Gender disparity and abuse in functional movement disorders: a multi-center case-control study

Journal of Neurology

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--Manuscript Draft--

Manuscript Number:	JOON-D-21-02833
Full Title:	Gender Disparity and Abuse in Functional Movement Disorders: a multi-center case-control study
Article Type:	Original Communication
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Abstract:	Background To determine gender differences in rates of sexual and physical abuse in functional movement disorders compared to controls and evaluate if the gender disparity of functional movement disorders is associated with abuse history. Methods We performed a retrospective case-control study of self-reported trauma data from 696 patients (512 women) with functional movement disorders from six clinical sites compared to 141 controls (98 women) and population data. Chi-square was used to assess gender and disorder associations; logistic regression was used to model additive effects of abuse and calculate the attributable fraction of abuse to disorder prevalence. Results Higher rates of sexual abuse were reported by women (35.3%) and men (11.5%) with functional movement disorders compared to controls (10.6% of women; 5.6% of men). History of sexual abuse increased the likelihood of functional movement disorders among women by an odds ratio of 4.57 (95% confidence interval, 2.31-9.07; $p < 0.0001$) and physical abuse by an odds ratio of 2.80 (95% confidence interval, 1.53-5.12; $p = 0.0007$). Population attributable fraction of childhood sexual abuse to functional movement disorders in women was 0.12 (0.05-0.19). No statistically significant associations were found in men, but our cohort of men was underpowered despite including multiple sites. Conclusions Our study suggests that violence against women may account for some of the gender disparity in rates of functional movement disorders. Most people with functional movement disorders do not report a history of abuse, so it remains just one among many relevant risk factors to consider.
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Author Comments:	Dear Dr. Roger A. Barker, Professor Dr. Massimo Filippi and Prof. Dr. Michael Strupp, Please find attached our manuscript entitled “Gender Disparity and Abuse in Functional Movement Disorders: a multi-center case-control study” for consideration as an Original Communication in “Journal of Neurology”. Our study explores the role of trauma in functional movement disorders and shows that violence against women accounts for some of the gender disparity in the frequency of functional movement disorders; it is an analysis of trauma and clinical data from six

	sites in three countries encompassing 696 patients with functional movement disorders, 141 controls and global population data. This manuscript adds new and important findings which are clinically relevant in the assessment of patients with functional movement disorders, especially the calculation of the attributable fraction of different forms of abuse to rates of functional movement disorders which has been hypothesized since the inception of modern neurology. The #MeToo movement has rightly raised awareness of misconduct and harassment and inspired societal change, so our study which addresses the association of violence and abuse with disorders seen frequently in neurology clinics is timely and relevant. In addition, the neurologic sequalae of abuse are increasingly relevant during this global pandemic where, tragically, domestic violence and abuse have increased at alarming rates. (A Pandemic within a Pandemic — Intimate Partner Violence during Covid-19. N Engl J Med 2020; 383:2302-2304. DOI: 10.1056/NEJMp2024046). Our previous article on this topic (Gender as a Risk Factor for Functional Movement Disorders: The Role of Sexual Abuse. Mov Disord Clin Pract. 2019 Dec 13;7(2):177-181. doi: 10.1002/mdc3.12863.) generated significant interest; despite being published in a niche, clinical practice journal it has already been cited multiple times and prompted important discussions with an accompanying Editorial and several Letters to the Editor. While a small portion of data in the present study was included in our prior paper, most of the data is new to this analysis, the analysis plan and goals are novel, the data comes from a greater diversity of sites and encompasses a much larger cohort. This has allowed novel findings with sufficient power to reach statistically significant conclusions regarding the role of different forms of abuse and calculation of a population attributable fraction of abuse to functional movement disorders, a topic that has not been explored at this scope previously. The present manuscript is not under consideration or submission elsewhere. We believe “Journal of Neurology” is the ideal journal for this manuscript given its broad audience, its past interest in functional neurological disorders and the populations included in our study. “Journal of Neurology” has been on the cutting edge of the study of functional movement disorders given the high prevalence of patients with these disorders in neurology clinics. Recent articles in your journal on functional neurological disorders including “Functional motor phenotypes: to lump or to split?” (Dec 2021) and “Management of functional neurological disorder” (July 2020) have generated great interest and we hope that our manuscript will as well. Thank you so much for considering our work, Isaiah Kletenik, MD

Gender Disparity and Abuse in Functional Movement Disorders: a multi-center case-control study

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Running Title: Gender & Abuse in Functional Movement Disorders
Word Count: Abstract: 245 words. Body: 1471 words.
Keywords: Functional movement disorder, psychogenic, sexual abuse, trauma, gender.

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Funding Sources and Conflicts of Interest: Funding for collection of data analyzed in this study comes from: the Intramural Program of the National Institute of Neurological Disorders and Stroke, Bethesda, MD USA; Chief Scientist Office, Scottish Executive, Edinburgh EH1 3DG, Scotland UK; National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College, London, UK.

The authors have no relevant conflicts of interest to report.

Abstract

Background: To determine gender differences in rates of sexual and physical abuse in functional movement disorders compared to controls and evaluate if the gender disparity of functional movement disorders is associated with abuse history.

Methods: We performed a retrospective case-control study of self-reported trauma data from 696 patients (512 women) with functional movement disorders from six clinical sites compared to 141 controls (98 women) and population data. Chi-square was used to assess gender and disorder associations; logistic regression was used to model additive effects of abuse and calculate the attributable fraction of abuse to disorder prevalence.

Results: Higher rates of sexual abuse were reported by women (35.3%) and men (11.5%) with functional movement disorders compared to controls (10.6% of women; 5.6% of men). History of sexual abuse increased the likelihood of functional movement disorders among women by an odds ratio of 4.57 (95% confidence interval, 2.31-9.07; $p < 0.0001$) and physical abuse by an odds ratio of 2.80 (95% confidence interval, 1.53-5.12; $p=0.0007$). Population attributable fraction of childhood sexual abuse to functional movement disorders in women was 0.12 (0.05-0.19). No statistically significant associations were found in men, but our cohort of men was underpowered despite including multiple sites.

Conclusions: Our study suggests that violence against women may account for some of the gender disparity in rates of functional movement disorders. Most people with functional movement disorders do not report a history of abuse, so it remains just one among many relevant risk factors to consider.

Introduction

Functional movement disorders (FMD) are frequently cared for in neurology clinics and involve abnormal movements, including tremor, dystonia, and weakness[1], where the clinician can demonstrate impaired voluntary movement in the presence of normal automatic movement.[2] Historically, FMD was considered a psychological disorder caused by the conversion of emotional and mental processes into symptoms, leading to the previous terminology of conversion disorder and psychogenic movement disorders. While recent work has begun to elucidate the disorder's underlying pathophysiology,[3] adverse experience and stressful life events remain important risk factors for FMD.[4] Given higher rates of sexual abuse against women among the general population[5] and a higher frequency of FMD among women,[3, 6-8] we hypothesize that the gender disparity of FMD is impacted by higher frequencies of abuse. In a prior analysis[9] we showed an association between sexual abuse and the gender disparity of FMD; here we expand the size and diversity of our cohort and quantify the attributable fraction of different forms of abuse to FMD.

Methods

We collected de-identified clinical data and trauma history from six FMD referral sites: National Institutes of Health (NIH), University of Louisville, University of Toronto, University of Edinburgh, National Health Service South London & Maudsley, and Portland Veterans Affairs (VA) Healthcare System. Population level estimates for childhood sexual abuse in the USA and UK were gathered from the Institute for Health

Metrics and Evaluation, which were based on a large systematic review of childhood sexual abuse prevalence[5] and weighted for analysis by country; estimates of prevalence of lifetime sexual and physical abuse were not available for a general population and were estimated from clinical controls who were recruited from general neurology and movement disorder clinics in two of the referral sites (Edinburgh and Louisville) with similar semiology to the FMD group but with symptoms judged to be related to organic disease.

Diagnosis of FMD was made by movement disorder specialists following Fahn & Williams criteria (NIH[10] and Louisville), DSM-5 criteria[11] (Edinburgh, Toronto and Portland VA), and ICD-10 code F44.4 "conversion disorder with motor symptom or deficit"[12](London). Self-reported information from trauma questionnaires (NIH, Louisville, Edinburgh, VA), clinical interviews (Toronto, Edinburgh), and chart review (London) were used to create a binary yes/no variable for lifetime and childhood history of sexual abuse and physical abuse. Scale items from a validated questionnaire (Trauma Life Events Questionnaire [NIH], Life Stressors Checklist [Louisville, Portland VA] and Childhood Trauma Questionnaire [Edinburgh]) that addressed self-report sexual and physical abuse were identified. Controls completed either the Life Stressors Checklist or Trauma Life Events Questionnaire.

Case-control analysis compared sexual and physical abuse prevalence between FMD and controls to determine the association between abuse history and FMD. Odds ratio (OR) estimates were calculated from 2x2 tables or logistic regression models. Odds ratios are

used for case-control studies because they permit reversing the conditioning, allowing assessment of the effects of abuse on FMD. Attributable fraction of exposure to sexual and physical abuse was calculated dependent on the assumption that the proportion of FMD in the population is small[3], in which case the OR is similar to the risk ratio. Therefore, exposure prevalence for other neurologic disease controls and the general population are set equal to the exposure prevalence among controls, and relative risks are approximated with the ORs from the case-control samples.

Ethical Standards: Data collection was with patient consent and approved by local institutional review boards under NIH 07-N-0190, Louisville 15.1043; Edinburgh Lothian Research Ethics Committee; NHS South London 08/H0606/71+5; Portland by VA Portland IRB; Toronto REB 21-5070 and, therefore, in accordance with the ethical standards of the 1964 Declaration of Helsinki and amendments. This secondary analysis was conducted entirely on retrospective de-identified data so was not considered human subject research and relied on those existing approvals.

Results

Our combined database comprised 696 patients (512 women) with a diagnosis of FMD. There was sufficient information reported to allow for evaluation of history of lifetime sexual abuse from 591 patients, childhood sexual abuse from 402 patients and lifetime physical abuse from 286 patients. Trauma history data from 141 controls with other neurological conditions (98 women) from the University of Louisville and University of Edinburgh was also collected. (Table 1).

Among people with FMD, 35.3% of women and 11.5% of men reported a lifetime history of sexual abuse and 25.6% of women and 10.6% of men reported a history of childhood sexual abuse; among controls, 10.6% of women and 5.6% of men reported a lifetime history of sexual abuse. Regarding lifetime history of physical abuse, 36.5% of women and 27.8% of men with FMD reported physical abuse and among controls 17.0% of women and 19.4% of men reported history of physical abuse. (Table 2.)

Among women, a history of sexual abuse increased the odds of FMD by a factor of 4.57 (95% confidence interval, 2.31-9.07; $p < 0.0001$), physical abuse increased the odds of FMD by a factor 2.80 (1.53-5.12; $p=0.0007$) while a history of sexual and physical abuse increased the odds of FMD by 7.99 (3.39-18.81; $p < 0.0001$) compared to other neurologic disease controls. Compared to controls, the attributable fraction of lifetime sexual abuse to FMD in women was 0.28 and of lifetime physical abuse in women was 0.23. Population attributable fraction (PAF) of childhood sexual abuse to FMD compared to the general population was 0.12 (95% CI; 0.05-0.19) among women. There were no statistically significant findings regarding an association between abuse and FMD in men despite the increase in sample size from our previous study.[9]

Discussion

Our large, international, multi-center case-control study including 696 patients with FMD shows that sexual abuse is reported at higher rates by women with FMD compared to men with FMD and other neurological disease controls of either gender. A history of

sexual or physical abuse increases the likelihood of FMD. Our calculations of attributable fraction suggest that sexual abuse may be responsible for 28% and physical abuse for 23% of FMD in women. The PAF of childhood sexual abuse suggest that, on a population level, about 12% of FMD prevalence in women could theoretically be eliminated if childhood abuse were eliminated.

These data suggest that some of the increased prevalence of FMD among women is related to the sequelae of abuse. There are many potential mechanisms for the possible relationship between abuse and FMD including effects on sense of agency,[13] interoception[14], central sensitization and neuroendocrine changes.[15] Gender differences also need to be considered in relation to societal differences[16] as well as potential biological differences. Childhood abuse has been associated with a number of other negative health outcomes including cardiovascular events, diabetes, chronic pain and obesity, with more pronounced effects in women as well.[17]

The present study was prompted in part by a desire to have larger sample sizes particularly of men given the need for data to inform this critical topic. This is the largest analysis of the relationship between FMD and abuse, but the cohort of men remained underpowered which limit our ability to reach specific conclusions.

Beyond the typical limitations inherent in any retrospective analysis, there are important limitations to our study related primarily to 1) differences between clinical sites and 2)

the ongoing challenge to accurately assess and measure trauma in the clinic and the general population.

While the diversity of our six clinical sites in three countries is a strength, it also proves a liability as some sites used different diagnostic criteria, trauma assessment tools, questionnaires for assessing symptoms, and demographic categories to report employment, race and ethnicity, all of which led to some variability. Recruitment of participants from specialized referral centers may have increased psychiatric comorbidities in our cohort. We were able to include a much larger cohort by allowing slightly different diagnostic criteria for functional movement disorders and different trauma assessment methods in different sites. While there were slightly higher numbers of cases of abuse reported by standardized questionnaire compared to interview and chart review, there was not a significant difference in reported rates of abuse by gender regardless of assessment method employed. (See Table 2.) Regarding possible concerns of selection bias due to a higher percentage of women than men in our study, the gender disparity in our cohort was similar to that described in populations of FMD from other referral centers[18, 19] and among the general population[7].

Population-level data regarding lifetime sexual and physical abuse that is comparable to trauma data gathered at our clinical sites was challenging to identify. This limited our calculation of PAF to childhood sexual abuse where comparable, country level, population data was available.[5] Despite the wide availability and clinical use of a number of validated measures to assess trauma, we were surprised at the paucity of

normative, population-level data employing these same questionnaires separate from a specific clinical population. In addition, while a cursory search can identify a number of different large, national, often governmentally run studies to assess population-level prevalence of trauma,[20] a more careful review illustrates that these studies use broader definitions of abuse than those in clinical use and very different assessment methods, making them incomparable to our data.[21]

Other limitations related to the study of trauma include the lack of data on other types of abuse such as childhood physical abuse, emotional abuse and neglect, and the fact that all the data relied on retrospective recall. Recent studies show that retrospective report of abuse identifies different populations than those where abuse is identified prospectively from childhood.[22] Disorders typically associated with abuse are less common in prospectively identified cohorts.[23] The challenges of retrospective report of abuse is not unique to our study and is a problem inherent to all studies of trauma. Two important recent studies demonstrated surprising discrepancies between the characteristics of cohorts with prospectively reported abuse (e.g. documented by courts and social services) who generally had much less psychiatric comorbidity than expected and retrospective reported abuse, as seen in our studies.[22, 23]

While some of the data here (NIH and Louisville) was analyzed in our previous study[9], most of the data is new to this analysis. We were able to confirm findings previously limited to populations from the Eastern United States in populations from the Western United States, Canada, England and Scotland and reach new conclusions about the role of

different forms of abuse. No additional covariates were used in our regression as our cohort was small, symptom duration data from different sites was incomparable, and gender was the variable of interest so should not be regressed. Gender was treated as a simple binary in data collection which unfortunately did not allow for analysis of the impact of transgender or gender non-binary identity.

Our present study adds relevant new data about the association of different forms of abuse with the gender disparity of functional movement disorders, a topic which has been the subject of anecdotal speculation for much of the history of neurology. In summary, our study shows higher rates of sexual and physical abuse among women with FMD compared to controls, and suggests that violence against women may account for some of the gender disparity in the frequency of FMD.

Acknowledgments:

The authors thank the many patients who participated in this study and the clinical and research staff at NINDS, University of Louisville, University of Edinburgh, University of Toronto, NHS South London & Southeast Scotland and the Portland VA. The authors also thank the Global Burden of Disease 2019 Collaborators, IHME, for sharing data used to calculate population attributable factor and to Alan Carson for advice.

Data availability: A summary of data not shared in this article can be reviewed pending individual organizational approval.

Funding Sources and Conflicts of Interest: Funding for collection of data analyzed in this study comes from: the Intramural Program of the National Institute of Neurological Disorders and Stroke, Bethesda, MD USA; Chief Scientist Office, Scottish Executive, Edinburgh EH1 3DG, Scotland UK; National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College, London, UK.

The authors have no relevant conflicts of interest to report.

Appendix 1: Author Contributions

Name	Location	Contribution
Isaiah Kletenik, MD	Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Project conception, organization and execution. Statistical analysis design and data acquisition. Manuscript drafting and editing.
Samantha K. Holden, MD, MS	University of Colorado School of Medicine, Aurora, CO	Project organization and execution. Statistical analysis design. Manuscript review and critique.
Stefan H. Sillau, PhD	University of Colorado School of Medicine, Aurora, CO	Statistical analysis design and execution. Manuscript editing.
Nicola O'Connell, PhD	Trinity College Dublin, Dublin, Ireland	Major role in the acquisition of data and revision of the manuscript.
Lindsey MacGillivray, MD, PhD	University Health Network and the University of Toronto, Toronto, Canada	Major role in the acquisition of data and revision of the manuscript.
Joel Mack, MD	Portland VA Medical Center/OHSU, Portland, OR	Major role in the acquisition of data and revision of the manuscript.
Beatrix Haddock	University of Washington, Seattle WA	Major role in the acquisition of data and interpretation.
M. Ashworth Dirac, MD, PhD	University of Washington, Seattle WA	Major role in the acquisition of data and interpretation.
Anthony S. David, MD	University College London, London, UK	Major role in the acquisition of data and interpretation.
Timothy R. Nicholson, MD	King's College London, London, UK	Major role in the acquisition of data and interpretation.
Sanaz N. Attaripour Isfahani, MD	University of California-Irvine School of Medicine, Irvine, CA	Major role in the acquisition of data and interpretation.

Carine W. Maurer, MD, PhD	Stony Brook University School of Medicine, Stony Brook, NY	Major role in the acquisition of data and interpretation.
Sarah C. Lidstone, MD, PhD	Toronto Western Hospital and the University of Toronto, Toronto, Canada	Major role in the acquisition of data and interpretation.
Mark Hallett, MD	National Institutes of Health, Bethesda, MD	Project conception, major role in data acquisition, interpretation of data and manuscript revision.
Kathrin LaFaver, MD	Northwestern University Feinberg School of Medicine, Chicago, IL	Project conception, major role in data acquisition, interpretation of data and manuscript revision.
Brian D. Berman, MD, MS	Virginia Commonwealth University, Richmond, VA	Project conception, organization and execution. Statistical analysis design. Manuscript revision.
Jon Stone, MB ChB, FRCP, PhD	University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK	Project conception, organization and execution. Major role in data acquisition. Statistical analysis design. Manuscript critique and revision.

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Characteristic	Functional Movement Disorder (FMD) Group (n=696)	Other Neurological Condition Controls (n=141)
Mean age – yr (SD)	44.94 (13.8)	46.3 (14.6)
Women – no. (%)	512 (73.6)	98 (69.5)
Race/ethnicity		
White – no. (%)	428 (61.5)	117 (83.0)
Black – no. (%)	69 (9.9)	13 (9.2)
Hispanic or Latino – no. (%)	4 (0.6)	0
Other – no. (%)	198 (28.4)	11 (7.8)
Marital status		
Married, partnered or co-habiting	331 (47.6)	79 (56.0)
Symptoms/semiology		
Weakness	292 (42.5)	46 (32.6)
Tremor or parkinsonism	191 (27.4)	29 (20.6)
Dystonia, myoclonus, spasm or ataxia	64 (9.2)	19 (13.5)
Gait abnormality	128 (18.4)	
Pain	172 (24.7)	21 (14.9)
Other/Unknown	64 (9.2)	26 (18.4)
Symptom/disorder duration – yr (SD)	2.67 (3.3)	8.44 (7.6)
Employment Status		
Employed/Student – no. (%)	188 (27.0)	71 (50.4)
Unemployed/Retired/Disability– no. (%)	391 (56.2)	60 (42.6)
Other or unknown – no. (%)	117 (16.8)	10 (7.1)

Table 1. Characteristics of functional movement disorder patients and other neurologic condition controls

	Women	Men
	Functional movement disorder patients	
History of lifetime sexual abuse - no./respondents (%)	153/434 (35.3%)	18/157 (11.5%)
By trauma assessment tool*		
Trauma questionnaire – no./respondents (%)	84/211 (39.8%)	8/76 (10.5%)
Interview or chart review – no./respondents (%)	83/308 (26.9%)	10/103 (9.7%)
History of childhood sexual abuse - no./respondents (%)	79/308 (25.6%)	10/94 (10.6%)
By trauma assessment tool*		
Trauma questionnaire – no./respondents (%)	34/120 (28.3%)	3/32 (9.4%)
Interview or chart review – no./respondents (%)	57/273 (20.8%)	7/84 (8.3%)
History of lifetime physical abuse - no./respondents (%)	78/214 (36.5%)	20/72 (27.8%)
By trauma assessment tool*		
Trauma questionnaire – no./respondents (%)	50/175 (28.6%)	16/55 (29.1%)
Interview or chart review – no./respondents (%)	36/124 (29.0%)	5/39 (12.8%)
	Controls (other neurologic condition patients)	
History of lifetime sexual abuse - no./respondents (%)	10/94 (10.6%)	2/36 (5.6%)
History of lifetime physical abuse - no./respondents (%)	16/94 (17.0%)	7/36 (19.4%)
	Population data 2019 (per IHME)[1]	
Prevalence of childhood sexual abuse used to calculate population attributable fraction		
UK - mean % (95% CI)	12.6% (9.7%-15.5%)	10.1% (7.2%-13.1%)
USA - mean % (95% CI)	15.8% (11.9%-21.2%)	6.2% (4.4%-8.4%)
UK and USA weighted average - mean % (95% CI)	15.3% (11.4%-19.2%)	6.9% (5.1%-8.6%)
Likelihood of FMD by exposure (compared to other neurological condition controls)		
Lifetime sexual abuse - OR (95% CI; P value)	4.57 (2.31-9.07; p<0.0001)	2.20 (0.49-20.41; p=0.38)
Lifetime physical abuse - OR (95% CI; P value)	2.80 (1.53-5.12; p=0.0007)	1.59 (0.56-4.99; p=0.35)
Sexual or physical abuse - OR (95% CI; P value)	3.93 (2.26-6.84; p<0.0001)	1.59 (0.56-4.99; p=0.35)
Sexual and physical abuse - OR (95% CI; P value)	7.99 (3.39-18.81; p<0.0001)	2.23 (0.44-11.21; p=0.30)
Attributable fraction of FMD to exposure (compared to neurological condition controls)		
Sexual abuse - attributable fraction	0.28	0.06
Physical abuse - attributable fraction	0.23	0.10
Sexual or physical abuse - attributable fraction	0.40	0.10
Population attributable fraction of childhood sexual abuse to FMD - attributable fraction (95% CI)	0.12 (0.05-0.19)	0.04 (0-0.11)

Table 2: Results of trauma assessment by gender for patients with FMD and controls and association between functional movement disorders and history/type of abuse. *Some participants completed both questionnaires and interviews. A history of abuse was considered present if reported in either assessment method. Differences between assessment methods is endemic to the study of trauma.

(CI = confidence interval, FMD = functional movement disorder, OR = odds ratio, UK = United Kingdom, USA = United States of America)

[1]Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare. (Accessed Dec 24, 2020)