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Original Research Paper

Disability outcomes of early cerebellar and brainstem symptoms in multiple sclerosis

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Abstract

Background: Cerebellar and brainstem symptoms are common in early stages of multiple sclerosis (MS) yet their prognostic values remain unclear.

Objective: The aim of this study was to investigate long-term disability outcomes in patients with early cerebellar and brainstem symptoms.

Methods: This study used data from MSBase registry. Patients with early cerebellar/brainstem presentations were identified as those with cerebellar/brainstem relapse(s) or functional system score ≥ 2 in the initial 2 years. Early pyramidal presentation was chosen as a comparator. Andersen-Gill models were used to compare cumulative hazards of (1) disability progression events and (2) relapses between patients with and without early cerebellar/brainstem symptoms. Mixed effect models were used to estimate the associations between early cerebellar/brainstem presentations and expanded disability status scale (EDSS) scores.

Results: The study cohort consisted of 10,513 eligible patients, including 2723 and 3915 patients with early cerebellar and brainstem symptoms, respectively. Early cerebellar presentation was associated with greater hazard of progression events (HR = 1.37, $p < 0.001$) and EDSS ($\beta = 0.16$, $p < 0.001$). Patients with early brainstem symptoms had lower hazard of progression events (HR = 0.89, $p = 0.01$) and EDSS ($\beta = -0.06$, $p < 0.001$). Neither presentation was associated with changes in relapse risk.

Conclusion: Early cerebellar presentation is associated with unfavourable outcomes, while early brainstem presentation is associated with favourable prognosis. These presentations may be used as MS prognostic markers and guide therapeutic approach.

Keywords: Multiple sclerosis, disability outcome, early symptomatology, prognostic marker, cerebellar, brainstem

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Introduction

Cerebellar and brainstem manifestations are a common feature of multiple sclerosis (MS). They are observed in 81.6% of all MS patients and 22.5% of first demyelinating events.[1] In addition, 10.1% and 16.6% of MS relapses are reported to be of cerebellar and brainstem presentations, respectively.[2] Despite their high incidence, the relationship between cerebellar and brainstem symptoms in early MS and disability accumulation remains unclear. While cerebellar dysfunction itself is often resistant to treatment,[3] understanding the prognostic value of early cerebellar and brainstem manifestations could help with earlier identification of patients who may benefit from

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targeted and aggressive therapies and further our understanding of early cerebellar/brainstem involvement in MS pathogenesis.

This study investigated disability outcomes of early cerebellar and brainstem symptoms using MSBase, an international MS registry. We first examined the associations between these early symptoms and long-term disability levels as well as the risk of disability progression. We then investigated their relationships with further relapse activity.

Methods

Approvals and consents

The MSBase registry[4] (registered with World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), ID ACTRN1260500045 5662) 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.

Database and study population

Data from 58,383 patients from 124 centres in 33 countries were extracted from the MSBase registry in March 2018. The inclusion criteria consisted of (1) diagnosis of clinically definite relapse-onset MS[5] or clinically isolated syndrome (MS course was recorded as per clinical judgement of treating neurologists),[6] (2) first expanded disability status scale (EDSS) recorded within 2 years of MS onset, (3) availability of the minimum data set – date of birth, sex, MS centres, MS onset and first relapse date, ≥ 3 visits with recorded EDSS scores, ≥ 6 months between second and last EDSS and EDSS frequency ≥ 1 per year and (4) ≥ 1 documented clinically significant early neurological symptom.

Clinical data were recorded as part of routine clinical practice, typically at the time of clinical visits. Data were entered through iMed patient record system or MSBase online data entry system. Data quality was assessed prior to screening for inclusion and statistical analysis using a standardised procedure.[7]

Presentations and outcomes

Duration of MS was calculated from patient-reported first clinical manifestation of the disease. Patients were censored at last recorded EDSS.

Early pyramidal symptoms are well known poor prognosis predictor in MS[8–12] and thus were chosen as a benchmark comparison in this study.

Patients were identified as having early cerebellar/brainstem/pyramidal symptoms if within the first 2 years of MS onset, there was evidence of either (1) ≥ 1 relapse with cerebellar/brainstem/pyramidal symptoms or (2) EDSS cerebellar/brainstem/pyramidal functional system score (FSS) ≥ 2.

The primary outcomes were disability levels and confirmed disability progression events. Disability was quantified using the EDSS.[13] The MSBase observational plan requires Neurostatus-accredited scorers at each participating centre.[14] Baseline EDSS was defined as the median of all recorded EDSS within the first 2 years. Disability progression events were defined as an increase in EDSS by 1.5, 1.0 or 0.5 steps if baseline EDSS was 0, 1.0–5.5 or ≥ 6, respectively, confirmed at ≥ 6 months and sustained for the remainder of follow-up.[15] While first signs of EDSS progressions were recorded irrespective of their association with prior relapses, only EDSS scores recorded ≥ 30 days from onset of a preceding relapse were used and confirmed progression events. Multiple progression events were allowed per patient. Occurrence of the EDSS progression events relative to the date of first MS symptoms was calculated.

The secondary outcome was incidence of relapses. Relapses were defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥ 24 hours, in the absence of concurrent illness or fever and occurring ≥ 30 days after a previous relapse.[16] The onset attack was termed the 'first relapse'.

Statistical analysis

Statistical analyses were performed using R, version 3.4.1.[17] All hypotheses were tested at a two-tailed 0.05 level of significance.

Andersen-Gill models (proportional hazard models with robust estimation of variance for multiple events) were performed to analyse the association between the impaired neurological domain within the first 2 years and cumulative hazards of (1) disability progression events and (2) relapses.

Linear mixed effect models were used to estimate the association between early cerebellar/brainstem/pyramidal symptoms and EDSS recorded throughout the follow-up. The random intercepts were included for patient ID (given the multiple observations per

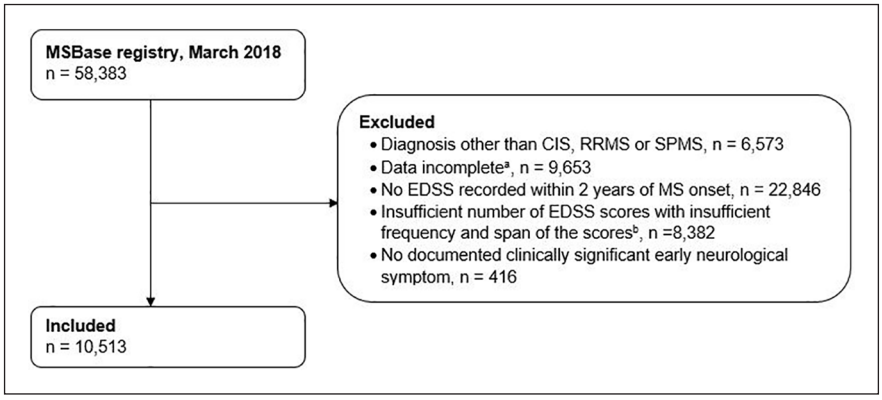

Figure 1. CONSORT flowchart of patient eligibility (primary analysis).
CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis; EDSS: expanded disability status scale.
[a]Patients excluded due to incomplete data had date of MS onset and/or date of first relapse missing.
[b]Patients excluded due to insufficient number of EDSS scores had <2 EDSS recorded, <6 months between second and last EDSS, or EDSS frequency <1 year

patient) and centre (to account for centre-specific effects, including any systematic differences in the years of patient inclusion). The models were adjusted for interaction terms for symptom of early presentation with time.

All models were adjusted for known MS prognostic markers. These included demographic markers (sex and age at onset), clinical markers in the initial 2 years (EDSS at first visit, number of relapses, number of impaired neurological domains, time between MS onset and first EDSS) and clinical markers at confirmed progression events (in Andersen-Gill models) or EDSS entries (in mixed effect models) (disease duration, MS course, proportion of follow-up on disease-modifying therapies (DMTs)). DMTs were categorised into three groups: Group 1 – interferon beta, glatiramer acetate and teriflunomide, Group 2 – dimethyl fumarate, fingolimod, siponimod, cladribine and daclizumab and Group 3 – natalizumab, ocrelizumab, ofatumumab, rituximab, alemtuzumab and mitoxantrone.

To identify any overlap between cerebellar and brainstem symptoms that could confound brainstem and cerebellar FSS, a questionnaire containing an unfiltered list of symptoms/signs related to these domains was distributed to a sample of study investigators to assess the consensus on the classification of cerebellar and brainstem symptoms.

A sensitivity analysis was performed to evaluate patients with and without early cerebellar/brainstem/pyramidal symptoms classified based on relapses and FSS separately. Another sensitivity analysis, focusing on long-term disability outcomes, was conducted by only including patients with at least 5 years of follow-up and with an early definite diagnosis of MS.

Results

Patient demographics

Out of 58,383 patients in the MSBase registry, 10,513 patients from 103 centres across 33 countries were retained with the inclusion criteria (Figure 1). Early cerebellar, brainstem and pyramidal symptoms were documented in 2723 (25.9%), 3915 (37.2%) and 5530 (52.6%) patients, respectively. For 673 patients, both early cerebellar and brainstem symptoms were documented. The median number of impaired domains in the first 2 years for our cohort was two out of seven domains. Complete remission from first relapse was observed in 652 (24%), 1151 (29%) and 1457 (26%) patients with early cerebellar, brainstem and pyramidal symptoms, respectively. The median time from MS onset to DMT initiation for patients with early cerebellar, brainstem and pyramidal symptoms were 0.83, 0.86 and 0.85 years, respectively. Further demographic and clinical characteristics of the study cohort are outlined in Table 1.

Disability accumulation

The cumulative hazards of disability progression events are shown in Figure 2 and Table 2. Patients with early cerebellar symptoms were at a higher risk of disability progression than those without early cerebellar symptoms (HR = 1.20, 95% CI = 1.08–1.33, $p < 0.001$). This was confirmed by the relatively higher EDSS

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Table 1. Demographic and clinical characteristics of the study cohort.

	At first visit	At last visit
Patients		
Patients, number (% female)	10,513 (70.5)	
Age, years, mean (SD)	32.4 (9.9)	39.3 (10.6)
Disease duration, years, median (IQR)	0.4 (0.1–0.9)	6.3 (3.5–10.3)
EDSS, median (IQR)	2.0 (1.0–2.5)	1.5 (1.0–3.0)
No. of relapses in the first 2 years, median (IQR)	2 (1–3)	
Disease course		
CIS, number (%)	4846 (46)	951 (9)
RRMS, number (%)	5643 (54)	9139 (87)
SPMS, number (%)	24 (0.2)	423 (4)
Neurological domains impaired within the first 2 years		
Total number of domains impaired, median (IQR)[a]	2 (1–3)	
Cerebellar, number of patients (% cohort)	2723 (26)	
As per EDSS/FSS[b,d]	1924 (18)	
As per relapse phenotype[c,d]	1471 (14)	
Brainstem, number of patients (% cohort)	3915 (37)	
As per EDSS/FSS[b,d]	1806 (17)	
As per relapse phenotype[c,d]	3233 (31)	
Pyramidal, number of patients (% cohort)	5530 (53)	
As per EDSS/FSS[b,d]	3520 (33)	
As per relapse phenotype[c,d]	4384 (42)	
Disease-modifying therapy (DMT)		
Number of patients not exposed to DMT		
During the first 2 years, number (%)	1719 (16)	
During the observation period, number (%)	1233 (12)	
Group 1[e], number exposed (%)		8108 (77)
Proportion of time on treatment[f], median (IQR)		0.64 (0.38–0.85)
Group 2[e], number exposed (%)		2247 (21)
Proportion of time on treatment[f], median (IQR)		0.31 (0.15–0.52)
Group 3[e], number exposed (%)		1325 (13)
Proportion of time on treatment[f], median (IQR)		0.35 (0.18–0.60)

CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis; EDSS: expanded disability status scale; FSS: functional system score; SD: standard deviation; IQR: interquartile range.
[a]Each patient might have had more than one impaired early domains if he or she had one relapse affecting more than one domain, multiple relapses affecting different domains or multiple impaired FSS/EDSS domains recorded in the first 2 years.
[b]Patients identified as having early cerebellar/brainstem/pyramidal symptoms by evidence of ⩾ 1 EDSS score with cerebellar/brainstem/pyramidal FSS ⩾ 2 within the first 2 years of MS onset.
[c]Patients identified as having early cerebellar/brainstem/pyramidal symptoms by evidence of ⩾ 1 relapse with cerebellar/brainstem/pyramidal symptoms, respectively, within the first 2 years of MS onset.
[d]The two methods of identifying the early neurological domain impaired are not mutually exclusive and therefore the sum may exceed the total number of patients with a given neurological domain affected.
[e]DMTs were categorised into three groups: Group 1 – interferon beta, glatiramer acetate and teriflunomide, Group 2 – dimethyl fumarate, fingolimod, siponimod, cladribine and daclizumab and Group 3 – natalizumab, ocrelizumab, ofatumumab, rituximab, alemtuzumab and mitoxantrone. A patient might have been exposed to more than one group of DMTs during the observation period.
[f]Proportion of time on treatment was only calculated for patients exposed to the relevant DMT.

scores observed in patients with early cerebellar dysfunction (β = 0.16, 95% CI = 0.14–0.18, $p < 0.001$).

In contrast, patients who presented with early brainstem symptoms had lower risk of progression events (HR = 0.89, 95% CI = 0.81–0.97, $p = 0.01$) and marginally lower EDSS scores (β = −0.06, 95% CI = −0.08 to −0.05, $p < 0.001$) when compared to those who did not.

Patients with early pyramidal symptoms were associated with a greater risk of disability progression

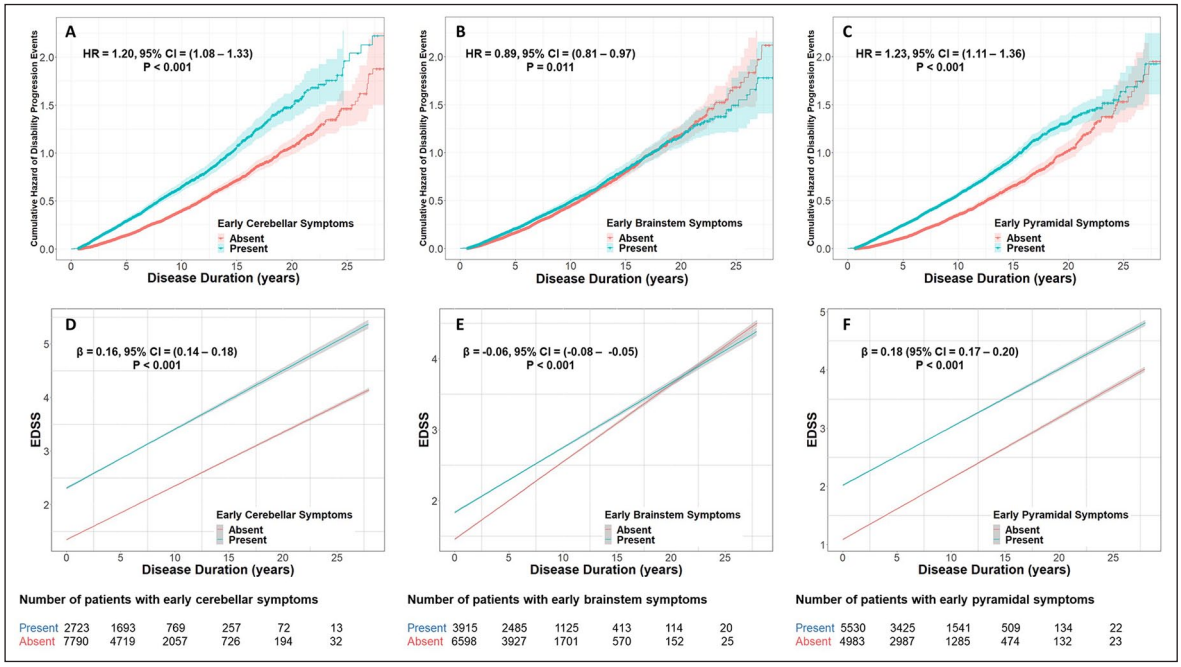

Figure 2. Disability outcomes.
HR: hazard ratio; β: regression coefficient; EDSS: expanded disability status scale.
Cumulative hazard functions for disability progression events (A, B, C) and mixed effect models of EDSS scores (D, E, F) stratified by the presence of early cerebellar (A, D), brainstem (B, E) and pyramidal (C, F) symptoms. Each patient contributed multiple disability progression event and EDSS entries. Shaded areas indicate 95% confidence interval (CI).
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.

(HR = 1.23, 95% CI = 1.11–1.36, $p < 0.001$) and higher EDSS scores (β = 0.18, 95% CI = 0.17–0.20, $p < 0.001$) than in those without early pyramidal symptoms.

A model combining both early cerebellar and pyramidal symptoms was used to assess for any confounding effects between the two domains. This model confirmed that the cumulative hazard of disability progression events was greater in patients with early cerebellar symptoms than in those without (HR = 1.24, 95% CI = 1.12–1.38, $p < 0.001$) and was independent from the occurrence of early pyramidal symptoms. Similarly, patients with early pyramidal symptoms were also at greater risk of disability progression (HR = 1.27, 95% CI = 1.14–1.40, $p < 0.001$), independently from the occurrence of early cerebellar symptoms. The interaction variable between cerebellar and pyramidal symptoms (β = 0.31, 95% CI = 0.30–0.33, $p < 0.001$) suggested a potentiation between these two associations.

Multivariable cumulative hazards models found no associations between the cumulative hazards of relapses and early presentation with cerebellar (HR = 0.96, 95% CI = 0.91–1.01, $p = 0.09$), brainstem (HR = 0.99, 95% CI = 0.95–1.03, $p = 0.63$) or pyramidal symptoms (HR = 1.01, 95% CI = 0.97–1.05, $p = 0.52$).

The responses of 27 of the study investigators to our consensus questionnaire indicated a high degree of consistency among investigators with symptoms mostly well separated. For all symptoms (with the exception of 'postural instability'), one diagnostic category was clearly dominant over the others. Out of 22 symptoms/signs listed, only four demonstrated overlaps: nystagmus (78% rated as both domains), dysarthria (70% rated as both domains), tandem walking impairment (26% rated as both domains) and postural instability with falls (44% rated as brainstem only and 41% rated as cerebellar only). The full responses are shown in Appendix 1.

Sensitivity analyses

The first sensitivity analysis was performed to evaluate disability outcomes of patients with and without early cerebellar/brainstem/pyramidal symptoms classified based on relapses and FSS separately. The results of six cumulative hazard models of disability progression are summarised in Table 3. The associations and their directions were consistent with the

Table 2. Multivariable models of cumulative hazard of confirmed disability progression events, stratified by early neurological domains impaired.

	Cerebellar		Brainstem		Pyramidal	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Early presentation with the studied symptom	1.20 (1.08–1.33)	<0.001	0.89 (0.81–0.97)	0.01	1.23 (1.11–1.36)	<0.001
Number of neurological domains affected (range 1–7)	1.10 (1.06–1.15)	<0.001	1.17 (1.12–1.22)	<0.001	1.10 (1.06–1.15)	<0.001
Sex (male)	1.17 (1.08–1.28)	<0.001	1.18 (1.08–1.29)	<0.001	1.17 (1.08–1.28)	<0.001
Age at MS onset (per decade)	1.27 (1.22 – 1.32)	<0.001	1.27 (1.22–1.32)	<0.001	1.27 (1.22–1.32)	<0.001
Baseline EDSS[a] (per 1 point)	1.00 (0.96–1.03)	0.87	1.00 (0.96–1.04)	0.93	0.99 (0.96–1.03)	0.699
Number of relapses within the first 2 years[b] (per relapse)	1.06 (1.03–1.09)	<0.001	1.06 (1.03–1.09)	<0.001	1.06 (1.03–1.09)	<0.001
Time from MS onset to first clinical visit (per year)	1.12 (1.05–1.20)	<0.001	1.12 (1.05–1.20)	<0.001	1.12 (1.05–1.20)	<0.001
Disease course						
RRMS	Ref		Ref		Ref	
CIS	0.65 (0.52–0.80)	<0.001	0.65 (0.52–0.81)	<0.001	0.66 (0.53–0.81)	<0.001
SPMS	2.21 (1.96–2.50)	<0.001	2.23 (1.98–2.52)	<0.001	2.23 (1.97–2.52)	<0.001
Proportion of time on DMT (per 10% increment)						
Group 1[c]	0.94 (0.93–0.96)	<0.001	0.95 (0.94 – 0.96)	<0.001	0.95 (0.93–0.96)	<0.001
Group 2[c]	0.86 (0.83–0.89)	<0.001	0.86 (0.83 – 0.89)	<0.001	0.86 (0.83–0.89)	<0.001
Group 3[c]	0.94 (0.92–0.96)	<0.001	0.94 (0.92 – 0.96)	<0.001	0.94 (0.92–0.96)	<0.001

CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis; EDSS: expanded disability status scale; DMT: disease-modifying therapy; HR: hazard ratio.
[a]Median of all recorded EDSS within the first 2 years.
[b]The onset attack was considered the first relapse.
[c]DMTs were categorised into three groups: Group 1 – interferon beta, teriflunomide and glatiramer acetate, Group 2 – dimethyl fumarate, fingolimod, cladribine, daclizumab and siponimod and Group 3 – natalizumab, ocrelizumab, rituximab, alemtuzumab, mitoxantrone and ofatumumab.

Table 3. Sensitivity analysis: definitions of early cerebellar, brainstem and pyramidal symptoms based on relapses and FSS separately.

Domain affected in the first 2 years	*n* (%)	Cumulative hazard of disability progression events	
		HR (95% CI)	*p*-value
Cerebellar			
As per FSS[a]	1924 (18)	1.25 (1.12–1.40)	<0.001
As per relapse phenotype[b]	1471 (14)	1.12 (1.00–1.25)	0.049
Brainstem			
As per FSS[a]	1806 (17)	0.91 (0.82–1.01)	0.077
As per relapse phenotype[b]	3233 (31)	0.86 (0.79–0.95)	0.002
Pyramidal			
As per FSS[a]	3520 (64)	1.18 (1.07–1.31)	0.001
As per relapse phenotype[b]	4384 (42)	1.15 (1.05–1.25)	0.002

FSS: functional system score.
Six Andersen-Gill models of disability progression events were performed to either definition (per relapse phenotype or per impaired EDSS functional system) for early cerebellar, brainstem and pyramidal symptoms to investigate if either definition was primarily responsible for the overall results.
[a]Patients identified as having early cerebellar/brainstem/pyramidal symptoms by evidence of ⩾1 EDSS score with cerebellar/brainstem/pyramidal FSS ⩾2 within the first 2 years of MS onset.
[b]Patients identified as having early cerebellar/brainstem/pyramidal symptoms by evidence of ⩾1 relapse with cerebellar/brainstem/pyramidal symptoms, respectively, within the first 2 years of MS onset, ⩾1 relapse with cerebellar/brainstem/pyramidal symptoms, respectively.

results of the primary analysis using the compound definition of early symptoms.

The second sensitivity analysis included 5608 patients with definite MS and ⩾5-year follow-up to evaluate long-term disability outcomes. The models confirmed the poor long-term prognosis of early cerebellar and pyramidal symptoms and the favourable disability outcomes of early brainstem symptoms. These results are summarised in Table 4.

Discussion

Using data from 10,513 patients in the observational international MSBase registry, we have demonstrated that the presence of cerebellar dysfunction, either at MS onset or at any time within the first 2 years, carried a 20% worse prognosis. Conversely, patients with early brainstem symptoms accumulate disability at an 11% slower rate, in comparison to those without (i.e. those whose early clinical presentation was driven by other neurological domains). These differences in prognosis were not mediated through differences in the frequency of MS relapses, as the risks of further relapses were similar in all compared patient groups.

The demographic and clinical characteristics of our cohort were comparable to those of previous studies. Cerebellar and brainstem manifestations were reported in 26% and 37% of our cohort during the first 2 years, respectively. Previous studies have reported cerebellar symptoms in 6.7%–17% and brainstem symptoms in 19.6%–22% of patients at disease onset.[2,11] The high prevalence of these symptoms in the early years of MS further emphasises the need to understand their influence on prognosis.

Cerebellar symptoms are common in advanced MS. However, it is unclear if the reverse is true, that is, whether the presence of early cerebellar symptoms indicates faster disability progression. Some previous studies found no association between early cerebellar presentation and the risk of disability progression.[10,12,18] However, Amato et al. showed that cerebellar manifestation at MS onset was associated with both higher disability (HR = 1.48, 95% CI = 1.09–2.01) and rapid shift to secondary progressive course (HR = 1.53, 95% CI = 1.01–2.32).[8] Similar results were reported by Riise and colleagues, who observed that the presence of early cerebellar symptoms was a strong predictor of faster disability accumulation (β = 0.68, 95% CI = 0.23–1.14 and HR = 1.60, 95% CI = 1.07–2.40).[11] In agreement with these studies, our work demonstrated an increased risk of disability progression found in patients with early cerebellar symptoms. This observation was further confirmed by sensitivity analyses of more than 5000 patients with long-term follow-up and was independent from the measured potential confounders of disability outcomes. The unfavourable outcomes could be explained by the early presence of gait

Table 4. Sensitivity analysis: patients with definite MS and ⩾ 5-year follow-up ($n = 5608$).

Domains affected in the first 2 years	*n* (%)	EDSS scores (Mixed effect models)		Disability progression (Andersen-Gill models)		Relapse (Andersen-Gill models)	
		β (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Cerebellar	1504 (26.8)	0.18 (0.16–0.21)	<0.001	1.15 (1.03–1.29)	0.012	1.00 (0.95–1.05)	0.96
Brainstem	2213 (39.5)	−0.07 (−0.09 to −0.04)	<0.001	0.90 (0.81–0.99)	0.034	0.95 (0.90–1.01)	0.11
Pyramidal	3046 (54.3)	0.18 (0.16–0.21)	<0.001	1.18 (1.06–1.32)	0.002	1.02 (0.97–1.07)	0.45

β: regression coefficient; HR: hazard ratio; CI: confidence interval; EDSS: expanded disability status scale.
The sensitivity analysis assessed long-term outcomes by only including patients with at least 5 years of follow-up and with an early definite diagnosis of MS.

ataxia, which may exacerbate motor symptoms, including gait impairment, and thus directly contributes to higher EDSS. The discrepancy between our result and that of some previous studies[10,12,18] was possibly due to differing definitions of study outcomes used. Indeed, Harding et al.[19] demonstrated that cerebellar symptoms at disease onset was only associated with time to certain disability milestones (EDSS 8.0 but not EDSS 4.0 and 6.0). Similarly, Scalfari et al.[20] suggested that even though the type of clinical onset was not associated with the latency from MS onset to SPMS, those presenting with cerebellar symptoms at onset accumulated disability faster once they reached secondary progressive phase.

In contrast, only few studies have specifically investigated the prognostic value of early brainstem symptoms in MS, with mostly mixed results.[8,10–12] In a 503 patient cohorts, brainstem symptoms at MS onset were not identified as a prognostic marker for disability (β = 0.10, 95% CI = −0.32 to 0.53) nor the rate of conversion into progressive MS (HR = 1.25, 95% CI = 0.82–1.91).[11] In contrast, Phadke[18] demonstrated a significantly better prognosis in patients with an initial isolated brainstem lesion (HR = 0.60, 95% CI = 0.38–0.95). Brainstem relapses were also found to be associated with a higher chance of complete recovery than relapses of other phenotypes.[2] Using disability accumulation rather than relapse recovery as study outcome, our results confirmed the relatively favourable prognosis of patients with early brainstem symptoms.

Cerebellar presentations can at times be confused for brainstem presentations in routine clinical practice. In fact, some studies have previously investigated the prognostic value of cerebellar and brainstem symptoms together as one domain.[3] Our study has shown that while the time between MS onset and DMT initiation was relatively similar between the two groups, the proportion of patients with complete recovery from first relapse was marginally higher in patients with early brainstem symptoms. Furthermore, the differential rates of disability accumulation between the two domains emphasise the need to separate cerebellar from brainstem presentations in clinical practice.

Several known confounders of MS disability outcomes were included in our statistical models. Consistent with previous studies, we have found that older age at onset,[9,21–23] male sex,[9,21–24] early secondary progressive course[15,25] and a higher relapse frequency during the first years of MS[9,21,23,26] were invariably associated with an increased likelihood of disability progression. Baseline EDSS, however, was not associated with long-term disability, most probably due to the narrow

range of EDSS recorded in the first 2 years in our cohort. In contrast, our study confirmed that patients with a higher number of impaired neurological domains in the initial 2 years are at risk of further disability accumulation,[8,22] with 10% increase in the cumulative hazard per each additional affected domain. This could potentially be attributed to the relationship between the number of impaired neurological domains and both the extent of central nervous system damage and the impact on ambulatory function (which is an important determinant of EDSS scores in EDSS > 4).[14] Finally, we have demonstrated that all three groups of DMTs were associated with lower risks of disability progression and slower disability accumulation, in keeping with the results of other studies.[27]

Our study was subject to limitations that are inherent in the observational nature of the studied data set. The study may be affected by selection bias, potentially introduced by the inclusion criteria, which might limit the generalisability of the results. We have mitigated the risk of selection bias by limiting inclusion criteria to the minimum necessary criteria to select patients with sufficient information about the relevant MS symptoms and disability. The reporting of cerebellar and brainstem signs in clinical practice can be at times imprecise.[28] We have, therefore, compared the outcomes in groups presenting with either cerebellar or brainstem signs and have also attempted to minimise the diagnostic inaccuracies by the requirement of Neurostatus certification at each participating centre. Furthermore, the responses to our questionnaire, whose purpose was to assess the level of agreement and consistency among a sample of study investigators, demonstrated excellent differentiation between the two domains. It should be noted that the respondents to the questionnaire were principal investigators at participating sites and may be only partially representative of the full cohort of study investigators. While we have adjusted the analyses for multiple known and measured prognostic markers, the results may be subject to unmeasured confounding. Quantification of MS-related disability with EDSS is limited by the non-linear nature of this scale.[29] Therefore, our primary analysis relied on 6 months confirmed disability progression, a standard metric used in the clinical trials of MS therapies,[15] and was complemented by the analysis of EDSS scores. While heterogeneity may exist in the studied global multicentric cohort, we have controlled for centre-specific management and within-patient dependence by incorporating centre and patient ID as random effects in the linear models and by clustering patients in the Andersen-Gill models. The treatment variables were included to adjust for modification of disability outcomes by therapy; a reader should resist the temptation to draw inference about treatment effectiveness based on the reported hazard ratios. Given that lesion size and load are associated with MS disability outcomes, the lack of MRI parameters prevented us from evaluation of this aspect of phenotypic prognostics. However, this emphasises the focus of our study on early presentations of cerebellar and brainstem symptoms based on clinical data, which are more readily available prognostic markers. The availability of degree of remission from first relapse, documented in only 56% of the cohort, remained another limitation in this study. Given that relapse phenotypes are inherently associated with different likelihood of recovery,[30] the differences in relapse recovery may act as a mediator between relapse phenotype and disability accumulation. Models of causal relationship should not adjust for mediators of the relationship of interest, as this leads to overadjustment and could introduce additional confounding.[31,32] Recovery from relapses serves as the mediator of the relationship between relapse phenotype and long-term disability outcomes and was therefore not adjusted for. Finally, there is a risk that patients with progressive MS forms may be misclassified as having relapsing–remitting MS by their physicians during the first 2 years of MS onset, partly due to the typically longer time required for the diagnosis of progressive MS.[33,34] Only 4% of our cohort was diagnosed with SPMS during the observation period. However, such low proportion of SPMS is not unexpected in a cohort where 75% patients were followed up for an average of 10.3 years from MS onset, and in the context of active immunotherapy, which is known to delay the onset of secondary progressive stage. There also tends to be a hesitation among clinicians to diagnose SPMS, as this would often limit patients' access to DMTs.

Conclusion

Using a large and representative MS cohort, this study has shown that early cerebellar presentation in MS is associated with a greater risk of disability accrual, whereas early brainstem presentation is associated with relatively favourable disability outcomes. Our findings could allow physicians to identify a subgroup of MS patients at higher risk of severe irreversible neurological disability, who may benefit from more aggressive therapies to mitigate such unfavourable disease trajectory.

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Supplemental material

Supplemental material for this article is available online.

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