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Original Research Paper

Time to diagnosis in multiple sclerosis: Epidemiological data from the German Multiple Sclerosis Registry

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Abstract

Objective: To investigate the time to diagnosis in multiple sclerosis (MS) in Germany.

Methods: Analysis of real-world registry data from the German Multiple Sclerosis Registry (GMSR) and performing a primary analysis in patients where month-specific registration of the dates of onset and diagnosis was available.

Results: As of January 2020, data of a total of 28,658 patients with MS were extracted from the GMSR, with 9836 patients included in the primary analysis. The mean time to diagnosis was shorter following the introduction of the first magnetic resonance imaging (MRI)-based McDonald criteria in 2001. This effect was most pronounced in younger adults below the age of 40 years with relapsing onset multiple sclerosis (ROMS), with a decrease from 1.9 years in 2010 to 0.9 years in 2020, while unchanged in patients aged 40–50 years (1.4 years in 2010 and 1.3 years in 2020). In the limited number of paediatric onset MS patients, the time to diagnosis was longer and did not change (2.9 years).

Conclusion: The current sensitive MRI-based diagnostic criteria have likely contributed to an earlier diagnosis of MS in Germany in younger adults aged 18–39 years with ROMS. Whether this translated to earlier initiation of disease-modifying treatment or had a beneficial effect on patient outcomes remains to be demonstrated.

Keywords: Epidemiology, diagnosis, registry, multiple sclerosis

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Introduction

As a chronic inflammatory and early neurodegenerative disease, multiple sclerosis (MS) causes substantial cognitive and physical impairment with a decline in the quality of life of individuals affected.[1,2] Disease-modifying therapies (DMTs) aim to modulate or (selectively) suppress the immune system to reduce both relapse rates and disability progression. Early diagnosis and timely initiation of treatment with DMTs are considered important for preventing or delaying progressive disability in MS patients.[3] Moreover, emerging evidence suggests the presence of a prodromal MS phase already involving neuroinflammatory and degenerative processes prior to a first MS-specific demyelinating event.[3] Thus, developing a concise definition of the MS prodrome including its clinical and paraclinical features, as well as comprehension of its pathophysiology, are focus points within current MS research.[4]

To date, a first clinical demyelinating event with a suspicion of MS is a prerequisite for the diagnosis of the disease.[5] To fulfil the diagnostic criteria of MS after a first episode, specific paraclinical findings on magnetic resonance imaging (MRI) and in cerebrospinal fluid (CSF) are required to prove a chronic and disseminated inflammatory disease. The latest revision of the McDonald criteria in 2017 simplified the MRI-based definition of dissemination in space and introduced CSF oligoclonal bands as markers of temporal dissemination.[5] Since then, several studies showed that the proportion of the patients with the diagnosis of definite MS after the first clinical event can be substantially increased,[6–11] on average from 37% to 68%. However,

the clinical impact of these changes on patient care in real-world settings has not yet been studied.[12] The time-to-diagnosis at a population level may reflect such impact, with potential influences on the selections of the first DMT used (low- vs higher-efficacy drug) from the beginning, relapse rates in the first year or time to secondary progression. Furthermore, it is unstudied to date if the increased sensitivity of the 2017 diagnostic criteria also is of relevance for certain subgroups of MS patients, such as those with progressive or paediatric onset MS.

To systematically evaluate and improve both the daily medical care and clinical outcomes for patients with MS, regional and national MS registries monitoring long-term disease progression and treatment response and safety based on real-world data are of great value.[13] Within Europe, at least 19 MS registries exist, of which the German Multiple Sclerosis Registry (GMSR), initiated by the German Multiple Sclerosis Society, represents one of the largest data collections.[14] Therefore, to retrospectively examine the time from the first clinical event to the diagnosis of MS in a large national cohort, as well as to study the potential effects of modifications of the diagnostic criteria on the time to diagnosis, we analysed real-world data from the GMSR.

Methods

Study population

The study is based on a national data set from the GMSR of patients diagnosed with MS as either a main or side diagnosis in Germany,[15] with data extraction as of 17 January 2020. In the primary analysis, data that were entered into the GMSR from 2015 onwards, when month-specific information on the dates of onset and diagnosis became available, were included (Figure 1). Furthermore, only data sets with basic information on the history and current status of the disease were included. As patients could be enrolled in the GMSR at any time during the course of the disease, the analysis contained data of patients diagnosed with MS before 2015 with a retrospective documentation of the time of diagnosis.

To corroborate the findings and address the issues with regard to a possible selection or recall bias, we performed a verification analysis in a larger legacy data set, which included older data entered prior to 2015 and without the month-specific record of the time of diagnosis. A density plot of age at onset revealed an age-related bias for diagnoses before 2010, with a strong underrepresentation of older ages (Supplemental Figure A). As this bias could possibly impair the reliability of the statistical exploration of age effects, such analyses were confined to diagnoses from 2010 onwards and to the largest subgroup of patients with relapsing onset multiple sclerosis (ROMS). The pseudonymous data contained information on descriptive personal data, time of diagnosis, symptom onset and initial symptoms.

Statistical analysis

Statistical analyses included descriptive statistics along with 95% confidence intervals or interquartile range or standard deviation (SD) as indicated. Generalized additive models were used to investigate calendar time effects for the date of diagnosis in the mean value of latency to diagnosis. Figures include density and contour plots – for densities and local averages – and boxplots. Analyses were performed and figures created using R v4.0.6.

Results

Within the data set, demographic statistics on age, gender, disease type and initial symptoms are shown in Table 1. The GMSR cohort and its subgroups showed the expected female gender predominance, and a large majority (>92%) were patients with ROMS. The subgroups of patients with month-specific documentation of dates of onset and diagnosis – the primary analysis subgroup – were overall representative of the full GMSR cohort, while patients diagnosed after 2010 had a shorter disease duration and lower Expanded Disability Status Scale (EDSS) scores (Table 1). We recently described the GMSR data structure, estimating that data represent about one-third of the people with MS seen in participating centres,[15] while additional analyses indicate reliable data on the disease history of patients (Supplemental *Data quality indicators*).

The primary analysis in 9836 individuals from the GMSR showed a decline in time to diagnosis over the last two decades in ROMS patients; the mean time to diagnosis in 2000 was 2.3 ± 4.8 years, while in 2020, it was 1.0 ± 2.6 years. This decline can be associated with the introduction and adaptation of the MRI-based McDonald criteria from 2001 onwards. In patients with progressive onset multiple sclerosis (POMS), a similar decline in time to diagnosis appeared to commence later, from 2010 onwards. However, large confidence intervals indicated that statistical significance was not reached (Figure 2(a)).

Counterintuitively, a comparably short mean time to diagnosis was retrospectively recorded for ROMS

Table 1. Proportions (%) along with 95% Clopper–Pearson confidence intervals are given; metric data are reported with mean value (±SD); for EDSS, the interquartile range (IQR = Q50 [Q25, Q75]) is also given.

	All GMSR patients (n = 28,658)	Primary analysis [month-specific registration] (n = 9836)	Subgroup of the primary analysis [diagnosed after 1 January 2010] (n = 5780)
Females (%)	71.5% [71.0–72.0]	71.7% [70.8–72.5]	70.3% [69.1–71.5]
Relapsing onset MS (%)	92.0% [91.7–92.3]	94.1% [93.6–94.5]	93.7% [93.1–94.3]
Age at onset (years)	33.1 (±10.7)	33.6 (±10.7)	35.1 (±11.2)
Age at diagnosis (years)	35.7 (±11.0)	35.2 (±10.9)	36.5 (±11.4)
Disease duration at enrolment (years)	11.4 (±9.9)	9.1 (±9.0)	3.6 (±4.4)
Time since enrolment (years)	3.5 (±2.7)	3.0 (±1.9)	2.6 (±1.6)
EDSS first visit (at enrolment, maximum 1 year after)	3.0 (±2.1) IQR = 2.5 [1.5, 4.0]	2.7 (±2.0) IQR = 2.0 [1.0, 4.0]	2.1 (±1.6) IQR = 2.0 [1.0, 3.0]
Symptom at onset			
Visual	41.4% [40.8–42.1]	37.3% [36.3–38.3]	35.2% [33.9–36.5]
Pyramidal	43.0% [42.3–43.6]	39.8% [38.8–40.8]	36.4% [35.1–37.7]
Brainstem	22.4% [21.8–23.0]	24.1% [23.3–25.0]	22.9% [21.8–24.1]
Cerebellar	24.4% [23.9–25.0]	23.8% [23.0–24.7]	22.2% [21.1–23.4]
Sensory	59.6% [59.0–60.3]	57.8% [56.8–58.8]	59.3% [58.0–60.6]
Bladder	9.6% [9.2–10.0]	9.3% [8.7–9.9]	8.4% [7.7–9.2]
Depression	15.5% [15.0–16.0]	15.8% [15.1–16.6]	15.8% [14.8–16.8]
Any other	6.4% [6.0–6.7]	6.5% [6.0–7.1]	6.4% [5.7–7.1]
Polysymptomatic	40.9% [40.3–41.5]	51.4% [50.5–52.4]	50.3% [49.0–51.6]

GMSR: German Multiple Sclerosis Registry; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale.

diagnosed in 1990 (1.2 ± 2.4 years) and earlier, which later increased to the higher values for diagnoses in 2000 (see above). A similar trend of an initial increase in time to diagnosis was observed in POMS, which persisted until 2010. A verification analysis in a larger data set of patients enrolled prior to 2015, including entries lacking the month-specific record of diagnosis (n = 53,262), resulted in a higher mean time to diagnosis in 1990 (2.4 ± 4.4 years) in ROMS; however, it confirmed the mentioned rise until the end of the last millennium, with a following decline (Supplemental Figure B).

Longitudinal plotting of time to diagnosis across age groups for diagnoses after 2010 in ROMS – with a homogeneous distribution of age at diagnosis over time (Supplemental Figure A, see 'Methods') – revealed an age-dependent dynamic over the last decade. However, it differed significantly between younger MS patients diagnosed before the age of 40 years and those diagnosed over the age of 40 years (p = 0.002), with a decline in the mean time to diagnosis in the younger adults aged 18–39 years (p < 0.001, Figure 2(b)). Furthermore, the adult MS group had a shorter time to diagnosis compared to the more scattered paediatric onset MS group (1.3 ± 3.5 years vs 2.9 ± 5.7 years, Supplemental Figure C). Overall, while the mean time to diagnosis decreased significantly in adult MS patients diagnosed with ROMS under the age of 40 years (2010: 1.9 ± 4.0 years and 2020: 0.9 ± 2.5 years), it remained low and did not change over time in patients diagnosed with ROMS at 40–50 years of age and above (2020: 0.9 ± 2.1 years). In addition, it was higher and did not change in paediatric onset MS patients (2020: 2.9 ± 5.7 years, Figure 2(b), Supplemental Figure D).

Discussion

In this study, data from a national German MS cohort, the GMSR, was analysed to reveal the time to diagnosis and its trends at a population level over time. The demographics of the patients included in the analysis were largely concordant with previous epidemiological data[16] and representative for the total cohort included in the GMSR (Table 1).

As a key finding of the study, we noted a decline in the mean time to diagnosis in ROMS with the introduction of the first MRI-based McDonald criteria in 2001. Restricting the analysis to patients diagnosed

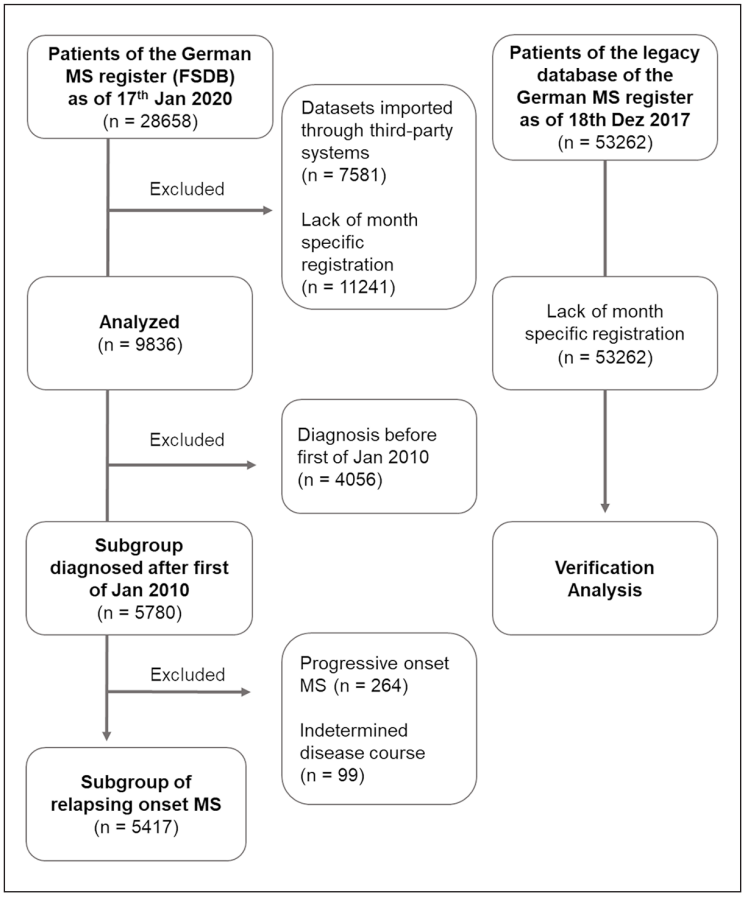

Figure 1. Flow chart demonstrating the data sets from the GMSR ('Forschungsdatenbank' (used since 2014); FSDB) evaluated and subgroups analysed, as well as a verification analysis performed based on the legacy database from the GMSR.

within the last decade to minimize a possible selection or recall bias, the decline in the mean time to diagnosis was mainly driven by the group of young adults (aged 18–39 years), while it remained largely unchanged in patients above 40 years of age. The delay between first symptoms and diagnosis was the longest in the data set of paediatric onset MS patients included in the study, although data validity in this age group was limited by the small sample size, resulting in a comparably greater variance. Since only adults are enrolled in the GMSR, all paediatric onset MS patients were included later during the course of the disease, rather than at the time of diagnosis, possibly introducing a relevant recall bias for this patient group in particular.

As one possible factor, the decline in time to diagnosis over time in younger adults in particular might be explained by the higher sensitivity of MRI-based McDonald criteria in this population with higher MRI activity[17] and reduced specificity in the elderly due to factors such as vascular comorbidity.[18,19] To this end, recent studies have demonstrated a successive increase in diagnostic sensitivity with recent revisions of diagnostic criteria (for a review, see Schwenkenbecher et al.[12]). Our study adds to these previous findings indicating that it might indeed be this higher sensitivity that translates in a reduction in time to diagnosis of definitive MS, as evidenced from real-world data on population level.

However, our findings need to be interpreted with caution as temporal associations found with adaptations of MS diagnostic criteria do not necessarily mean causation. Several other factors might contribute to the decrease in diagnostic delay reported here. For instance, the broader availability of MRI scans, the more frequent application and technical advances in neuroimaging[20] might also increase the sensitivity of any MRI-based diagnostic criteria, and thereby shorten the time to diagnosis, regardless of the recent revisions. Furthermore, improvements in structural settings, that is, awareness campaigns, medical care structures, resulting in an increase in medical utility,[21]

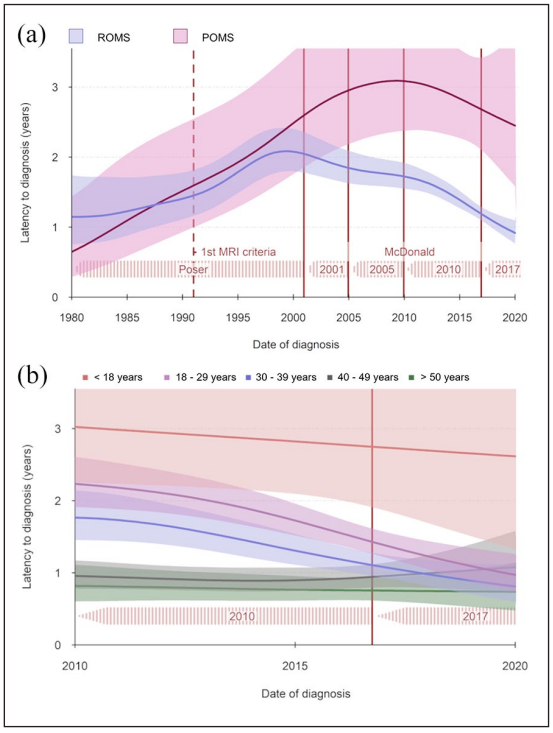

Figure 2. (a) Mean time to diagnosis (±95% CI) across all age groups over the last decades in relapsing onset (ROMS, blue) and progressive onset MS (POMS, red). Red vertical lines indicate the introduction of revised MS diagnostic criteria. (b) Time to diagnosis for different age groups over time in the last decade. The red vertical line indicates the 2017 revision of MS diagnostic criteria.

are potential contributors. Of note, while an improvement in sensitivity after successive revisions has also been documented in case of POMS,[22] we were unable to demonstrate a robust decrease in time to diagnosis in this group. Besides considerably smaller case counts, the recent advent of a first approved disease-modifying treatment[23] might have contributed to a re-attribution of previous undiagnosed cases, thus reversing a potential decrease in time to diagnosis in this subgroup. In addition, the requirement of a documented progression over 12 months remained unchanged as part of the diagnostic criteria for progressive onset MS,[5] and may interfere with immediate diagnosis after a first clinical event.

Overall, our findings were in line with data from the Swedish national registry available online, which shows similar trends.[24] Canadian data reporting on diagnoses of MS prior to 2005 revealed that, at that time, younger age was a risk factor for a longer time from symptom onset and diagnosis of ROMS in adult patients.[25] Within the Swiss registry data, a delay in the diagnosis of MS in younger patients was attributed to a lag in initial clinical presentation upon first symptoms.[26] With regard to paediatric onset MS, recent studies from both Swedish[27] and Danish[28] registries also indicated a longer time to diagnosis in this group of patients compared to adults, again corroborating our results.

Interestingly, in the Swedish registry,[24] as well as in this German data set, crude mean estimates showed an increase in time to diagnosis during the 1990s, prior to the following continuous decline. The study design may have contributed to this finding, at least in the GMSR, exposing one of the possible limitations to this study. The retrospective documentation of the dates of first symptoms and diagnosis may have introduced a recall bias in particular for the early cases diagnosed in the 1990s. A long temporal distance between symptom onset and documentation may in part explain the comparably short time to diagnosis noted in these early cases. We performed a verification analysis on historical data, which confirmed the increase in time to diagnosis in the last decade of the 20th century. While we cannot completely exclude that a similar recall bias also influenced the results of this larger analysis, additional factors may have also influenced this unexpected result. The introduction of approved DMTs in 1993, refinements of the MS diagnostic criteria, and a broader availability of MRI techniques may have contributed to a larger number of ex-post diagnoses of a disease that had been untreatable in the pre-DMT era. Considering these limitations and the contour plot of the raw data, our findings appear to be most valid for data collected after 2010, explaining why we studied changes to the time to diagnosis in different age groups in this subpopulation.

In summary, the data from the GMSR, a large national cohort, documents an earlier diagnosis in adult ROMS patients younger than 40 years of age in particular within the last decade that might be attributed to a successful implementation of recent diagnostic criteria in the context of the German medical care system. Such affect is in line with previous publications that were suggestive of a higher sensitivity of the 2017 revised MS diagnostic criteria. Confirmation from other national registries is warranted, as well as studies focusing on the effects of an earlier diagnosis on the time to DMT use relative to symptom onset and the possible effects on patient outcomes, such as relapse rates in the first years of the disease or the time to secondary progression. Future attempts to increase diagnostic sensitive might focus on potential weaknesses in current diagnostic criteria with comparably long diagnostic delay, including patients with progressive or paediatric onset MS.

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Supplemental Material

Supplemental material for this article is available online.

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