

Gender differences in referrals for deep brain stimulation for essential tremor

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Key words: Essential tremor, deep brain stimulation

Word count: 989/1000

References: 5/5

Illustrations: 1/1

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Abstract (for review purposes only, 50/50 words)

Deep brain stimulation (DBS) is an established treatment for essential tremor (ET). Gender differences in DBS have been recognized for Parkinson's disease. In this systematic chart review, we also observed a gender differences in DBS for ET. The

main reason was an underrepresentation of women in referrals for surgical evaluation.

Declarations of interest

P.R. none

S.T.J. was funded by the Prof. Klaus Thiemann Foundation.

P.S. none

A.G. none

G.R.F. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Project-ID 431549029—SFB 1451. G.R.F. serves as an editorial board member of Cortex, Neurological Research and Practice, Neurolmage: Clinical, Zeitschrift für Neuropsychologie, and DGNeurologie; receives royalties from the publication of the books Funktionelle MRT in Psychiatrie und Neurologie, Neurologische Differentialdiagnose, and SOP Neurologie; receives royalties from the publication of the neuropsychological tests KAS and Köpps; received honoraria for speaking engagements from Bayer, Desitin, DGN, Ergo DKV, Forum für medizinische Fortbildung FomF GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer, and Sportärztebund NRW.

V.V.V. has received honoraria for active participation in congresses and advisory boards from Medtronic, Boston Scientific and Functional Neuromodulation.

K.A. has received honoraria for educational meetings, travel and consultancy from Medtronic, St. Jude Medical and Boston Scientific.

A.R. has received honorarium from UCB and was supported by a grant from Medtronic.

P.M-M. has received honoraria from the International Parkinson and Movement Disorder Society (MDS) for management of the Clinical Outcome Assessment Program.

L.S. none

Af.S. none

L.T. reports grants, personal fees and non-financial support from SAPIENS Steering Brain Stimulation, Medtronic, Boston Scientific and St. Jude Medical.

An. S. is funded by the Gussyk program and the Advanced Cologne Clinician Scientist program of the Medical Faculty of the University of Cologne and has received funding from the Prof. Klaus Thiemann Foundation.

K.R.C. has received funding from Parkinson's UK, NIHR, UCB, and the European Union; he received honoraria from UCB, Abbott, Britannia, US Worldmeds, and Otsuka Pharmaceuticals; and acted as a consultant for AbbVie, UCB, and Britannia.

E.K. has received grants from the German Ministry of Education and Research, the German Parkinson- Fonds, the German Parkinson Society; honoraria from: Oticon GmbH, Hamburg, Germany; Lilly Pharma GmbH, Bad Homburg, Germany; Bernafon AG, Bern, Switzerland; Desitin GmbH, Hamburg, Germany.

H.S.D. reports funding of his work by the EU Joint Programme - Neurodegenerative Disease Research (JPND), the Prof. Klaus Thiemann Foundation, the Felgenhauer Foundation, and the Koeln Fortune Program, and honoraria by Boston Scientific, Medtronic and Stadapharm.

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Manuscript

Deep brain stimulation (DBS) is an established, safe, and effective treatment for movement disorders, including essential tremor (ET). Gender differences in DBS treatment have been recognized for Parkinson's disease (PD) [1]. For a multicenter cohort of patients with PD, we recently demonstrated that an underrepresentation of women out of proportion to prevalence data mainly resulted from an underrepresentation at the stage of referral, despite the fact that women were more likely to be found suitable surgical candidates and that they responded equally favorable to DBS treatment [2]. Comparable benefit of DBS for women and men is also reported for ET [3].

We thus aimed to explore the presence of gender differences in DBS for ET as well. To this end, we conducted a systematic chart review of consecutive patients with ET referred to the University Hospital Cologne for indication evaluation of DBS from January 2015 to September 2020 and recorded the total number of referrals, positive and negative indication assessments, and performed DBS surgeries in women and men. The ethics committee of the University of Cologne approved this retrospective analysis (vote no. 23-1037-retro).

A one-sample binomial test was employed to compare the gender ratios in our cohort with those in the general ET population. Further, we analyzed differences in gender proportions using Chi-square tests regarding the following key steps: (1) referrals for DBS indication evaluation, (2) positive and negative decisions of indication evaluations, and (3) DBS surgery. Relative risks for women compared to men were calculated as the ratio of the probabilities of a certain outcome in both groups. Moreover, the total relative risk for DBS treatment of women compared to men was derived by multiplying the relative risks of referral with those of the following steps (positive indication evaluations and DBS surgery).

Fifty patients with ET were referred for preoperative evaluation in the investigated period, of whom 18 (36%) were female, and 32 (64%) were male (ratio M:F 1.8:1). The proportion of women with ET referred for DBS indication evaluation was significantly lower than the female share in the general ET population of approximately 50% with equal prevalence among men and women [4] (one-sample binomial test, $p=0.016$), resulting in a relative risk of 0.56 (RR 0.56; 95%CI 0.30–1.03) of referral for women with ET.

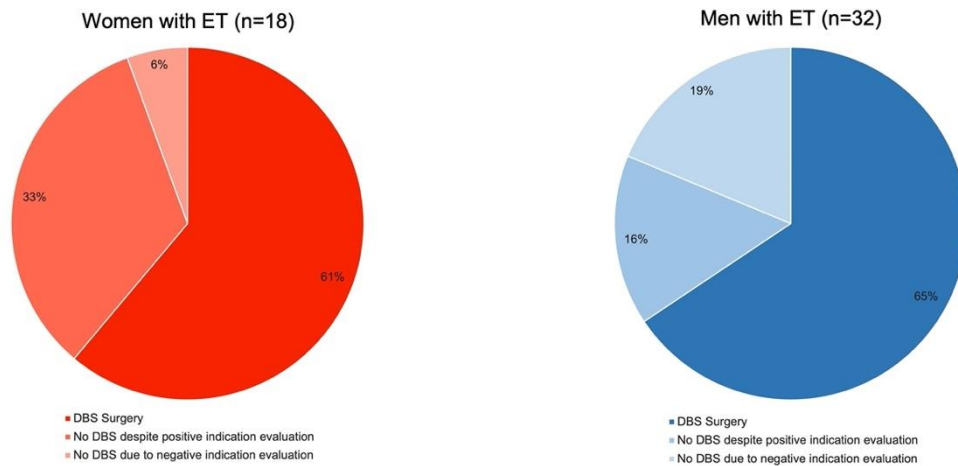
Forty-three patients met criteria for DBS with a gender ratio of M:F 1.5:1 (26 men, 17 women). Of these, 32 patients underwent DBS surgery with a gender ratio of M:F 1.9:1 (21 men, 11 women). The eligibility rate was 13% higher in women as compared to men, but the association of female gender with eligibility for DBS was not statistically significant (RR 1.16; CI 0.95–1.42, $p=0.197$). Indication evaluations were negative in 7 patients (1 woman and 6 men). The reasons for negative indication assessments were comorbidity in the one rejected woman and in the men clinically relevant neuropsychological impairment ($n=1$), depression ($n=2$), sufficient tremor control by medication ($n=2$), and a relevant functional component of the tremor ($n=1$).

Among patients eligible for DBS, the proportion of operated women was smaller (21/26 [81%] of male vs. 11/17 [65%] of female patients), albeit not statistically significant (RR 0.8; 95% CI 0.54–1.19; $p=0.238$). The total relative risk of receiving DBS treatment for women compared to men referred to our center with ET was 0.52 (95%CI, 0.18–1.5). The reasons for not undergoing DBS surgery despite positive indication evaluations were patient wish to postpone surgery (5 women, 2 men), and fear of surgical complications (2 men). The remaining two patients (1 woman, 1 man) did not return to our center after asking for additional time for consideration at discharge. DBS targeted only the thalamic ventral intermediate nucleus (VIM) in 1 female patient, and the VIM plus the posterior subthalamic area (PSA) in the remaining 31 patients.

These results need to be interpreted with caution due to several limitations. Our cohort was small ($n=50$) and monocentric, which only allowed for an exploratory approach. ET and disability resulting from this disorder are common and disproportionally few ET patients are referred for DBS treatment (in our center only about 10 patients per year). Hence, the calculation of the relative risks resulted in wide confidence intervals crossing 1 and only the statistical comparison of gender ratios of prevalence data and patients referred for evaluation reached statistical significance. Additionally, the retrospective chart review did not allow backtracking of the complete referral history, making it impossible to unmask potential bias by referring physicians. We were also not able to distinguish between patients with ET or those with possible ET plus as defined in the consensus criteria of the Movement Disorders Society.

Still, our results are consistent with our own observations on gender differences in DBS treatment for PD and the literature on other movement disorders [1,2,5]. Especially the marked underrepresentation at the stage of referral for surgical evaluation (M:F 1.8:1) was significantly disproportionate to the approximately equal prevalence of ET among women and men (M:F 1:1) [4]. And although women were more likely to be eligible for surgery, a smaller fraction of female surgical candidates eventually received DBS. Despite the fact that the gender differences did not reach statistical significance at the two latter stages of the surgical treatment process, this strongly suggests non-clinical determinants. Among these, a gender referral bias to specialty care and more reservation towards surgery among women have been discussed, as gender differences have long been identified for other invasive procedures [2]. As our retrospective analysis cannot uncover the reasons in our cohort, further systematic research will have to explore the specific determinants in DBS surgery and their medical and social components. Especially, the possibility of a “gender gap” (i.e., bias and inequity mainly related to female gender despite otherwise comparable demographic and clinical characteristics) needs to be explored. As a starting point, our findings may help to create awareness, promote further research and foster the implementation of gender equity in the surgical treatment of movement disorders.

A



B

Steps to DBS	Women		Men		Total		Relative risk	[95%-CI]	P
	n	%	n	%	n	%			
Referral	18		32		50		0.56	[0.30 to 1.03]	0.016 ^c
Positive indication evaluation	17	94,4 ^a	26	81,3	43	86,0	1.16	[0.95 to 1.42]	0.197 ^d
DBS surgery	11	64,7 ^b	21	80,8	32	74,4	0.80	[0.54 to 1.19]	0.238 ^e
total relative risk of DBS treatment for women with essential tremor compared to men							0.52	[0.18 to 1.50]	

Illustration 1.

A) The pie charts illustrate ratios of women (left, red) and men (right, blue) who underwent DBS surgery or did not undergo DBS surgery either despite positive indication evaluation or due to negative indication evaluation.

B) The table summarizes gender ratios at referral, eligibility for DBS and DBS surgery, and the relative risk of women compared to men at each step. The p-values refer to the tests under ^c, ^d, and ^e. ^aPercentage of patients referred for evaluation. ^bPercentage of patients with positive indication. ^c Binomial test, comparison of gender ratios of prevalence data (0.5 female) and patients referred for evaluation (0.36 female). ^d Chi²-Test for gender ratio in patients with positive indication compared to patients referred for evaluation. ^e Chi²-Test for gender ratio in patients with DBS surgery compared to patients with positive indication.

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