Sexual habits before multiple sclerosis: a National case control study

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The trigging off agent for multiple sclerosis (MS) is despite intensive epidemiological and biomedical research still unknown. The disease is typically diagnosed in reproductive age and recent findings have suggested that MS could be a sexually transmitted disease.
Aim To assess the influence of different sexual practices in young age on the risk of developing MS, and specifically to explore the possible impact of oral sex and oral sperm exposure on this risk.
Design National case–control study.
Methods *Inclusion*: Danish women with a first time MS discharge diagnosis from a neurological department at most 40 years old during the period 1998–2005, and an age and geographically matched control group. The response rate to our postal questionnaires was 75% for cases and 61% for controls. A total of 604/619 completed case/control questionnaires were included in the analysis. Data underwent logistic regression analysis.
Results We found no difference between women with and without MS for years of schooling, oral herpes infections, genital herpes, blood transfusions, age at sexual debut, age at coital debut, number of sexual partners before and after age 20 years, anal sex, condyloma attack or chlamydia infections. Family disposition with an affected father, mother or sibling, increased the risk of MS 9.1, 6.9 and 4.1 times, respectively. A total of 68% of cases and of 72% of controls had oral sex sometimes or often before their 20th year. Among women entertaining oral sex, 53%, respectively, 54% had experienced oral sperm exposure. Also oral sex after 20 years was similar in women with and without MS.
Conclusion Neither oral sex in early reproductive age, oral sperm exposure, oral sex after 20 years, sexual debut, nor number of sexual partners had any association to the risk of later developing MS. This study does not support the hypothesis that MS is a sexually transmitted or acquired disease. Multiple Sclerosis 2008; 14: 67–72. http://msj.sagepub.com

Key words: coital debut; multiple sclerosis; oral sex; risk factors; sexual habits

Introduction

Two-thirds of people with multiple sclerosis (MS) are women. Typically the disease has clinical debut in reproductive age, and the age of diagnosis has decreased over decades, undoubtedly partly due to better diagnostic equipment, but also coinciding with a decrease in the coital debut.

The disease was unknown on the Faroe Islands before Second World War, during which British soldiers were placed on the Islands. Already during the war and also in the decades after the war, several new cases of MS appeared, mainly among young women [1].

The geographical distribution of MS demonstrates high prevalence areas in the temporal zones above and below 40° of latitude, including the USA, Canada, Northern Europe, New Zealand and Tasmania. In these countries, a relatively free sexual practice has been prevailing for decades.

These epidemiological findings were summarized by Hawkes, who suggested that MS in genetically susceptible individuals could be a sexually transmitted disease [2].

If sexual practice has an influence on the risk of developing MS, it could be due to transmission of a micro-organism or to some kind of antigen exposure. Researchers have sought intensively for an infectious agent without any convincing breakthrough.

MS was for decades one of very few diseases more prevailing in 'better off' women, a difference,

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which since has vanished. At the same time oral sexual practice has (at least in Denmark) been more prevalent in women with long education than in women with short education [3].

Finally, some [4] although not all [5] migration studies suggest that the trigging off agent for MS most often is achieved in young age, several years before the first clinical symptoms appear.

Therefore, we found it worth searching for a possibly sexually related antigen, which might initiate an immunological process leading ultimately to anti-myelin antibodies and clinical MS.

Hypothesis

Genetically predisposed women are during their early sexual practice exposed to one or more antigens, which initiate an immunological process that years later manifest itself in clinical MS.

Specifically sperm antigens presented orally may induce such a process, because the pharynx is immunologically quite active.

Aim

The aim of this study is to assess in detail the sexual practice in early reproductive age among women who later develop MS and to compare it with the same sexual practices among healthy women of the same age. Specifically to investigate whether early oral sexual practice and oral sperm exposure was more prevalent among women with MS, than among women of same ages in general.

Materials and methods

Since 1977 discharge diagnoses from all hospitalised patients have been centrally recorded in the National Register of Patients (NRP). In order to include only new cases of MS, we identified all women with an MS diagnosis during the period 1977–1997 (ICD-8: 340 and ICD-10: DG359) in the NRP and excluded them from the study population in case of new referrals to hospital for MS during the study period. Then, all women in Denmark with a first discharge diagnosis of MS from any of the 16 neurological departments during the period 1 January 1998 through 31 October 2005, and who were at most 40 years old at the time of diagnosis were identified and included. Thereafter an age- and geographically matched but otherwise randomly selected control group of women without MS was established from Statistics of Denmark, which includes all Danish citizens.

Design: Postal questionnaire based case–control study

During the study period 1998–2005, we identified 1177 women in the NRP fulfilling the inclusion criteria. Eleven were dead since diagnosis leaving 1166 women alive per November 2005. These women with MS were matched with 1166 women born on the same date, with the same current postal zip-code and with no address protection. Five of the controls, however, had moved from the indicated address, leaving 1161 control women with an available address. Of the identified 1166 cases, 210 had address protection, and six were not at the address, leaving 950 available women with MS.

Permission to contact each patient was obtained from the head of each of the existing 16 neurological departments. The study was approved by the data protection agency (Datatilsynet no. 2003-41-3267).

Thus, 950 case and 1161 control questionnaires were sent out by April–May 2006. One reminder was sent to non-responders within five weeks after the primary application.

Cases not confirming their diagnosis and controls indicating to have MS or another serious neurological disease were excluded.

The issues included in the questionnaires are given in Tables 1 and 2. Cases were asked to confirm their diagnosis, age at first symptom related to MS and age at which they were told the diagnosis. Women were asked to refuse participation in preference of giving incomplete or untrue answers to questions.

Statistical analysis

Logistic regression analyses were performed in SAS (proc logistic). We chose to adjust all estimates for family disposition, which is a well-known risk factor for MS, for age in 10-years age groups, and for postal code in 13 administrative regions. A paired analysis including complete pairs was also performed.

Although the women indicated date of an eventual blood transfusion thereby making it possible to exclude all case transfusions after diagnosis, we could not conduct a similar restriction among controls. Consequently we made two estimates; one including all transfusions among cases and controls, and another one restricted to transfusions before age 20 years.

Results

After one reminder 716 (75.4%) case and 709 (61.1%) control questionnaires were returned.

Table 1 Exposures among cases (+MS) and controls (−MS)

	+MS *n* (%)	−MS *n* (%)	OR (95% CI)
Included	604 (100)	619 (100)	
Age			
15–24 years	32 (5.3)	29 (4.7)	–
25–34 years	217 (35.9)	226 (36.5)	–
35+ years	355 (58.8)	364 (58.8)	–
Family disposition			
Mother MS	16 (2.7)	2 (0.3)	6.9 (1.5–30.8)
Farther MS	11 (1.8)	1 (0.2)	9.1 (1.1–72.1)
Sibling MS	20 (3.3)	5 (0.9)	4.1 (1.5–11.1)
Years of schooling			
7–8 years	10 (1.7)	6 (1.0)	1.3 (0.4–3.7)
9–10 years	155 (26.0)	161 (26.1)	1.0 (0.7–1.2)
11–12 years	430 (72.3)	450 (72.9)	Reference
Smoking			
Never	209 (34.7)	277 (44.9)	Reference
Previous	174 (28.9)	178 (28.8)	1.3 (1.0–1.7)
1–10 cigarettes per day	83 (13.8)	60 (9.7)	1.9 (1.3–2.7)
11–20 cigarettes per day	97 (16.1)	81 (13.1)	1.6 (1.1–2.3)
>20 cigarettes per day	39 (6.5)	21 (3.4)	2.5 (1.4–4.4)
Blood transfusion			
Blood transfusion	12 (2.0)	5 (0.8)	2.5 (0.8–7.1)
Blood transfusion before 20 years	4 (0.7)	1 (0.2)	5.2 (0.6–48.5)
Infections			
Oral herpes	182 (30.1)	186 (30.0)	1.0 (0.8–1.3)
Genital herpes	45 (7.5)	41 (6.6)	1.0 (0.7–1.8)
Condyloma	77 (12.7)	86 (13.9)	1.1 (0.6–1.2)
Chlamydia infection	82 (13.6)	96 (15.5)	0.8 (0.6–1.2)

OR's for different exposures adjusted for family disposition.

Among cases 80 declined to participate and 32 denied having (definite) MS. The majority of these 32 women had opticus neuritis, and a definite diagnosis of MS, therefore not necessarily present. Among the controls three indicated to have MS and 87 refused to participate, leaving 604 cases, 619 controls and 358 complete matched case–control pairs available for analysis. The adjustment for age and postal code did not influence the odds ratios (OR's), and they were hence removed from the model. The results from the paired analysis (not reported) were essentially identical, but with wider confidence intervals due to the reduction in number.

Ideally the effect of Sibling with MS should be estimated stratified according to number of siblings, but this was not possible due to the size of the data. Instead we confirmed that the distribution of number of siblings was identical among cases and controls.

The distribution of actual age among the included cases and controls is given in Table 1 and is identical. Among cases the average time from first symptom until the woman were told the diagnosis was 3.3 years, and from first symptom until the diagnosis appeared in the register was 4.9 years.

More cases than controls had family members with MS (Table 1). MS in one of the parents increased the risk of MS 7–9 times, whereas siblings with MS increased the risk four times. No association was found with length of schooling.

More women with MS were current smokers than women without MS, and the OR in Table 1 indicate that women are more likely to have MS the more they smoke ($P_{\text{trend}} < 0.001$).

More women with than without MS had received blood transfusions; OR 2.5 (95% CI 0.8–7.1). Restriction to transfusions before 20 years implied an OR of 5.2 (95% CI 0.6–48.5). Although elevated, none of these estimates were significantly above unity.

Oral herpes, genital herpes, condyloma and chlamydia infections were equally distributed among cases and controls.

Sexual experiences

Slightly more women with MS (24.1%) than without (18.9%) had sexual debut at 14 years or younger, a tendency which was less clear for the coital debut (Table 2).

Table 2 Sexual practice in women with and without multiple sclerosis (MS)

Sexual experiences	+ MS *n* (%)	− MS *n* (%)	OR (95% CI)
Included	604 (100)	619 (100)	
Sexual debut			
≤14 years	143 (24.1)	114 (18.9)	1.4 (1.0–1.9)
15–16 years	241 (40.6)	263 (43.5)	Reference
17+ years	209 (35.2)	242 (39.1)	1.0 (0.8–1.3)
Coital debut			
≤15 years	215 (36.4)	196 (32.2)	1.3 (1.0–1.8)
16–17 years	212 (35.9)	253 (41.5)	Reference
18+ years	163 (27.6)	160 (26.3)	1.3 (1.0–1.7)
Sexual partners <20 years			
0–1	182 (30.9)	178 (29.1)	Reference
2–4	240 (40.7)	270 (44.1)	0.8 (0.6–1.1)
5+	167 (28.4)	164 (26.8)	1.0 (0.8–1.4)
Sexual partners ≥20 years			
0–2	240 (41.2)	227 (37.5)	Reference
3–6	194 (33.3)	184 (30.4)	1.0 (0.8–1.3)
7+	144 (25.6)	194 (32.1)	0.8 (0.6–1.0)
Anal sex			
Never	353 (59.2)	353 (58.2)	Reference
Sometimes	237 (39.8)	248 (40.9)	0.9 (0.7–1.2)
Often	6 (1.0)	6 (1.0)	1.0 (0.4–3.3)
Oral sex before 20 years			
Never	189 (31.6)	173 (28.5)	Reference
Sometimes	319 (53.3)	338 (55.6)	0.9 (0.7–1.1)
Often	90 (15.1)	97 (16.0)	0.8 (0.6–1.2)
Oral sex after 20 years			
Never	107 (18.4)	99 (16.5)	Reference
Sometimes	293 (50.4)	321 (53.4)	0.8 (0.6–1.2)
Often	181 (31.2)	181 (30.1)	0.9 (0.6–2.4)
Oral sperm exposure			
Never	270 (59.2)	275 (46.0)	Reference
Sometimes	263 (45.1)	274 (45.8)	1.0 (0.8–1.2)
Often	50 (8.2)	49 (8.2)	1.1 (0.7–1.6)

OR adjusted for family disposition.

Among cases, the number of sexual partners before age 20 years ranged from 0 to 100, with one partner as the most prevalent number (21%). Moreover 72% had less than five partners, 18% 5–9 partners, 6% 10–14 partners, 2.5% 15–19 partners and 1.5% more than 19 partners. Among controls, the distribution was 73, 18, 4, 2 and 2%, respectively. The OR's were correspondingly close to one (Table 2).

Total number of sexual partners was equally distributed among cases and controls (data not shown).

Anal sex was prevailing among 41% of cases and 42% of controls, and 1% experienced this sexual practice often.

Oral sex before 20 years is given in Table 2 and Figure 1. This practice was more frequent among the younger than among the older birth cohorts, and equally frequent among cases and controls with OR just below unity.

Oral sex after 20 years was also more frequent among the younger than the older birth cohorts (data not shown), but again equally prevalent among cases and controls.

Finally, among women performing oral sex, 53.3% of cases and 53.0% of controls, had experienced oral sperm exposure, again with an OR for MS close to one.

Discussion

Non-sexually related variables

MS in mothers increased the risk of MS 6.9 times (1.5–30.8), MS in fathers 9.1 times (1.1–71.1) and in siblings 4.1 times (1.5–11.1). These figures are comparable with the results from a recent historical Danish cohort study, which found the risk of MS in women to be increased 3.2, 7.6 and 4.9 times, respectively, with the same family dispositions [6].

We found that women with MS were currently more likely both to smoke and to smoke more than women without MS, but have no information about smoking habits before the disease onset. It is not unlikely that smoking in some cases could be a consequence of the disease rather than a cause of it. Being a possible risk indicator (rather than a confounder), was the reason why we did not adjust for smoking in the multivariate analysis. Other studies have found smoking to be more prevalent in women with MS before the disease debut [7, 8]. In Norway, a 1.8 (1.1–2.9) rate ratio of smoking in MS patients was demonstrated [8] and a meta-analysis found OR's for MS in smokers of 1.3–1.5 [7], estimates comparable with ours.

No significant difference in blood transfusions between women with and without MS was demonstrated, although there was a tendency for the OR's to be elevated. Due to the small numbers we cannot rule out even a strong association. A Scottish case–control study found that 4.7% of women with MS had received a blood transfusion before disease onset, the same proportion as in the control group, corresponding to an OR of 1.0 (0.3–3.3) [9].

No difference was found concerning either oral herpes, genital herpes, condyloma or chlamydia infections. Although some previous studies have demonstrated a positive association between

Fig. 1	15-24	25-34	35+	Total	15-24	25-34	35+	Total
Sometimes	51.6	59.5	49.4	53.2				
Often	32.3	16.7	12.5	15.1				
Sometimes					50.0	54.5	56.7	55.6
Often					37.5	21.0	11.4	16.0

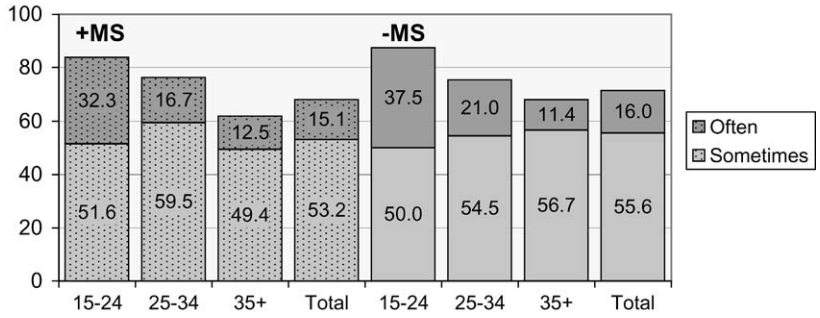

Figure 1 Oral sex (%) before age 20 years among women who later develop MS (n = 598) and among women without MS (n = 608) stratified according to actual age.

chlamydia infections and MS, others did not, and our study does not support an association [10].

Sexual practice

Although the sexual debut was a little earlier among women with MS than among controls the corresponding OR was only borderline significant 1.4 (1.0–1.9), $P = 0.04$, and for coital debut, we found the same OR for late coital debut as for early. The former result could thus be a statistical coincidence.

As emigration studies suggest the trigging off agent to be acquired between 15 and 20 years of age, the women were asked about number of partners before and after 20 years, but we found exactly the same distribution among cases as among controls. Anal sex was also equally distributed.

The core variables according to our hypothesis were oral sex before 20 years and oral sperm exposure among women practicing oral sex. Oral sex was fairly frequent among both cases and controls, and more frequent in younger than older birth cohorts, but no difference was found according to MS. The frequency of oral sexual practice in Denmark is comparable with the practice in the United Kingdom [11]. Likewise about half of women with and without MS entertaining oral sex had experienced oral sperm exposure, about 8% frequently so.

Our findings of no difference in oral sexual practice and oral sperm exposure between women with MS and controls (all before age 20) contradict both our own hypothesis, and also the hypothesis recently suggested by Hawkes that women with MS could have a differential sexual practice before disease debut [7]. Finally, our findings do not confirm that a higher prevalence of some virus antibodies in women with MS as compared to controls is acquired as a consequence of a differential sexual practice.

The relatively high response rate taking the intimate questions into account, and the fact that cases and controls reported rather identical practices suggests some validity of our retrospective data, although some recall bias, of course, cannot be ruled out.

Selection bias in responding women could still be in effect. For example, women with a particular sexual practice as young could be less willing to participate than women without such a practice. However, it is not very likely that such a possible selection bias according to previous sexual habits would be differentially in effect between cases and controls. Thus, selection bias (if any) is not likely to invalidate the core results of the effect of sexual practice on MS although a minor influence cannot be ruled out.

Conclusion

Our results do not support speculations that MS is a sexually transmitted disease, nor that the cause of the disease is associated somehow with women's sexual practice.

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Conflicts of interest: We have none to declare.

Contributors: Øjvind Lidegaard (guarantor) planned, designed and conducted the study, planned the analysis, interpreted the results and wrote the manuscript.

Anne Louise Svendsen made the statistical analysis of data, interpreted the results and revised the manuscript.

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