Short report

Shift of multiple sclerosis onset towards older age

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ABSTRACT

Objective To explore whether age at onset increased over time despite a shortened interval from the initial clinical demyelinating event to the diagnosis of multiple sclerosis (MS), as promoted by updated diagnostic criteria.

Methods This was an independent, multicentre, retrospective study based on data from 4345 patients with relapsing-onset MS attending three tertiary MS Clinics in Italy. After stratifying the year of MS onset into four periods (<1991, 1991–2000, 2001–2010, 2011–2021), we analysed the temporal trends in age at onset and interval from onset to diagnosis; we then explored the female-to-male ratio and onset location across different classes of age at onset.

Results We observed an increased mean age at onset, and a shortened mean interval to diagnosis over time (p<0.0001). Accordingly, there were more MS onsets at the older age classes of 40–49, 50–59 and ≥60 years (p<0.0001). In cases with age at onset ≥40 years, we also found an increased female-to-male ratio (p=0.007), more frequent spinal cord (p=0.0004) and less frequent supratentorial onset (p=0.008).

Conclusion Our study shows a forward shift towards an older age at onset of MS, thus suggesting considerable thought on the place-in-therapy of most currently used disease-modifying treatments, and on the standard of care to an older population.

INTRODUCTION

Age at onset of multiple sclerosis (MS) extends from childhood to adult life, although most patients experience their first clinical demyelinating event at 20–30 years.1 Early onset, otherwise called paediatric or juvenile MS, is defined when the first clinical demyelinating event occurs before the age of 16–18 years, and this accounts for approximately 3%–10% of all MS cases.2–5 Late-onset MS is generally considered as those cases with disease onset after 50 years of age. The incidence of late-onset MS has increased over time, especially in women,6–8 but this would not seem to be explained by a prolonged prodromal phase,9 also considering the evolution of the diagnostic criteria towards an earlier diagnosis.9

In this study, we sought to confirm, in a large real-world sample, whether age at MS onset increased over time despite a shortened time to diagnosis.

METHODS

This was an independent, multicentre, retrospective study based on data collected in the real-world setting. We analysed data of patients diagnosed with MS according to different criteria available over time,9 and regularly attending three tertiary MS Clinics in Rome (S. Camillo-Forlanini Hospital, S. Andrea Hospital and Policlinico Gemelli, Rome, Italy). We included only patients with relapsing-onset MS, whereas we excluded those experiencing an insidious development of neurological symptoms with subsequent irreversible disability, whose exact onset date cannot be determined, suggesting a primary progressive disease course.10

Rome, the largest city in Italy and among the most populous in Europe, accounts for approximately 2 770 226 inhabitants (www.istat.it); it is located in the Latium, a high-risk area for MS,11 with an estimated prevalence of 11 350 patients in 2018 (www.aism.it).

For each included patient, we collected the following data: birth date; sex; onset date (ie, the date of the first clinical demyelinating event as reported by patients or their relatives); date of diagnosis according to the applicable diagnostic criteria; onset locations, established on clinical grounds, as optic nerves, supratentorial, brainstem/cerebellum, spinal cord, multifocal. All analyses were stratified by MS-onset epochs, categorised into four periods according to the calendar year: <1991, 1991–2000, 2001–2010, 2011–2021. The following comparison analyses were then done across each period: (1) mean±SD age at onset and interval from onset to diagnosis; (2) proportions with onset at different age classes (<18, 18–29, 30–39, 40–49, 50–59 and ≥60 years); (3) female-to-male sex ratio and (4) onset location across different classes of age at onset. Temporal tendencies over periods were analysed by the Jonckheere-Terpstra test and the χ² test for trend for continuous and categorical variables, respectively.

RESULTS

Out of 4612 regularly attending our MS Centres, we excluded 267 (5.8%) patients (125 men, 142 women) with a primary progressive disease course. Their mean (SD) age at ‘presumed’ onset was 43.5 (10.2) years; only three of them had an early-onset MS (ie, before 18 years), while 94 (35.2%) had late onset MS (ie, over 50 years).

We analysed data from 4345 patients with relapsing-onset MS, including 1403 (32%) men and...
Multiple sclerosis

2942 (68%) women, whose MS arose from 1960 to 2021. Their mean (SD) age at onset was 31.7 (10.3) years, ranging from 5 to 71 years, and their mean (SD) interval from onset to diagnosis was 3.2 (5.0) years, ranging from 0 to 39 years. Onset locations were available for 4318 patients and were as follows: spinal cord, n=1245 (28.8%); optic nerve, n=985 (22.8%), brainstem/cerebellum, n=907 (21.0%); supratentorial, n=804 (18.6%); multifocal, n=377 (8.7%).

We observed an increased mean age at onset, and a shortened mean interval to diagnosis over time (p<0.0001; figure 1A). While the proportions of early-onset MS remained stable (5.0% to 6.8%), we observed fewer MS onset at the age class of 18–29 years, and more MS onset at the older age classes of 40–49, 50–59 and ≥60 years over time (p<0.0001). The proportion of late-onset MS went from 1% before 1991 to almost 10% after 2010 (figure 1B).

Figure 1 Temporal trends in mean age at onset and mean interval to diagnosis (A), classes of age at onset (B), female-to-male ratio (C), and clinically defined onset locations (D). *P<0.01 by the Jonckheere-Terpstra test (A), and by the χ² test for trend (B–D).

Female-to-male sex ratio was broadly stable over time (2.00, 2.03, 2.11, 2.18 in the periods <1991, 1991–2001, 2001–2011, 2011–2021, respectively; p=0.33). We conducted then a further analysis on female-to-male sex ratio across age classes, but we had to merge the age classes 40–49, 50–59 and ≥60 years due to excessive granularity of data. The female-to-male sex ratio slightly increased in patients aged 18 years, but it did not reach the statistical significance (p=0.07), whereas there was a relevant increase in the female-to-male sex ratio in age classes ≥40 years (p=0.007; figure 1C).

Data on onset location were missed in 27 cases. Onset locations in optic nerves, brainstem/cerebellum and multifocal sites remained stable, whereas there were more frequent spinal cord (p=0.0004) and less frequent supratentorial onset (p=0.008) over time (figure 1D). These latter estimations were only driven by changes in age classes ≥40 years (p<0.0001), as the frequency of different onset locations did not change over time in other age classes (data not shown).

DISCUSSION

The mean age and, accordingly, the proportion of patients with late-onset and very late-onset MS attending our centres increased in the last years, despite a shortened time to diagnosis. The proportion of patients with late-onset MS went from 1% before 1991 to almost 10% after 2010, and this increase concerned mainly women. In these patients, the clinical onset at spinal cord level was more frequent than in younger age classes.

Our findings are in line with previous incidence studies, and might be explained by a complex interplay between several environmental factor and lifestyle habits that are changing over time (eg, obesity, smoking, sun exposure, infections). Another
plausible explanation encompasses the growing availability of MRI and updated diagnostic MRI-based criteria that allow more accurate distinction between demyelinating and vascular or unpecific lesions, and that emphasise the role spinal cord for the differential diagnosis.13

However, exploring the reasons why there was such an increase of late-onset MS goes beyond our objectives, and requires a different study design. We would instead point out that our findings have practical clinical implications, especially in the management of disease-modifying treatments (DMTs). First, we should bear in mind that patients above 50–60 years in the management of disease-modifying treatments (DMTs). First, we should bear in mind that patients above 50–60 years

Second, several meta-analyses suggest no benefit by DMTs on disability progression over the age of 53 years,14 and an increased risk of neoplasms with depletive agents (alemtuzumab, cladribine, ocrelizumab) above 45 years of age.15 Third, the ageing-related occurrence and accumulation of comorbidities can affect the efficacy and safety of DMTs.16

Fourth, the ‘immuno-senescence’ phenomenon can contribute to the age-associated growing incidence of opportunistic infections in patients treated with DMTs.17

In conclusion, our study shows a forward shift towards an older age at onset of MS in patients attending our centres. If our findings are further confirmed in larger and well-designed population-based studies, we will need to reconsider the place-in-therapy of most currently used DMTs, and to readjust the standard of care to an older population.

Contributors
Conception and design of the study, drafting a significant portion of the manuscript/figures: LP, ML, SR and SH. Acquisition and analysis of data, revision of manuscript content: LP, ML, SR, CT, MM, CP and CG. Supervision and drafting the final version of the manuscript: CT, MM, CP and CG.

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Competing interests
None declared.

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Ethics approval
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