A significant decrease in diagnosis of primary progressive multiple sclerosis: A cohort study

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A significant decrease in diagnosis of primary progressive multiple sclerosis: A cohort study

Helga Westerlind, Leszek Stawiarz, Katharina Fink, Jan Hillert and Ali Manouchehrinia

Abstract
Background: Several reports indicate changes to prevalence, incidence, female-to-male ratio in multiple sclerosis. Diagnostic criteria, course definitions and clinical management of the disease have also undergone change during the recent decades.
Objective: To investigate temporal trends in the diagnosis of primary progressive multiple sclerosis (PPMS) in Sweden.
Methods: Through the Swedish MS registry we investigated the proportion of PPMS diagnosis in birth, diagnosis and age period cohorts using Poisson regression.
Results: A total of 16,915 patients were categorised into six birth-cohorts from 1946 to 1975 and seven date-of-diagnosis-cohorts from 1980 to 2014. We observed a decrease in the uncorrected analysis of diagnosis of PPMS from 19.2% to 2.2% and an average decrease of 23% ($p < 0.001$) per 5-year birth-cohort in the adjusted analysis. An average 21% ($p < 0.001$) decrease per diagnosis-cohort was seen. In the age-specific diagnosis period cohorts the same decreasing trend of PPMS diagnosis was observed in almost all groups.
Conclusion: The diagnosis of PPMS has significantly decreased in Sweden specifically after introduction of disease-modifying treatments. Such decrease can have severe impacts on the future research on PPMS. Our data also suggest that the current trend to emphasise presence or absence of inflammatory activity is already reflected in clinical practice.

Keywords: Multiple sclerosis, chronic progressive, prevalence, incidence

Introduction
Typically around 10%–15% of the newly diagnosed multiple sclerosis (MS) patients are assigned a course of primary progressive multiple sclerosis (PPMS). PPMS is characterised by an insidious onset and gradual but steady progression of neurological disability in the absence of relapses.1,2 Compared with the more common MS course, relapsing remitting multiple sclerosis (RRMS), the clinical features of PPMS differ in several aspects.3 As a result, PPMS has often been recognised as a discrete diagnostic entity of MS enticing considerable research interest as a potentially separate disease entity. However, when PPMS is compared with secondary progressive multiple sclerosis (SPMS) (following RRMS) the sharply defined clinical features appear less distinctive. In fact, few epidemiologic, genetic or pathological differences have been established between PPMS and SPMS.4,5 Accordingly, the 2013 revisions of MS clinical course by Lublin et al.2 propose a modified description of both types of progressive MS.

Several epidemiologic reports indicate significant changes in the past decades of the incidence and prevalence of MS,6 in the proportion of females7–10 and clinical characteristics.11–13 In addition, the diagnostic criteria, clinical management (particularly introduction of disease-modifying treatments (DMTs)) and definitions of clinical course have seen several major alterations; the effects of these on the diagnosis of PPMS have not yet been examined. Here, we investigate the temporal trend in the diagnosis of PPMS in Sweden using data from the national Swedish multiple sclerosis registry (SMSreg).
Materials and methods

SMSreg

The SMSreg was officially started in 2001 as a national quality registry. It was partly built on pre-existing local databases to which patients had been recruited in the preceding decades.\textsuperscript{14} To date the SMSreg contains clinical data on about 17,000 MS patients (80\% of the prevalent cases in Sweden) including diagnostics, disease course, disability and treatment. The four MS phenotypes in SMSreg are assigned by neurologists and include RRMS, SPMS, PPMS and progressive relapsing multiple sclerosis (PRMS). The 16,915 patients who were in the registry in September 2015 were included in this study.

Statistical analysis

In the investigation of a temporal trend in the diagnosis of PPMS, we carried out three separate analyses. In the first analysis, patients were divided into birth-cohorts as previously described\textsuperscript{10–16} and grouped into PPMS and relapsing onset multiple sclerosis (ROMS). Those with the uncommon PRMS course were dropped from further analyses. In the analyses of birth-cohorts, the dataset was truncated to patients born after 1945 but before 1976 in order to avoid the survival bias among the oldest cohorts of patients previously reported by us\textsuperscript{15} and to try to ensure that most of the patients have received their diagnosis. In the second analysis, patients were grouped into seven diagnosis-cohorts based on the date of diagnosis from 1980 to 2014 with no age restriction. For each birth- and diagnosis-cohort group, the crude diagnosis rate of PPMS per 1000 person-year of follow-up was calculated. Poisson regression models controlling for age (in 5-year age bands), sex, time to diagnosis from disease onset (diagnosis delay) and age of onset were used to investigate the trend in the diagnosis of PPMS. As individuals in the younger cohorts might not yet be diagnosed, we also performed a sensitivity analysis by excluding the two youngest birth-cohorts.

Our third analysis approach was the use of age period cohort (APC) models to investigate whether any trend in rates can be seen in specified age groups (age-specific trend). In our APC model, the rate of PPMS diagnosis was approximated as a function of age (at diagnosis) combined with a function of period (date of diagnosis) and a function of cohort (year of birth) using natural spline functions.\textsuperscript{17,18}

Additional sensitivity analyses were performed to evaluate the influence of missing data on the results. In these analyses, patients with missing phenotype and PRMS patients (here referred to as uncategorised patients) were compared with ROMS and PPMS patients across series of variables including mean age of onset, diagnosis age, diagnosis delay, first recorded expanded disability status scale (EDSS) score recorded within a year from diagnosis and sex ratio. Statistical analyses were performed using Stata (StataCorp. 2009. \textit{Stata Statistical Software: Release 11}; StataCorp LP, College Station, TX, USA). The study was approved by the Regional Ethics Review Board (EPN) at Karolinska Institutet.

Results

Out of 16,915 patients with MS (McDonald and/or Poser criteria) we excluded 54 due to missing date of birth and 1147 with missing disease course. The mean age of onset was 33.5 (standard deviation (SD): 10.9) years and mean age at the last clinic visit was 49.7 (SD: 13.4) years. In total, 58.5\% had RRMS, 30.7\% had SPMS, 1.4\% had PRMS and 9.3\% were classified as PPMS. Mean age at the onset in PPMS was 43.6 (SD: 10.3) years and in ROMS was 32.4 (SD: 10.9) years. In the analyses of trends, 2564 patients with missing date of diagnosis and 227 PRMS patients were excluded. The characteristics of included patients are presented in Table 1.

DMTs exposure

Starting from 1995, 195 PPMS patients were exposed to first-line DMTs. The median duration of exposure to first-line DMTs was 41 (interquartile range (IQR): 16–87) months. Patients started on first-line DMTs were significantly younger at onset compared with untreated patients (40.6 vs 44.6; \(p<0.001\)). Median duration of exposure to second-line DMTs was 13 (IQR: 6–24) months in 128 patients. There was no significant difference between age at the onset of treated and untreated patients with second-line DMTs. A total of 32 patients were exposed to both first- and second-line DMTs.

Diagnosis of PPMS in the 1945–1975 birth-cohorts

In total, 8692 patients born during 1946–1975 and with full data were included in the analysis of birth-cohorts. During the 1946–1975 period, 752 (8.6\%) patients were diagnosed with PPMS with the overall crude diagnosis rate of 2.14 (95\% confidence interval (CI): 1.99–2.29) per 1000 person-year. The proportion of PPMS patients declined from 19.2\% to 2.2\% (see Table 1 for full results). In absolute number, while 213 PPMS patients were diagnosed during the 1946–1950 birth-cohort, only 32 had PPMS in the 1971–1975
### Table 1. Demographic and clinical characteristics of included patients.

<table>
<thead>
<tr>
<th>Birth-cohort</th>
<th>Total with known phenotype (% female)</th>
<th>Diagnosed per onset phenotype</th>
<th>Diagnosed per disease phenotype</th>
<th>Age at onset (age at diagnosis) (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary progressive (%)</td>
<td>Relapsing onset (%)</td>
<td>PP (% women) RR (% women) SP (% women)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relapsing onset (%)</td>
<td>Uncategorised (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>213 (19.2)</td>
<td>895 (79.4)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>1946–1950</td>
<td>1108 (68.5)</td>
<td>213 (19.2)</td>
<td>895 (79.4)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>1951–1955</td>
<td>1326 (70.6)</td>
<td>180 (13.5)</td>
<td>1147 (85.2)</td>
<td>18 (1.3)</td>
</tr>
<tr>
<td>1956–1960</td>
<td>1466 (71.7)</td>
<td>140 (9.5)</td>
<td>1326 (89)</td>
<td>24 (1.6)</td>
</tr>
<tr>
<td>1961–1965</td>
<td>1640 (72.2)</td>
<td>113 (6.9)</td>
<td>1527 (91.7)</td>
<td>24 (1.4)</td>
</tr>
<tr>
<td>1966–1970</td>
<td>1552 (70.5)</td>
<td>74 (4.7)</td>
<td>1478 (93.12)</td>
<td>34 (2.1)</td>
</tr>
<tr>
<td>1971–1975</td>
<td>1463 (69.7)</td>
<td>32 (2.2)</td>
<td>1431 (96.6)</td>
<td>18 (1.2)</td>
</tr>
<tr>
<td>Diagnosis-cohort</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1980–1984</td>
<td>400 (71.5%)</td>
<td>50 (12.4)</td>
<td>350 (87)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>1985–1989</td>
<td>595 (72.2%)</td>
<td>68 (11.2)</td>
<td>527 (87.1)</td>
<td>10 (1.6)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>964 (72.1%)</td>
<td>120 (12.3)</td>
<td>844 (86.9)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>1734 (72%)</td>
<td>178 (10.1)</td>
<td>1556 (88.5)</td>
<td>23 (1.3)</td>
</tr>
<tr>
<td>2000–2004</td>
<td>2584 (71.6%)</td>
<td>220 (8.3)</td>
<td>2365 (90)</td>
<td>42 (1.6)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>2805 (69.5%)</td>
<td>245 (8.6)</td>
<td>2560 (90)</td>
<td>37 (1.3)</td>
</tr>
<tr>
<td>2010–2014</td>
<td>3066 (68.1%)</td>
<td>194 (6.2)</td>
<td>2872 (91.8)</td>
<td>63 (2)</td>
</tr>
</tbody>
</table>

PP: primary progressive; RR: relapsing remitting; SP: secondary progressive.

Demographics for the birth-cohorts included in the study.
The crude diagnosis rate ranged from 3.97 (95% CI: 3.47–4.54) in the 1946–1950 birth-cohort to 1.27 (95% CI: 1.01–1.6) per 1000 person-year in the 1971–1975 cohort (Figures 1(a) and 2).

On average, a 23% (95% CI: 18–27, \( p < 0.001 \)) decrease in the diagnosis of PPMS per birth-cohort was observed while including covariates (Figure 1(b)). Excluding the youngest birth-cohorts (1966–1970 and 1971–1975) from the analysis did not considerably change the results (average incidence rate-ratio: 0.79, 95% CI: 0.74–0.86, \( p < 0.001 \); Table 2). The proportion of women in the PPMS group was 55.5% in birth-cohorts, varied between 69.2% and 75% in RRMS and ranged from 63.9% to 72.9% in SPMS (Table 1). We observed an average of 8% (95% CI: 6.3–9.6, \( p < 0.001 \)) increase per birth-cohort in the number of females born during 1946–1975. We did not observe a significant change in the sex ratio in the PPMS group (Supplementary Figure 1).

Diagnosis of PPMS during 1980–2015 diagnosis-cohorts

From the 12,333 patients included in this analysis (with no age restrictions), 1075 (8.7%) were diagnosed with PPMS with an overall crude diagnosis rate per 1000 person-year of 2.25 (95% CI: 2.12–2.39). The diagnosis rate significantly decreased from 3.59 (95% CI: 2.72–4.74) in the 1980–1984 cohort to 1.6 (95% CI: 1.39–1.84) in the 2010–2014 cohort with an average 21% (95% CI: 18–24, \( p < 0.001 \)) decrease per diagnosis-cohort when controlling for all the founders (Table 2).
The estimated diagnosis rate from the APC model decreased from 3.31 (95% CI: 3.16–3.46) in the 1980–1984 diagnosis-cohort to 1.65 (95% CI: 1.55–1.75) in the 2010–2014 diagnosis-cohort. The age-specific trends in rates of PPMS diagnosis is shown in Figure 3. Not including the 60- to 69-age group, the diagnosis rate almost halved across the younger age groups.

**Table 2.** Crude and adjusted diagnosis rate-ratios by birth- and diagnosis-cohorts.

<table>
<thead>
<tr>
<th>Birth-cohort</th>
<th>Crude diagnosis rate-ratio (95% confidence interval)</th>
<th>Coefficient for trend</th>
<th>Adjusted(^a) diagnosis rate-ratio (95% confidence interval)</th>
<th>Coefficient for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946–1950 Ref.</td>
<td>0.73 (0.60–0.89)</td>
<td>(p&lt;0.001)</td>
<td>0.77 (0.63–0.94)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>1951–1955</td>
<td>0.55 (0.44–0.68)</td>
<td></td>
<td>0.61 (0.49–0.76)</td>
<td></td>
</tr>
<tr>
<td>1961–1965</td>
<td>0.42 (0.34–0.53)</td>
<td></td>
<td>0.51 (0.40–0.66)</td>
<td></td>
</tr>
<tr>
<td>1966–1970</td>
<td>0.32 (0.24–0.41)</td>
<td></td>
<td>0.38 (0.28–0.51)</td>
<td></td>
</tr>
<tr>
<td>1971–1975</td>
<td>0.16 (0.11–0.24)</td>
<td></td>
<td>0.22 (0.14–0.33)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis-cohort</th>
<th>Crude diagnosis rate-ratio (95% confidence interval)</th>
<th>Coefficient for trend</th>
<th>Adjusted(^a) diagnosis rate-ratio (95% confidence interval)</th>
<th>Coefficient for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1984 Ref.</td>
<td>0.87 (0.84–0.90)</td>
<td>(p&lt;0.001)</td>
<td>0.79 (0.76–0.82)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>1985–1989</td>
<td>0.85 (0.59–1.23)</td>
<td></td>
<td>0.71 (0.49–1.04)</td>
<td></td>
</tr>
<tr>
<td>1990–1994</td>
<td>0.90 (0.65–1.25)</td>
<td></td>
<td>0.68 (0.48–0.96)</td>
<td></td>
</tr>
<tr>
<td>1995–1999</td>
<td>0.71 (0.52–0.98)</td>
<td></td>
<td>0.50 (0.36–0.70)</td>
<td></td>
</tr>
<tr>
<td>2000–2004</td>
<td>0.60 (0.44–0.81)</td>
<td></td>
<td>0.38 (0.28–0.53)</td>
<td></td>
</tr>
<tr>
<td>2005–2009</td>
<td>0.60 (0.44–0.82)</td>
<td></td>
<td>0.33 (0.24–0.46)</td>
<td></td>
</tr>
<tr>
<td>2010–2014</td>
<td>0.44 (0.32–0.60)</td>
<td></td>
<td>0.24 (0.17–0.33)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for sex, diagnosis delay and age of onset.

**APC model**

The estimated diagnosis rate from the APC model decreased from 3.31 (95% CI: 3.16–3.46) in the 1980–1984 diagnosis-cohort to 1.65 (95% CI: 1.55–1.75) in the 2010–2014 diagnosis-cohort. The age-specific trends in rates of PPMS diagnosis is shown in Figure 3. Not including the 60- to 69-age group, the diagnosis rate almost halved across the younger age groups.

**Analyses of missing data**

A comparisons across the basic clinical and demographic features of patients with PPMS, ROMS and uncategorised patients can be seen in Supplementary Table 1. We also tested a scenario where all the uncategorised patients would have been misclassified PPMS patients and analysed the two groups together. This decreased the adjusted trend in the incidence rate-ratio of birth-cohorts to 0.89 (95% CI: 0.85–0.93, \(p<0.001\)) and diagnosis-cohorts to 0.89 (95% CI: 0.86–0.91, \(p<0.001\)); however, the significance remained at the same level.

**Discussion**

We report a significant decline in the number and proportion of patients diagnosed with PPMS over the past decades in Sweden. We investigated the data by assessing birth-cohorts, diagnosis-cohorts and APCs, and all showed a significant decline of patients assigned a PPMS course. This decline remained significant even after excluding the youngest cohorts of patients of which many may not yet be diagnosed. Although the factors responsible for such a decrease can only be speculated upon, our data suggest that this decline is most probably due to a shift in the clinical practice caused by the introduction on DMTs.

To the best of our knowledge, our study is the first cohort study on a population level to report a significant decline in the diagnosis of PPMS. Several previous papers reported have confirmed findings presented...
here and decrease in the number or percentage of PPMS patients,\textsuperscript{11,19} and a few investigated temporal trends in the incidence of MS by clinical phenotype.\textsuperscript{20,21} Our study population was representative of 80% of all prevalent cases of MS in Sweden and therefore potentially generalisable to other patient populations and countries with comparable clinical practice.

When using the diagnosis-cohorts, a steady decline in the number of PPMS patients was observed from the 1996–2000 cohort and onward interestingly coinciding with the introduction of DMTs in Sweden. Those PPMS patients who received DMTs were significantly younger at the time of MS onset (40.6 vs 44.6). Thus, it seems that the availability of drugs could have shifted the clinical practice in a way so that younger patients with active inflammation and/or faster disability progression fulfilling PPMS criteria are assigned another course in order to not be disqualified from treatment. One interesting question is if small effects, caused by early intervention in PPMS could be a contributing factor in misclassification of true PPMS patients. However, our project was not designed to investigate this and the sample size across time being small leaves us only to speculate upon this factor.

The mean age at the onset of MS was 46.9 years in PPMS and 38.7 years in ROMS in the oldest birth-cohort (1946–1950). An explanation for the older age of onset can be described by the presence of survival bias among the patients with a late MS onset who survived long enough to be included in SMSreg. A similar bias can also be seen when using diagnosis-cohorts where an increase in age at onset occurs for both the PPMS and ROMS patients where our earliest diagnosis-cohort is impacted by those patients who have survived for at least 15 years after the disease onset to the SMSreg start date (late 1990s). This has created an artificially lower age at onset in the earliest diagnosis-cohorts. In the later diagnosis-cohorts, when the coverage of the registry improves, the onset age indeed stabilises, as would be expected with such a bias. The decline in the number of SPMS patients (seen in Table 1) can be explained by shorter follow-up of patients in the recent cohorts and is unlikely to reflect any meaningful change in incidence of SPMS.

Another possible explanation for the decreasing rate of PPMS would be that the clinical criteria, or the interpretation of these criteria, has changed, making PPMS criteria harder to fulfil. In such a case, however, older PPMS cohorts should be contaminated by patients who should have rightly been assigned RRMS/SPMS. In that case, given the constant and equal sex ratio in our PPMS cohorts and in previous reports,\textsuperscript{22,23} we would have expected a higher sex ratio in older cohorts, which was not the case. In fact, testing the sex ratio for PPMS was found to be significantly different from the ROMS ratio (data not shown). It therefore seems more likely that rather than misclassified ROMS patients in the earlier cohorts, some PPMS patients in the younger cohorts are misclassified as RRMS.

MS diagnosis criteria as well as the disease clinical course definitions have undergone several significant modifications during the past decades. Changes in the sensitivity and specificity of MS diagnosis criteria and particularly introduction of neuromyelitis optica spectrum disorder could potentially influence the diagnosis of PPMS in two probable ways. First, the new more sensitive criteria and in particular availability of magnetic resonance imaging (MRI) as well as less recall bias for initial symptom in the contemporary cohorts might have led to better differential diagnosis and identification of more benign or inflammatory active cases of MS who would have been missed otherwise or presented in clinics during the progressive stage leading to diagnosis of PPMS. Previous research has shown lower levels of disability as measured by the first recorded EDSS score in contemporary cohorts of MS.\textsuperscript{12} When investigating the first EDSS recorded within a year from the diagnosis date we could not see any significant decrease in the PPMS group. However, our contemporary ROMS patients were significantly less disabled at their first clinic visit (data not shown).

Second, the amount of clinical, laboratory and imaging requirements for diagnosis of PPMS varies between criteria. While 6 months of clinical progression was required for PPMS diagnosis according to the 1965 Schumacher et al.\textsuperscript{24} and 1983 Poser et al.\textsuperscript{25} criteria, 1 year of continued progression is recommended in the original and revised McDonald criteria.\textsuperscript{26–28} In addition, while a diagnosis of PPMS requires positive laboratory or imaging results in the McDonald criteria, PPMS diagnosis could previously be established on the ground of clinical evidence and also when patient did not satisfy the requirements for any other diagnosis category. As the Poser criteria requires less supportive evidence for diagnosis of PPMS, many of the patients in the older cohorts with unclear diagnosis could have been categorised as PPMS. Given the degree of changes in the diagnosis criteria of PPMS over time (particularly between
for all birth-cohorts in the PPMS group was 43.1. Given that the mean age at diagnosis (T) analysis were close to 40 years of age at the time of diagnosis, the youngest individuals included in birth-cohorts might have been diagnosed with PPMS with and/or without activity and/or worsening. In the light of our data, it seems this is already on going in the clinics.

A true change in MS course towards a phenotype of more expressed inflammation and relapses should also be considered as a potential explanation. One may hypothesise that an environmental factor, such as smoking, could have shifted the initial course from progressive to relapsing over time. Of note, smoking prevalence in the Swedish general population has significantly declined during the past decades, especially among men, and since 1993 women have higher smoking rates. Given the increased risk of PPMS in current cigarette smokers and men, the decline in the number of PPMS patients could possibly be attributed to the decrease in the prevalence of male smokers. In this case, PPMS and RRMS should not be mixed when studying environmental risk factors, as this may imply different causal mechanisms. Our study was not designed to investigate the effects of the environment, but, although an environmental effect cannot be excluded, we believe the arguments for the effect being mainly attributed to the clinical practice are convincing enough to attribute a major effect to the change in clinical practice.

The youngest individuals included in birth-cohort analysis were close to 40 years of age at the time of data extraction. Given that the mean age at diagnosis for all birth-cohorts in the PPMS group was 43.1 years (Table 1), it would be reasonable to expect more patients to eventually be diagnosed with PPMS in the younger cohorts. As confirmed by the sensitivity analysis when excluding the two younger cohorts, this is not likely to change the overall trend towards a decreasing number of PPMS patients. In addition, the proportion of PPMS patients decreased from almost 19.2% to 2.2%, or in absolute numbers from 213 to 32 and we hold it unlikely that such a large number of patients will be diagnosed with PPMS in the younger cohorts within the next few years. Our other analyses based on diagnosis-cohorts and APC model which are less sensitive to diagnosis-delay bias also yielded similar results. As shown in the APC model, the diagnosis rate significantly declined even in those with highest probability of PPMS diagnosis (50–59 age group).

Implications of findings
The research and clinical implications of our findings may be significant. With the current rate of decline in the number of PPMS patients, future research on the phenotype will struggle with even lower number of patients than today. On the other hand, the lack of proven efficacy of any of the currently available DMTs on the clinical course of PPMS will have unnecessarily increased the economic burden of MS.

Conclusion
We conclude that the number of patients with PPMS has significantly declined in Sweden in recent years. Several factors could contribute to this decline, including changes in clinical practice provoked by introduction of DMTs, changes in the diagnostic criteria, better access to health care and shorter diagnosis delay or a true biological shift in onset-types of MS. The mechanisms behind such a change are intriguing, but seem likely to be at least partly a consequence of a shift in clinical practice given the observed tendency to treat young PPMS patients. Our findings should ideally be confirmed in other cohorts to exclude that this is an isolated finding for Sweden or if the decline is global. However, if the decline is due to misclassification of diagnosis caused by DMT availability, ocrelizumab, with its expected efficiency in PPMS, may open up for more diagnosis of PPMS in the future.

Based on our data it appears that clinical definitions and subtyping of MS patients had been shifted towards the new recommendation of clinical course definitions by Lublin et al. The strongest argument for the concept of PPMS remains the equal gender ratio indicative of some biological relevance of keeping PPMS a separate disease course.

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References


