were calculated as totals based on costs of outpatient, inpatient, and emergency room visits, medicine, and primary health sector care. We estimated the indirect and direct costs related to epilepsy. All costs accruing from the epilepsy diagnosis and epilepsy medication costs were included in the epilepsy-related cost calculation.

In the analyses, only patients who were eligible for the whole period were included. If a patient or a control individual died during the post-period they were excluded from the cost calculation. This prevented the possibility of overestimating the effect due to the lower costs for dead patients and controls.

2.5. Income

Calendar year income is a stock variable, so we cannot follow a patient's income before and after the index date in the same way we are able to with the health care costs. Therefore, the pre-period income in the income analysis was taken as the calendar year before the index year, and post-income was the income two years after the index year. Patients younger than 18 years of age at the time of VNS implantation were excluded from the income calculation, because no children (those aged 15 years or younger) and very few patients under the age of 18 have income information. Of the total population of epilepsy patients who had undergone VNS surgery, 43% were under 18 years of age in the pre-VNS implantation period. Costs and income were considered in euros, adjusted to 2015 prices.

2.6. Occupation

Occupation was estimated in the November of the year before the index year and of subsequent years. The significance of the difference in occupational status between cases and controls was tested using a chi-square test.

3. Results

We included a total of 101 patients who had undergone VNS implantation and 390 control patients. One additional patient underwent VNS but died within the observational period and was excluded from this analysis.

The descriptive data are summarized in Table 1. Variables that were not matched were tested for significant differences using the chi-square test for count variables and the *t*-test for continuous variables. Due to the small number of observations compared with

Table 1
Basic characteristics of VNS patients and controls two years after implantation.

	Case N = 101			Control N = 390			p
	N	%	Mean	N	%	Mean	
Age							
0–19 years	48	47.5	25	188	48.2	25	
20–39 years	35	34.7		136	34.9		
40+ years	18	17.8		66	16.9		
Gender							
Male	44	43.6		173	44.4		
Female	57	56.4		217	55.6		
Years since diagnosis			17			17	
Education[a]							
Primary	69	68.3		197	50.5		<0.001
Secondary	0	0.0		17	4.4		
Vocational	4	4.0		57	14.6		
College	4	4.0		41	10.5		
Unknown	24	23.8		78	20.0		
Charlson							
Charlson Index			0.04			0.03	0.816

[a] The significance of educational level was tested in a comparison of the groups of primary education vs. higher than primary education. Some people were excluded from this analysis because their data were incomplete.

Table 2
Health care cost analysis two years after VNS implantation.

	Pre-period			Two-year post-period		
	Case	Control	p	Case	Control	p
N	101	390		101	390	
Cost	Mean (€)	Mean (€)		Mean (€)	Mean (€)	
All health care cost						
Outpatient services	763.3	341.1	0.000	563.0	367.2	0.810
Inpatient admissions	9873.4	1129.1	0.000	3187.7	933.8	<0.001
Emergency room (ER)	117.8	38.7	0.000	98.7	33.3	<0.001
Medicine (prescription medicine)	4362.7	506.4	0.000	4129.4	546.8	<0.001
Primary health sector	960.0	394.5	0.000	1122.7	414.0	<0.001
Epilepsy-related health care cost						
Outpatient services	374.7	16.1	0.000	291.1	16.5	<0.001
Inpatient admissions	6523.0	63.8	0.000	2435.2	89.7	<0.001
Emergency room (ER)	12.9	0.7	0.000	3.5	0.0	0.100
Medicine (prescription medicine)	3794.0	232.9	0.000	3206.2	239.4	<0.001

the many children in the dataset, information about education was limited. Persons with missing information were excluded from the chi-square test in the analysis of educational level. The limited numbers also made it feasible only to compare those in primary education with those with higher than primary education. Patients with VNS implantation tended to have a lower level of education than the epilepsy control group. A bootstrapped *t*-test was used to compare the heath care costs of cases and controls. Only matches by age, gender and diagnosis date were controlled for in the *t*-test. Information about education and comorbidity is summarized in the descriptive table, but this was not used in the estimates of costs.

3.1. Health care costs

Pre- and post-VNS implantation yearly health care costs for the cases and their control groups are shown in Table 2. The table shows the total health care cost broken down into outpatient, inpatient, and emergency room visits, medicine and primary health sector costs, and those related to the epilepsy diagnoses. There were significant differences between VNS cases and controls with respect to inpatient admissions, emergency room visits, use of prescription medicine and the primary health sector, and in epilepsy outpatient services.

Table 3 illustrates the change in costs from the pre- to the post-period for cases and controls to estimate the effect of VNS. Comparing cases and controls before and after VNS implantation showed significantly greater reductions in inpatient admissions,

Table 3
Change in health care costs from one year before to two years after VNS implantation (2015 prices).

	Change in healthcare cost		
	Case	Control	p
N	101	390	
Cost	Mean (€)	Mean (€)	
All healthcare cost			
Outpatient services	−200.3	26.1	0.850
Inpatient admissions	−6685.7	−195.3	<0.001
Emergency room (ER)	−19.1	−5.3	0.970
Medicine (prescription medicine)	−233.3	40.4	0.640
Primary health sector	162.6	19.5	0.530
Epilepsy-related healthcare cost			
Outpatient services	−83.7	0.4	0.110
Inpatient admissions	−4087.8	25.8	<0.001
Emergency room (ER)	−9.3	−0.7	0.050
Medicine (prescription medicine)	−587.8	6.4	<0.001

Table 4A
Occupational status from one year before to two years after VNS implantation.

	Pre-period					Post-period				
	Case		Control		p^*	Case		Control		p^*
N	101		390			101		390		
Occupation	*N*	%	*N*	%		*N*	%	*N*	%	
Occupational status					<0.001					<0.001
Disability pension	38	37.6	37	9.5		52	51.5	48	12.3	
Employed	13	12.9	162	41.5		12	11.9	166	42.6	
Unemployed and not in labor force	19	18.8	69	17.7		15	14.9	92	23.6	
Children < 16	31	30.7	122	31.3		22	21.8	84	21.5	

* $p < 0.01$.

Table 4B
Income in the pre-period and two years post-VNS implantation (2015 prices).

	Pre-period			Post-period		
	Case	Control	*p*	Case	Control	*p*
*N**	58	221		58	221	
Income	Mean (€)	Mean (€)		Mean (€)	Mean (€)	
Income total	29,540.6	34,848.6	0.043	31,496.5	37,795.5	0.019

* $p < 0.01$.

emergency room visits and use of prescription medication among those receiving the VNS treatment.

3.2. Analysis of the effect in the two-year population: occupational status and income

Table 4 shows the occupational status in the year before VNS implantation and two years thereafter. Children were excluded from the test. Significantly more patients in the VNS group were on disability pension both before and after implantation. Slightly more VNS-implanted persons converted to disability pension after implantation (Table 4A). The income level among the employed was lower in the VNS group before and after implantation compared with controls.

4. Discussion

We showed that VNS implantation was associated with a significant reduction in a number of socioeconomic variables, including inpatient admissions, emergency room visits and the use of prescription medication. We did not identify any significant effects on occupational status (employment or income). In fact, more people with VNS implantation were receiving a disability pension during the period compared with controls.

Previous studies have shown a reduction in the frequency of seizures in patients with medically intractable epilepsy following VNS implantation [4–6,14]. Data suggest that hospitalization and emergency visits become less frequent after implantation [5,11,15,16]. Implantation of VNS has been associated with increased outpatient resource use and decreased inpatient admissions, resulting in a reduction in long-term epilepsy-related medical costs after implantation [5,8,17]. Similar data have also been found in children with intractable epilepsy [15] and also in those with comorbid autism disorders [18] treated with VNS. None of the studies evaluated the long-term social effects, including employment outcome. These findings are supported by our study, in which medical costs were reduced after VNS implantation. There are currently no data available to evaluate the long-term effect on social outcomes, but we found no improvement in them (including the employment status variables) in the short term after implantation. Whether VNS treatment may influence these factors depends on several factors.

VNS may preferentially be offered to patients with severe epilepsy when their mental and physical health, educational level and social status are already affected. Former studies of epilepsy patients show that patients' health, educational and social circumstances are affected years before diagnosis and disease management. These effects are especially important in the younger population, where education and consequently long-term outcomes are affected [3]. Any potential effects of VNS on these factors are expected to be limited since the disease is already severe by the time of implantation. We cannot rule out the possibility that applying the technology to patients with less severe disease, or making an earlier intervention will have a more positive effect. It is a general problem with expensive and invasive treatments that they tend to be used for those who are most ill, for whom the potential benefits are more variable. Further studies are needed to evaluate whether patients with less severe disease could benefit more from VNS implantation. The number of treated patients and the follow-up time in our data precluded the subgroup analysis required to address this matter.

We now consider the strengths and limitations of the study. There are several problems with evaluating the health, social and economic effects of VNS and other types of invasive treatment. The strength of the study resides in the inclusion of all treated patients, the completeness of the health, social and economic data available from the Danish registration system, which includes all health and social contacts with registrations of factual education, income and transfers. We aimed to identify the overall welfare effect of VNS and did not subdivide the patients into those with seizure reduction (responders) and non-responders. The potential effect on medication reflects the effect of the treatment: in patients with positive results with respect to seizure frequency the medication was typically reduced. We include evaluation of effects in patients with chronic and even progressive disease during the observation period. Consequently, a potentially positive effect may be obscured by disease or comorbid effects. In contrast to previous studies evaluating the effect in case series, we defined a control group based on certain criteria to compensate for the problem of the period-effect of chronicity. The main difficulty is to define controls with the same disease severity as the case group; we should identify controls based not only with respect to age, gender and sociodemographic variables, but also in terms of the severity

of the epilepsy, the comorbidities and medication use. This is partly covered by the social variables: members of the VNS group are less well educated and have a higher level of disability pension uptake at the time of VNS implantation. This reflects the selection of patients submitted for VNS as this treatment is offered to those most severely affected, for whom little alternative treatment is possible (e.g., additional medication, surgery). Lastly, the number of patients observed limited the statistical power and precluded any subgroup analysis, e.g. of children and adults or of specific syndromes. Further studies including more cases and a carefully selected control for such variables are needed.

5. Conclusion

We found that implantation of VNS was associated with a reduction in components of health care use such as hospital services and epilepsy-related prescription medication. We found no effect on the social characteristics of disability pension uptake, employment rate and income level.

Author contributions

Poul Jennum (PJ) and Jakob Kjellberg (JK): creation, initiation and management of the project. PJ is the main author. JK and RI performed the statistical analyses and commented on the manuscript. AS and JC commented on the methods and critically revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest statement

None of the authors reports any conflict of interests.

References

[1] Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res 2007;76:60–5.
[2] Hunter RM, Reilly C, Atkinson P, Das KB, Gillberg C, Chin RF, et al. The health, education, and social care costs of school-aged children with active epilepsy: a population-based study. Epilepsia 2015;56:1056–64.
[3] Jennum P, Gyllenborg J, Kjellberg J. The social and economic consequences of epilepsy: a controlled national study. Epilepsia 2011;52:949–56.
[4] Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015;4:CD002896.
[5] Chambers A, Bowen JM. Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. Ont Health Technol Assess Ser 2013;13:1–37.
[6] Privitera MD, Welty TE, Ficker DM, Welge J. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2002;CD002896.
[7] Hoppe C, Wagner L, Hoffmann JM, von Lehe M, Elger CE. Comprehensive long-term outcome of best drug treatment with or without add-on vagus nerve stimulation for epilepsy: a retrospective matched pairs case–control study. Seizure 2013;22:109–15.
[8] Camp C, Smithson WH, Bunker M, Burke T, Hughes D. Impact of vagus nerve stimulation on secondary care burden in children and adults with epilepsy: review of routinely collected hospital data in England. Epilepsy Behav 2015;52:68–73.
[9] Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy – an update. Seizure 2008;17:387–8.
[10] Forbes RB, Macdonald S, Eljamel S, Roberts RC. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. Seizure 2003;12:249–56.
[11] Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology 2002;59:S44–7.
[12] Boon P, D'Have M, Van Walleghem P, Michielsen G, Vonck K, Caemaert J, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia 2002;43:96–102.
[13] Boon P, Vonck K, D'Have M, O'Connor S, Vandekerckhove T, De Reuck J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. Acta Neurol Belg 1999;99:275–80.
[14] Fisher RS, Eggleston KS, Wright CW. Vagus nerve stimulation magnet activation for seizures: a critical review. Acta Neurol Scand 2015;131:1–8.
[15] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paediatr Neurol 2012;16:449–58.
[16] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011;22:370–5.
[17] de Kinderen RJ, Postulart D, Aldenkamp AP, Evers SM, Lambrechts DA, Louw AJ, et al. Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy. Epilepsy Res 2015;110:119–31.
[18] Levy ML, Levy KM, Hoff D, Amar AP, Park MS, Conklin JM, et al. Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. J Neurosurg Pediatr 2010;5:595–602.