Sex as a determinant of relapse incidence and progressive course of multiple sclerosis

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The aim of this work was to evaluate sex differences in the incidence of multiple sclerosis relapses; assess the relationship between sex and primary progressive disease course; and compare effects of age and disease duration on relapse incidence. Annualized relapse rates were calculated using the MSBase registry. Patients with incomplete data or <1 year of follow-up were excluded. Patients with primary progressive multiple sclerosis were only included in the sex ratio analysis. Relapse incidences over 40 years of multiple sclerosis or 70 years of age were compared between females and males with Andersen-Gill and Tweedie models. Female-to-male ratios stratified by annual relapse count were evaluated across disease duration and patient age and compared between relapse-onset and primary progressive multiple sclerosis. The study cohort consisted of 11570 eligible patients with relapse-onset and 881 patients with primary progressive multiple sclerosis. Among the relapse-onset patients (82552 patient-years), 48362 relapses were recorded. Relapse frequency was 17.7% higher in females compared with males. Within the initial 5 years, the female-to-male ratio increased from 2.3:1 to 3.3:1 in patients with 0 versus ≥4 relapses per year, respectively. The magnitude of this sex effect increased at longer disease duration and older age (P < 10⁻¹²). However, the female-to-male ratio in patients with relapse-onset multiple sclerosis and zero relapses in any given year was double that of the patients with primary progressive multiple sclerosis. Patient age was a more important determinant of decline in relapse incidence than disease duration (P < 10⁻¹²). Females are predisposed to higher relapse activity than males. However, this difference does not explain the markedly lower female-to-male sex ratio in primary progressive multiple sclerosis. Decline in relapse activity over time is more closely related to patient age than disease duration.

Keywords: multiple sclerosis; sex; risk factors; MSBase; prediction

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale

Introduction

Episodic exacerbations are defining phenomena for relapsing-remitting multiple sclerosis and can be directly associated with residual disability (Hirst et al., 2008). Even though the evidence remains inconclusive (Hutchinson, 2011), an association between high relapse rate in the first 2 years after disease onset and later accumulation of irreversible neurological impairment has been suggested (Scalfari et al., 2010; Kalincik et al., 2012). There have been only a limited number of studies delineating predictors of relapse activity, with only one study examining a large retrospective cohort (Held et al., 2005; Mowry et al., 2009; Tremlett et al., 2009). These studies suggested several predisposing factors, such as sex, age, ethnicity and time from multiple sclerosis onset. However, their outcomes, in particular those related to effect of sex on relapse incidence, have often been discordant.

There is a marked predominance of females among patients with multiple sclerosis with relapse-onset course. The sex ratios are 3:1 in relapsing-remitting and 3:2 in secondary progressive multiple sclerosis, but in primary progressive multiple sclerosis
both sexes are represented equally (Runmarker and Andersen, 1993; Confavreux and Vukusic, 2006b; Alonso and Hernan, 2008; Koch-Henriksen and Sorensen, 2010).

We have used MSBase, a longitudinal, international, observational registry of patients with multiple sclerosis, to evaluate the effect of sex on relapse activity up to 40 years of multiple sclerosis duration or 70 years of age. We have directly compared the impacts of age and disease duration on relapse frequency in a predominantly contemporary multiple sclerosis cohort. We have also tested the hypothesis that the female-to-male ratio increases gradually with relapse activity and that the primary progressive disease represents a non-relapsing extreme along this continuum.

Patients and methods

Ethics statement

The MSBase registry (Butzkueven et al., 2006) was approved by the Melbourne Health Human Research Ethics Committee, and by the local ethics committees in all participating centres (or exemptions granted, according to applicable local laws and regulations). If required, written informed consent was obtained from enrolled patients, in accordance with the Declaration of Helsinki.

Patients and follow-up

Longitudinal clinical data from 18 885 patients from 55 multiple sclerosis centres in 25 countries were extracted from the MSBase registry in February 2012. Data recorded between the years 1951 and 2012 were used. The majority of the patients were enrolled in the MSBase registry in the year 2000 or later (75%), with 20% enrolled in years 1990–2000, 3% enrolled in years 1980–1990 and 0.9% of patients enrolled before 1980. The participating centres contributed between two and 1239 cases fulfilling the study inclusion criteria, with recorded annualized relapse rate (ARR) in relapse-onset multiple sclerosis, ranging from 0.1 to 2 and female-to-male ratio ranging from 0.9:1 to 4.4:1. The country-specific ranges were 2–3282 for the number of eligible patients, 0.2–2 for ARR in relapse-onset multiple sclerosis and 0.9–4.4:1 for female-to-male ratio. Patients with incomplete data (i.e. not fulfilling the minimal data set requirement, see below) or <1 year of recorded clinical follow-up were excluded. The minimal data set consisted of patient date of birth, sex, multiple sclerosis centre, dates of multiple sclerosis onset and clinical follow-up, disease course and disability (at inclusion and censoring), start and end dates of disease modifying treatment exposure and list of clinical relapses (including date of onset and relapse treatment status). Patients with relapse-onset multiple sclerosis (i.e. clinically isolated syndrome, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis or relapsing-progressive multiple sclerosis) were included in all analyses. Patients with primary progressive multiple sclerosis were only included in the analyses comparing female-to-male ratios between relapse-onset and primary progressive multiple sclerosis (see below). Finally, patients with relapse-onset multiple sclerosis and at least 10 years of recorded follow-up, and all patients with primary progressive multiple sclerosis were included in a subgroup analysis of female-to-male ratios stratified by relapse activity.

The analysed data were recorded as part of routine clinical practice. The usual data entry practice at most centres was real time or near-real time data entry in relation to clinical visits. The MSBase protocol stipulates minimum annual updates of the minimum data set, but patients with less frequent visits were not excluded from the analyses. Data entry portal was either the iMed patient record system or the MSBase online data entry system.

A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 h, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse (Schumacher et al., 1965). Date of onset was recorded for each clinical relapse. Formal scoring of relapse-associated disability was not required upon relapse entry. Disability was scored by accredited scorers (online Neurostatus certification was required at each centre) using the Expanded Disability Status Scale (EDSS). Duration of multiple sclerosis was calculated as the time from the patient-reported first clinical manifestation of the disease and relapsing/progressive onset of disease was assessed by participating neurologists. Primary progressive multiple sclerosis was defined as the disease with at least 1 year of progression from its first clinical manifestation and with zero recorded relapses. In each patient, unadjusted ARRs stratified by disease duration or patient age were calculated by including the initial relapse and the number of relapses for years for which clinical data were available. Censoring was defined to occur on the day of the last recorded clinical visit. Information about patient death and its relation to multiple sclerosis was not collected in the database.

To assure quality of the analysed data, only information from centres contributing at least 10 active records (i.e. cases with regular annual updates of clinical information) to the MSBase registry was used, as stipulated in the study protocol. A date of onset was required for all recorded events, including relapses, visits (with or without EDSS), changes in disease course and changes in treatment. Before the analysis the recorded data were verified using a series of automated procedures to identify any invalid or inconsistent entries.

Statistical analysis

Statistical analyses were carried out using Statistica 10 (Statsoft) and R (http://www.R-project.org). All hypotheses were tested at the two-tailed 0.05 level of statistical significance, after applying the Benjamini-Hochberg correction for multiple hypothesis testing. Two proportional hazards models with robust variance estimation (Andersen-Gill) and Efron approximation method, adjusted either for patient age or disease duration, were used to estimate cumulative hazard of relapses for each sex (cumulative hazard function is interpreted as the most probable count of repeatable events that would be expected for each individual by defined time, if the exposure to the risk started at Time 0). The outcome variable was time to relapse with multiple entries per patient allowed. The models were adjusted for pregnancy (proportion of time pregnant from the study enrolment or the previous recorded event to the next event/censoring, treated as time-varying variable) and immunomodulatory therapy, when any change in therapy with or without relapse was treated as a relapse (response) or non-relapse (censoring) event. The immunomodulatory agents considered were interferon β-1a 22 μg or 44 μg subcutaneous injection thrice weekly, interferon β-1a 30 μg intramuscular injection once weekly, interferon β-1b 250 μg subcutaneous injection every other day, glatiramer acetate 20 mg subcutaneous injection daily, natalizumab 300 mg intravenous infusion once monthly, fingolimod 0.5 mg orally once daily, dimethyl fumarate 240 mg orally twice or thrice daily, cladribine 10 mg orally once monthly for 2 months, and teriflunomide 7 mg or 14 mg orally once daily.

Two Tweedie models with index parameters 1.5 (i.e. compound Poisson-Gamma models) adjusted for sex, pregnancy and treatment
Results

Of the 18,885 patients in the MSBase registry (17,021 with relapse-onset multiple sclerosis, 1018 with primary progressive multiple sclerosis and 846 with the information about disease course missing), data from 11,570 relapse-onset and 881 (7%) primary progressive multiple sclerosis and 846 with the information about disease course were adjusted for age at multiple sclerosis onset, disease course, pregnancy (proportion of time in any completed year) and immunomodulatory therapy (proportion of time in any completed year).

MSBase registry, Feb 2012
n = 18,885

Excluded
- diagnosis other than MS or CIS, n = 983
- data incomplete, n = 3458
- relapses not recorded, n = 1993

CIS, RRMS, SPMS, RPMS
n = 11,570

PPMS
n = 881

Figure 1 CONSORT flowchart of patient disposition. CIS = clinically isolated syndrome; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RPMS = relapsing-progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Numbers of patients with relapse-onset multiple sclerosis included in the analysis stratified by disease duration and age are shown in Fig. 2A and B. In 82,552 patient-years of observation recorded among the relapse-onset patients, 48,362 relapses were recorded. Of these, 42% were concurrent with clinical visits. Figure 2C and D shows unadjusted ARR with respect to disease duration and age. Within the first year of multiple sclerosis, the relapse rate was relatively high (1.1 relapse/year), which was a result of its inflation by inclusion of the first recorded clinical event. Thereafter, the ARR gradually decreased from 0.5 to 2 years to 0.1 at 40 years. Also, a marked decline in ARR with age was seen, when ARR decreased from 0.9 at the age of 17 to 0.1 at the age of 70. Importantly, females tended to show higher unadjusted ARR during the initial 18 years of multiple sclerosis duration and between 27 and 49 years of age. These differences were further enhanced by adjusting the ARR for multiple sclerosis duration/patient age, pregnancy and treatment (Fig. 2E and F). Females showed consistently higher adjusted ARR [on average by 17.7%, 95% confidence interval (CI) = 15.1–20.3%] than males throughout the disease duration and at every chronological age (risk ratio = 1.08, 95% CI = 1.06–1.11, \( P < 10^{-16} \)).
Table 1 Characteristics of the studied population with relapsing multiple sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Cohen’s d</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>8295</td>
<td>3275</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion, years*</td>
<td>37.0 ± 11.2</td>
<td>37.2 ± 11.2</td>
<td>0.02</td>
</tr>
<tr>
<td>At censoring, years*</td>
<td>44.1 ± 11.7</td>
<td>44.4 ± 11.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<tr>
<td>Caucasian, n (%)</td>
<td>5102 (62)</td>
<td>1992 (61)</td>
<td></td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>123 (2)</td>
<td>64 (2)</td>
<td></td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>269 (3)</td>
<td>7 (2)</td>
<td></td>
</tr>
<tr>
<td>African, n (%)</td>
<td>44 (0.5)</td>
<td>12 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>227 (3)</td>
<td>117 (4)</td>
<td></td>
</tr>
<tr>
<td>Not specified, n (%)</td>
<td>2530 (31)</td>
<td>1023 (31)</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, years*</td>
<td>5.8 (3–9.5)</td>
<td>5.9 (3.1–9.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion, years*</td>
<td>2.9 (0.4–9.3)</td>
<td>2.5 (0.4–8.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>At censoring, years*</td>
<td>11.3 (6.2–18.1)</td>
<td>10.8 (6.1–17.5)</td>
<td>0.04</td>
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<tr>
<td>Relapses, n</td>
<td>35 725</td>
<td>12 637</td>
<td></td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS, n (%)</td>
<td>2981 (36)</td>
<td>1240 (38)</td>
<td></td>
</tr>
<tr>
<td>RRMS, n (%)</td>
<td>4731 (57)</td>
<td>1721 (53)</td>
<td></td>
</tr>
<tr>
<td>SPMS, n (%)</td>
<td>412 (5)</td>
<td>182 (6)</td>
<td></td>
</tr>
<tr>
<td>RPMS, n (%)</td>
<td>171 (2)</td>
<td>132 (4)</td>
<td></td>
</tr>
<tr>
<td>At censoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS, n (%)</td>
<td>1521 (18)</td>
<td>669 (20)</td>
<td></td>
</tr>
<tr>
<td>RRMS, n (%)</td>
<td>5488 (66)</td>
<td>1984 (61)</td>
<td></td>
</tr>
<tr>
<td>SPMS, n (%)</td>
<td>1115 (13)</td>
<td>490 (15)</td>
<td></td>
</tr>
<tr>
<td>RPMS, n (%)</td>
<td>171 (2)</td>
<td>132 (4)</td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion, EDSS*</td>
<td>2.1 (1.5–3.5)</td>
<td>2.5 (1.5–4.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>At censoring, EDSS*</td>
<td>2.5 (1.5–5)</td>
<td>3 (1.5–6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Received DMDs, n (%)</td>
<td>3956 (48)</td>
<td>1617 (49)</td>
<td></td>
</tr>
</tbody>
</table>

*Median (interquartile range); otherwise mean ± SD are shown.
CIS = clinically isolated syndrome; DMDs = disease-modifying drugs;

Table 2 Characteristics of the group with primary progressive multiple sclerosis

<table>
<thead>
<tr>
<th></th>
<th>881 (55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (females, %)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>At inclusion, years*</td>
<td>49.4 ± 11.0</td>
</tr>
<tr>
<td>At censoring, years*</td>
<td>53.9 ± 11.2</td>
</tr>
<tr>
<td>Follow-up duration, years*</td>
<td>2.6 (0.5–7.0)</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
</tr>
<tr>
<td>At inclusion, years*</td>
<td>5.8 (2.6–11.4)</td>
</tr>
<tr>
<td>At censoring, years*</td>
<td>10.8 (6.2–17.5)</td>
</tr>
<tr>
<td>Disability</td>
<td></td>
</tr>
<tr>
<td>At inclusion, EDSS*</td>
<td>5 (3.5–6.5)</td>
</tr>
<tr>
<td>At censoring, EDSS*</td>
<td>6 (4–7)</td>
</tr>
<tr>
<td>Received DMDs, n (%)</td>
<td>190 (22)</td>
</tr>
</tbody>
</table>

*Median (interquartile range); otherwise mean ± SD are shown.
DMDs = disease-modifying drugs.

Discussion

In a large, mostly contemporary population of patients followed in the MSBase registry, females have a higher relapse rate than males throughout the course of multiple sclerosis. The sex ratio in primary progressive multiple sclerosis is markedly different from that in relapse-onset multiple sclerosis and is discrete from the gradient determined by the relapse frequency. We have confirmed a strong inverse relationship between relapse frequency and either disease duration or age. Of these two collinear factors, chronological age is more closely related to the relapse incidence.

In the only available retrospective cohort study of predictors of relapse incidence, Tremlett et al. (2008) showed that females had 14.3% higher ARR than males. We have confirmed this observation by demonstrating a similar sex effect of 17.7%. Compared to Tremlett et al. (2008) our recorded ARR was approximately double (0.59 versus 0.23, range 0.1–0.9 versus 0.08–0.29 depending on patient age, respectively), despite the presumed higher proportion of patients receiving disease-modifying treatment. This could be attributed to the inclusion of the first clinical episodes in the relapse count in our study and the near real-time data entry in the MSBase registry, which could have partially ameliorated the expected under-reporting of the relapses recorded retrospectively.

Other literature reporting incidence of relapses in multiple sclerosis only describes relatively short follow-up periods. A series of studies identified young age (West et al., 2006; Mowry et al., 2009) and short disease duration (Held et al., 2005) but not sex as being independently predictive of higher relapse incidence during 1-year observational periods. The discrepancies between these studies and our present analysis could be explained by the differences in statistical power determined by the size of the cohorts and the analytical designs. With respect to the low effect-to-noise ratio, the other studies were most probably
underpowered to assess the effect of sex, as they only evaluated information derived from 105–727 patient-years.

We have seen that females are over-represented among patients with high relapse frequency, in particular later in the disease course and at older chronological age. This suggests that the attenuation of clinically apparent episodic inflammatory activity is delayed in females compared with males. In addition, higher mortality from multiple sclerosis-unrelated causes in males could potentially contribute to this phenomenon; however, the lack of detailed mortality data in the MSBase registry prevented the evaluation of this potential confounder. Importantly, the follow-up duration, which did not differ between the enrolled females and males, did not support sex-dependent study drop-out.

The difference in relapse risk associated with sex probably only plays a small role in explaining the reported differences in sex ratios between patients with relapse- and progressive-onset multiple sclerosis (Confavreux and Vukusic, 2006b; Kampman et al., 2013). As males show less frequent relapse activity throughout the disease course and lifespan, one could argue that their disease is

Figure 2  Incidence of relapses in females and males with relapse-onset disease course, stratified by disease duration and chronological age. Patient disposition (A and B) is only shown for patients with complete respective observational years. Annualized relapse rate unadjusted for other potential confounders (C and D) and adjusted for age (E) or disease duration (F), treatment and pregnancy using Tweedie models are shown (E and F). Each patient contributed a single ARR at censoring. P-values for effects of sex, disease duration and age are shown (Tweedie regression). Cumulative hazard functions for relapses in female and male subpopulations, adjusted for age (G) or disease duration (H), treatment and pregnancy using Andersen-Gill models (G and H), with each patient contributing multiple time-to-relapse entries. All results are stratified by disease duration (A, C, E, G) and patient age (B, D, F, H). Error bars and dashed lines show 95% CIs.
more likely to be classified as progressive. However, the sex ratio among patients with primary progressive multiple sclerosis is still distinct from that among patients with relapse-onset multiple sclerosis and no relapse activity observed during the study period (Figs 3 and 4). Thus, we rejected the hypothesis that sex difference in propensity to relapses is fully accountable for the different sex ratios between relapse- and progressive-onset multiple sclerosis. From this perspective, primary progressive multiple sclerosis cannot be viewed as a mere extreme along the continuum of relapse activity in relapsing-remitting multiple sclerosis.

It is of further interest how the relapse incidence interacts with progression of disability. It has been previously suggested that early relapses may be associated with the development of permanent disability (Lublin et al., 2003; Hirst et al., 2008; Tremlett et al., 2009; Leray et al., 2010; Scalfari et al., 2010; Kalincik et al., 2012). There is also evidence both supporting (Confavreux et al., 2003; Confavreux and Vukusic, 2006a; Leray et al., 2010) and opposing (Trojano et al., 1995; Amato et al., 1999; Simone et al., 2002) the common view of faster disability accrual in males. Clearly, the associations between sex and disability warrant further clarification in observational studies, with the perspective of elucidating the complex interactions between sex, relapses and disability.

Multiple sclerosis duration and patient age are two largely collinear variables, whose effect on disease outcomes is difficult to differentiate. Whether the multiple sclerosis relapse activity is determined predominantly by the time from multiple sclerosis onset, or by patient age, is not known. Whereas some works identified disease duration as an independent predictor of relapse incidence (Held et al., 2005), others reported independent effect of age (Inusah et al., 2010). Tremlett et al. (2008) described a faster decline in ARR with disease duration in patients with later multiple sclerosis onset. It is possible that this interaction effect was in fact driven by the effect of age, but a direct statistical comparison between the effects of age and disease duration was not reported. In our present study, we have directly compared these two collinear variables using a multivariate Tweedie model. Our analysis indicates a dominant role of chronological age (~2% per year decrease in ARR) over that of disease duration (~1% per year decrease in ARR). This observation is complementary to
previous works, which demonstrated that age at onset of progressive phase is remarkably similar between patients with primary progressive versus relapsing-remitting/secondary progressive disease course, suggesting that presence and duration of relapsing phase is, to a great extent, defined by patient age (Confavreux and Vukusic, 2006b; Leray et al., 2010; Scaffari et al., 2011).

Our analysis was carried out in a large international observational cohort: the MSBase registry. The studied population was representative of patient populations managed at large academic multiple sclerosis centres, which might limit generalization of our observations to a prevalent population. Inclusion in the MSBase might have posed a risk of recruitment bias; this was subject to the criteria for patient inclusion at the participating centres. Also, preferential data entry of patients with relapse-onset disease course at the study sites could have resulted in a relative under-representation of patients with primary progressive disease (which in our study was ~7%). Selection bias was potentially introduced by the applied inclusion criteria. However, the fact that female-to-male ratios were comparable between the included and excluded populations rendered this situation unlikely. Survival bias could potentially have been introduced in case the patients with more pronounced disability were more often lost to follow-up. This hypothetical situation might favour the sex with slower disability accrual. On the other hand, given the parallel patient disposition of both sexes with respect to disease duration and patient age, the survival bias was improbable (Fig. 2A and B). The information before year 2000 represented data transferred from other clinical databases, and constituted only a small proportion of the evaluated data. The ARR and subsequently the differences studied in our analysis could have been underestimated by the possible relapse under-reporting. The differences in relapse reporting at the participating centres, as implied by the variability in the centre-specific ARRs, could have inflated the under-reporting error. On the other hand, the fact that only 42% of the recorded relapses were concurrent with a recorded clinical visit and that EDSS validation of relapses was not required indicates that relapse over-reporting could have occurred. For all of these potential founders, we presume that their influence applied consistently across the studied population, regardless of patient sex, age or disease duration. It should be noted that our analysis contained remarkable statistical power provided by 82,552 patient-years from a longitudinal patient cohort with a mean follow-up period of 6 years. Overall, we were able to analyse ARR over 40 years of disease duration and 70 years of age.

In this study we evaluated the effect of sex on the incidence of multiple sclerosis relapses throughout the disease and lifespan and in the relapse-onset versus primary progressive course in a longitudinally followed large patient population. The outcomes help elucidate patterns of multiple sclerosis activity determined by sex and in the future might lead to our improved understanding of multiple sclerosis aetiopathogenesis.

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