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The Relationship between Handedness and Risk of Multiple Sclerosis

Hannah Gardener, ScD[1,*], **Kassandra L. Munger, MSc**[1], **Tanuja Chitnis, MD**[2], **Donna Spiegelman, ScD**[1,3], and **Alberto Ascherio, MD, DrPH**[1,4,5]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[2]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3]Department of Biostatistics, Harvard School of Public Health, Boston, MA

[4]Department of Nutrition, Harvard School of Public Health, Boston, MA

[5]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Left-handedness has been studied as a marker for *in utero* exposure to sex steroid hormones, and an increased risk of autoimmune and immune disorders among left-handed individuals has been suggested.

Objective—This study examines the relationship between hand preference and risk of multiple sclerosis (MS), a presumed autoimmune disorder of unknown etiology.

Methods—The study population comprised participants in the Nurses' Health Study, an ongoing prospective cohort study of 121,701 female nurses in the United States with follow-up from 1976–2002. The nurses were asked to report their natural hand preference (right, left, ambidextrous, forced to change).

Results—During follow-up 210 incident MS cases were confirmed. A 62 percent increased risk of MS was observed among women who were naturally left-handed as compared to those who were naturally right-handed (95 percent CI: 1.04–2.53).

Conclusions—This study suggests a modest increase in risk of MS among left-handed women. Further investigation of this relationship is suggested in other populations including both males and females. While the current results suggest that prenatal exposure to sex hormones may play a role in MS risk, direct examination of the relationship between in-utero hormone exposure and hand preference is necessary before any conclusions can be drawn.

Keywords

Multiple Sclerosis; Cohort Study; Functional Laterality; Hormones; Epidemiology; Risk Factors; Prenatal exposure delayed effects

*Corresponding author: Hannah Gardener. Department of Neurology, University of Miami Miller School of Medicine. PO Box 016960 (M-877), Miami, FL 33101, Ph. 305-243-9286, Fax. 305-243-7081, hgardener@med.miami.edu.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system with pathological features consistent with an autoimmune mechanism, but unknown etiology. Twin studies and migration studies have provided support for a role of genetics as well as an important role of environmental exposures in MS risk [1,2]. In addition, a potential influence of maternal factors is suggested by the higher recurrence risk for maternal half-siblings than paternal half-siblings [3].

Handedness has been examined as a marker for in-utero sex steroid hormone exposure [4–6]. A controversial hypothesis by Geschwind, Behan, and Galaburda proposed that elevated exposure or sensitivity to testosterone *in utero* affects cerebral laterality, increasing the risk of anomalous dominance (abnormal distribution of functions across the hemispheres) and left-handed preference [7–11]. A potential relationship between sex hormones and risk of MS is suggested by their role in the modulation of immune response [8,12]. In particular, high testosterone exposure during the prenatal period is believed to impair development of the thymus glad which plays an important role in immune system function [7,8,10].

A relationship between left-handedness and immune and autoimmune disorders has been reported in some but not all studies [5–7,13–15]. A meta-analysis in 1994 indicated a modest yet statistically significant 13 percent increase in risk for any immune disorder among left-handed individuals [13]. When disorders were considered individually, significant associations were found for ulcerative colitis/Crohn's disease, asthma, and allergies [13]. The only study that has specifically examined MS risk in relation to handedness did not find an association, but the power of this study, including only 118 cases, was low [9].

Therefore, we examined whether being left-handed was associated with risk of MS among participants in a large ongoing prospective cohort of female nurses in the US, the Nurses' Health Study (NHS) [16].

MATERIALS AND METHODS

Sample

The Nurses' Health Study—The NHS cohort began in 1976 with 121,701 female nurses age 30 to 55 who were identified by the nursing boards of 11 US states. Following the initial questionnaire in 1976, these nurses receive a follow-up questionnaire every two years to collect information on demographic factors, lifestyle factors (e.g. smoking, hormone use, activity, menopausal status) and diet, in addition to newly diagnosed disease outcomes. A participation rate of approximately 90 percent has been achieved over time. Although we have documented MS also among 116,680 participants in the Nurses' Health Study II, information on handedness is not available from this cohort.

Outcome assessment

Cases were defined as physician-confirmed MS. Ascertainment has been described in detail previously [17,18]. Briefly, nurses were asked to report major illnesses throughout follow-up and were asked specifically about lifetime diagnosis of MS in 1992. Diagnosis within the past two years was asked on subsequent questionnaires. Permission to review medical records was requested of everyone who reported a diagnosis. Confirmation of self-reported diagnosis was achieved by asking the treating neurologist to complete a questionnaire on the diagnostic certainty (definite, probable, possible, not MS), clinical history (date of diagnosis and date of symptom onset), clinical signs, and laboratory tests. In the rare instances when a neurologist was not involved in diagnosis or failed to respond, the individual's internist was contacted for confirmation of diagnosis. A case was confirmed if the diagnosis was considered definite or

probable by the treating neurologist/internist or by medical record review. The validity of this approach has been reported before [19]. Individuals with self-reported MS prior to baseline were excluded because their diagnoses had not been confirmed (N=134).

Handedness assessment

The 1992 NHS questionnaire included the following question: "Which of the following describes you? (mark all that apply)", with the following possible responses: naturally right-handed, naturally left-handed, forced to change, ambidextrous. Anyone who reported being ambidextrous or both naturally left- and right-handed was coded as ambidextrous. Of the remaining, those who reported being left-handed, including those who *also* reported being forced to change, were coded as left-handed. Likewise, anyone who reported being naturally right-handed, excluding those who were ambidextrous, were coded as right-handed. And those who reported being forced to change handedness but did not report being either naturally left- or right-handed or ambidextrous were coded as "forced to change with unknown innate handedness".

Of the study participants, 104,091 (86%) responded to the 1992 questionnaire, and of those 88,791 (85%) answered the handedness question. In total, 6.0% of individuals were coded as left-handed, 87.9% were coded as right-handed, 5.3% were coded as ambidextrous, and 0.8% were coded as forced to change hands with unknown innate preference. The percentage of left-handed individuals in this cohort is consistent with similar US study populations [4,20,21].

The primary comparison of interest was left-handed individuals vs. right-handed individuals. Several sensitivity analyses were also conducted, including as left-handed also women forced to change handedness with unknown innate preference, or those who reported being both naturally left-handed and ambidextrous

Covariates

The following factors that have been found to be associated with risk of MS were included as covariates in multivariate analyses: latitude at birth (north, middle, south) [19], sibship size [22], socioeconomic status (SES) [23], cigarette smoking [17,24,25], and vitamin D intake [18]. Cohort members were asked to identify their state of birth in 1992. The continental United States was divided into north (states generally north of 41–42 degrees north latitude), south (states lying south of 37 degrees south latitude), and middle tiers. Nurses were asked to report their number of full biological siblings (including deceased) on the 1996 questionnaire.

High SES has been shown to be related to an increased risk of MS [22]. Paternal occupation at age 16 was assessed in 1976 and was used as a proxy for early life SES. Father's occupation was dichotomized as professional/managerial: yes vs. no.

Birthweight was also considered as a covariate. The 1992 NHS questionnaire asked the nurses to report their birthweight within the following categories: <5, 5–5.5, 5.5–7, 7–8.5, 8.5–10, 10 + lbs.

Data analysis

Each cohort member contributed person-time of follow-up from the return date of the baseline questionnaire (1976) to the date of diagnosis, death, or end of follow-up (June, 2002), whichever came first. Cox proportional hazards models were used to estimate the rate ratios (RR) and 95 percent confidence intervals (CI) for the relationship between hand preference and MS stratified by age in months and calendar year, with and without adjustment for latitude at birth (north, middle, south), sibship size (0, 1, 2+), SES (paternal occupation: professional or managerial yes/no), pack-years of cigarette smoking in adulthood (never, <10 packs/year,

10–24 packs/year, 25+ packs/year), and vitamin D (cumulative average quintile of intake). An additional multivariate model also controlled for birthweight (<5.5, 5.5–8.5, 8.5–10, 10+ lbs). The missing indicator method was used when controlling for covariates with missing data [26].

All participants have given their informed consent, and this research was approved by the Institutional Review Board at Brigham and Women's Hospital in Boston, Massachusetts.

RESULTS

Table 1 shows the characteristics of the study population overall and among those who self-classified as left-handed and right-handed. As shown, there were no marked differences between those who were left-handed and right-handed in terms of the suggested MS risk factors. The full sample included 210 incident cases of MS accrued through 2002 with information on hand preference. Table 2 shows the rate ratios and 95 percent confidence intervals for the univariate age-adjusted and multivariate-adjusted analyses of the relationship between handedness and risk of MS.

A 65 percent increased risk of MS was observed among women who were naturally left-handed as compared to those who were right-handed (95% CI: 1.05–2.57, p=0.03). After controlling for the other suggested risk factors for MS the effect estimate only changed slightly and remained significant (RR=1.62, 95% CI: 1.04–2.53, p=0.03). When the analysis was further adjusted for birthweight, the effect estimate and 95% CI remained exactly the same. The risk of MS among ambidextrous women was not significantly different from that of right-handed women (multivariate RR=0.99, 95% CI: 0.52–1.87, p=0.97).

In secondary analyses, the classification of left-handedness was altered to examine whether the findings were sensitive to various adjustments. When the 747 individuals who reported being forced to change handedness with unreported natural hand-preference were also included in the left-handed group, under the assumption that they were more likely to have been naturally left-handed, the increased risk of MS persisted (multivariate RR vs. right-handed=1.64, 95% CI 1.08–2.50). However, when the individuals who self-reported as naturally left-handed *and* ambidextrous but *not* right-handed (N=991) were combined with the left-handed group, the elevated risk was attenuated yet remained marginally significant (multivariate RR=1.50, 95% CI: 0.97–2.30, p=0.07).

Results were similar after excluding 303 women who reported being left-handed and having been forced to change handedness (multivariate-adjusted RR=1.66, 95% CI: 1.05–2.62).

DISCUSSION

In this large prospective cohort study with 210 incident cases of MS, a significant 62 percent elevation in risk was observed among women who identified themselves as naturally left-handed as compared to those who were naturally right-handed. The results remained stable regardless of whether those who were forced to change handedness were excluded from the left-handed group, as well as when we included those who reported being forced to change handedness with unreported natural hand preference. The observed association appeared to be specific to those who were left-handed, as the effect estimate was attenuated towards the null when all non-right-handed individuals (left-handed, ambidextrous, and forced to change) were combined and compared to those who were exclusively right-handed.

The mechanisms underlying the increased MS risk in left-handed women are uncertain. Although a relationship between steroid hormone exposure *in utero* and handedness has been suggested, the causes of hand preference remain unknown. While some studies have indicated

a positive relationship between left-handed preference and surrogate markers for prenatal steroid hormone exposure (e.g. low 2D:4D digit ratio [27,28], diethylstilbestrol exposure [29], congenital adrenal hyperplasia [30]), other studies have not [31–34]. In addition, even if we are to assume that left-handedness is a marker for *in utero* exposure to sex steroid hormones, the specific hormones that may influence disease risk are not known. Although a potential role of *in utero* testosterone exposure in immune system development has been suggested [7,8, 10] estradiol may also be implicated as maternal testosterone is aromatized to estradiol in the placenta and in fetal neural tissues [8,35]. Among left-handed individuals, a modestly increased risk of breast cancer [4,36,37], inflammatory bowel disease [6,14], colorectal cancer mortality [38], and cerebrovascular mortality [38] has also been reported. However, the relation between handedness and these and other disorders has not been consistent, as several studies have also failed to find a significant association [20,39,40].

Other potential mechanisms that may underlie the association between hand preference and risk of MS include prenatal complications and genetic factors, and the combination of these. The genetic contribution to both MS risk and handedness is believed to be substantial [1,41], and it is possible that there may be overlapping and associated genetic risk factors. Most notably, the results of a small recent study offered preliminary evidence that the HLA alleles associated with an increased risk of MS may be more common among left-handed individuals [42]. This same study also demonstrated elevated levels of circulating autoantibodies, total T-cells, and T-helper cells in left-handed as compared to right-handed individuals.

Prenatal stress and distress has been observed as a risk factor for non-right-handedness in several studies [43–45]. Likewise, prenatal stress may influence the risk of MS and other immune-related disorders as it is believed to modulate the hypothalamic-pituitary-adrenal axis, increasing adenocorticotropic hormone, cortico-tropic releasing hormone, and cortisol, which may result in impaired immune function and thymic atrophy [46,47].

The primary strengths of this study are the use of a large cohort with thorough case ascertainment, confirmation of self-reported diagnosis, and comprehensive data on other established risk factors for MS. Despite these important strengths, limitations are noted. Most importantly, handedness was simply classified as left-handed, right-handed, or ambidextrous based on the response to a single question. Although multi-item questionnaires and performance tools have been developed to measure laterality on a range of tasks including writing, brushing teeth, throwing a ball, and using utensils, and can incorporate measurements of both preference and performance [48,49], a level of agreement greater than 95% has been reported between a single global question of hand preference and a 10-item performance battery given to 1223 individuals [50]. The positive predictive value among self-reported left-handers was 70% in males and 68% in females [50]. Therefore, misclassification is likely to be modest and, if present, would most likely be nondifferential, biasing estimates towards the null.

Because this study included only women, we do not know whether the relation between handedness and MS also applies to men. Differential effects of testosterone on lateralization in males and females have been reported [31]. It has also been hypothesized that although excess prenatal testosterone exposure may increase the risk of autoimmune disorders, testosterone exposure after puberty may actually be protective, resulting in the observed decrease in risk for MS and other autoimmune diseases among males [6]. Due to the varying influences of sex hormones across the lifespan replication of the current study in males is suggested.

While the current study provides support for a potential relationship between left hand preference and risk of MS, further examination is recommended in other study populations.

More importantly, direct examination of the relationship between prenatal hormone exposure and risk of MS is needed.

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TABLE 1

Characteristics of the Study Population, Overall and Stratified by Handedness

Variable	Study Population	Right-handed	Left-handed
Mean ± standard deviation			
Age at baseline (years)	42.8 ± 7.2	42.9 ± 7.2	41.0 ± 6.9
Cigarette smoking (pack years)	9.9 ± 14.1	9.9 ± 14.1	9.9 ± 13.5
Vitamin D consumption IU	316.6 ± 266.6	315.5 ± 267.1	313.1 ± 243.2
N (%)			
Race/ethnicity			
Hispanic	783 (0.9)	699 (0.9)	24 (0.5)
Black	1032 (1.2)	938 (1.2)	57 (1.1)
Asian	624 (0.7)	559 (0.7)	18 (0.3)
Scandinavian	6405 (7.2)	5649 (7.2)	352 (6.6)
Other Caucasian	76513 (86.2)	67197 (86.2)	4666 (88.0)
Other race/ethnicity	3405 (3.8)	2948 (3.8)	186 (3.5)
Latitude tier at birth			
North	35611 (34.7)	31040 (41.8)	2356 (45.9)
Middle	42270 (41.2)	37293 (50.2)	2410 (46.9)
South	6753 (6.6)	5966 (8.0)	369 (7.2)
Paternal occupation			
Managerial or professional	22754 (28.3)	19753 (28.0)	1537 (33.1)
Other	57518 (71.7)	50770 (72.0)	3284 (70.8)
Number of siblings			
0	8784 (10.9)	7547 (10.7)	593 (12.3)
1	21147 (26.3)	18400 (26.0)	1361 (28.3)
2	50461 (62.8)	44715 (63.3)	2860 (59.3)
Birthweight (lbs.)			
<5.5	7778 (11.0)	6603 (10.7)	569 (12.9)
5.5–8.5	53543 (75.7)	46945 (75.9)	3300 (74.8)
8.5–10	7784 (11.0)	6818 (11.0)	461 (10.4)
10+	1670 (2.4)	1491 (2.4)	83 (1.9)

TABLE 2

Hand preference and the risk of MS in the Nurses' Health Study

Variable	# Participants	# Cases	Age-adjusted Rate Ratio and 95% CI†		Multivariate-adjusted* Rate Ratio and 95% CI†	
Handedness						
Naturally left-handed	5,303	22	1.65	(1.05–2.57)	1.62	(1.04–2.53)
Ambidextrous	4.720	10	0.99	(0.52–1.87)	0.99	(0.52–1.87)
Forced to change‡	749	3	1.80	(0.57–5.65)	1.79	(0.57–5.65)
Naturally right-handed	77,990	175	1.0 (ref)		1.0 (ref)	

*Controlling for age in months, latitude tier at birth, SES (paternal occupation at age 16), sibship size, pack-years of cigarette smoking, quintile of vitamin D intake

†Confidence interval (CI)

‡With unreported innate hand preference