MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Contribution of different relapse phenotypes to disability in multiple sclerosis

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Multiple Sclerosis Journal

2017, Vol. 23(2) 266–276

DOI: 10.1177/1352458516643392

Abstract

Objective: This study evaluated the effect of relapse phenotype on disability accumulation in multiple sclerosis.

Methods: Analysis of prospectively collected data was conducted in 19,504 patients with relapse-onset multiple sclerosis and minimum 1-year prospective follow-up from the MSBase cohort study. Multivariable linear regression models assessed associations between relapse incidence, phenotype and changes in disability (quantified with Expanded Disability Status Scale and its Functional System scores). Sensitivity analyses were conducted.

Results: In 34,858 relapses recorded during 136,462 patient-years (median follow-up 5.9 years), higher relapse incidence was associated with greater disability accumulation ($\beta = 0.16$, $p < 0.001$). Relapses of all phenotypes promoted disability accumulation, with the most pronounced increase associated with pyramidal ($\beta = 0.27$ (0.25–0.29)), cerebellar ($\beta = 0.35$ (0.30–0.39)) and bowel/bladder ($\beta = 0.42$ (0.35–0.49)) phenotypes (mean (95% confidence interval)). Higher incidence of each relapse phenotype was associated with an increase in disability in the corresponding neurological domain, as well as anatomically related domains.

Conclusion: Relapses are associated with accumulation of neurological disability. Relapses in pyramidal, cerebellar and bowel/bladder systems have the greatest association with disability change. Therefore, prevention of these relapses is an important objective of disease-modifying therapy. The differential impact of relapse phenotypes on disability outcomes could influence management of treatment failure in multiple sclerosis.

Keywords: Prognosis, outcome research, multiple sclerosis, observational study, cohort studies, relapse phenotype

Date received: 1 November 2015; revised: 24 February 2016; accepted: 15 March 2016

Introduction

The accumulation of disability in patients with multiple sclerosis (MS) is highly variable. High relapse rate has previously been established as a negative prognostic factor.[1–3] It has also been suggested that the clinical presentation of relapses (relapse phenotype) is an important determinant of individual prognosis and thus could influence treatment outcomes.[4] Previous studies have reported a relationship between onset symptom location and prognosis,[4–11] yet studies reporting any relationship between subsequent relapse phenotypes and prognosis have been limited.[12]

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The fact that patients show a tendency to repeatedly develop relapses of a certain phenotype[13–15] suggests that an association between relapse phenotype and disability accumulation in the same system is likely to exist. Our study assessed the relationship between disability accumulation and relapse phenotype using the international MSBase cohort, which encompasses a large, representative MS population with long-term, prospectively acquired follow-up data. We first evaluated the association between overall disability outcomes and the number of relapses. Next, we evaluated associations between overall disability outcomes and number of relapses classified by phenotype. Finally, we examined associations between domain-specific disability outcomes and number of relapses classified by phenotype, including interactions among anatomically associated domains.

Materials and methods

Ethics

MSBase (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee[16] and the local ethics committees in all participating centres (or exemptions were granted, according to local laws and regulations). Enrolled patients provided written informed consent as required.

Participants

Data from 32,349 patients from 87 MS centres in 27 countries were extracted from the MSBase registry dataset in January 2015. Inclusion criteria consisted of diagnosis of clinically definite MS (according to the 2005 or 2010 revised McDonald criteria) or clinically isolated syndrome (CIS), relapse-onset MS (i.e. relapsing-remitting multiple sclerosis (RRMS) or secondary progressive MS), at least two Expanded Disability Status Scale (EDSS) scores recorded over at least 1 year (EDSS scores within 30 days of a previous relapse were excluded) and the availability of the minimum dataset. The minimum dataset requirements included date of birth, sex, MS centre, MS course at dates of inclusion and censoring, dates of disease-modifying therapy commencement and cessation, and clinical relapses (including relapse onset date and phenotype). For the analysis of the associations between relapse and disability phenotypes, at least two Kurtzke Functional System (KFS) scores recorded over at least 1 year were required. Only relapses recorded during the prospective follow-up period (see below) were included for the analysis.

Data entry into the MSBase registry is real time, or near real time, in relation to clinical visits. Relapse information is recorded by treating physicians according to patient reports and clinical examination. The MSBase protocol stipulates minimum annual updates of the minimum dataset, but patients with less frequent updates were not excluded from the analysis (if the inclusion criteria were fulfilled). The portals for data entry were either the iMed clinical record system or the MSBase online data entry system. Data quality assurance procedures were described elsewhere.[17] To enhance reproducibility of the clinical assessment of disability, Neurostatus certification was required at each participating centre.

Study design

The prospective follow-up period was defined as the time between the first and last recorded EDSS scores. Where KFS score was the primary outcome, the time between the first and last recorded corresponding KFS scores was used instead. The inclusion and censoring dates were defined as the dates of the first and the last recorded EDSS score, respectively. Changes in EDSS or KFS scores were calculated as differences in EDSS or KFS scores at the inclusion versus the censoring dates.

Relapses were defined as the occurrence of new symptoms, or exacerbation of existing symptoms, persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse.[18] Confirmation by increased EDSS was not required. Relapses were divided into seven phenotypes according to the presenting symptoms and signs: pyramidal, sensory, bowel/bladder, cerebellar, brainstem, visual and cerebral. Polysymptomatic relapses included multiple phenotypes.

Data analysis

Statistical analysis was performed using the R package (version 3.1.0).[19] All hypotheses were tested at a two-tailed 0.05 level of significance and Benjamini–Hochberg correction was used to control false-discovery rate.

For all three analytical steps, multivariable regression models were designed to estimate the effects of continuous and categorical independent determinants of patients' change in EDSS score or KFS score over the prospective follow-up period. The overall total number of relapses experienced during the follow-up period was included to assess its effect on overall EDSS change (step 1). In order to evaluate the effect

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of relapses over an extended follow-up period, an additional analysis of patients with at least 10-year prospective follow-up was conducted. In two separate models, associations between disability accrual and additional relapse properties were examined: the mono- or polysymptomatic relapse presentation and treatment with corticosteroids. The number of relapses for each of the seven phenotypes experienced during the follow-up period was used in seven models assessing associations between relapse phenotypes and overall EDSS change (step 2). As part of step 2, independent association of each phenotype with the EDSS change was evaluated in a single multivariable regression model that included all seven relapse phenotypes. Finally, 49 multivariable regression models were designed to assess associations between each of the seven relapse phenotypes and changes in the seven KFS scores (step 3). In addition, sex, age, MS centre, MS course at inclusion, duration of the follow-up period, disease duration, the proportion of the follow-up period that the patient was treated with disease-modifying therapy, date of inclusion, baseline EDSS (recorded at inclusion), proportion of relapses treated with steroids and proportion of relapses that occurred while on disease-modifying therapy were assessed as independent predictors in all models. The Akaike Information Criterion was used to assess goodness of fit of the models.

Sensitivity analyses were conducted (a) to assess the effect of the minimum required relapse count by excluding, from all analyses, patients with no relapses recorded during the follow-up period, (b) to evaluate the associations between relapse incidence and change in EDSS confirmed for ⩾12 months[20] and (c) in patients with long-term prospective follow-up from early after disease onset, recorded as part of the MSBase Incident Study (MSBASIS) study.[21,22]

Results

Patient and relapse characteristics

Out of the 32,349 patients with data in the MSBase registry, 19,504 patients with 136,462 patient-years from 77 MS centres were retained for the analysis after inclusion/exclusion criteria were applied (Figure 1). The number of patients retained per centre ranged from 1 to 2,570 (Online Supplementary Table 1). Median prospective follow-up period was 5.9 (interquartile range: 3.1–9.8) years per patient. The mean relapse rate was 0.25 per year (standard deviation: 0.36). Patient characteristics at inclusion and censoring are outlined in Table 1 and their comparison to the excluded patients is provided in Online Supplementary

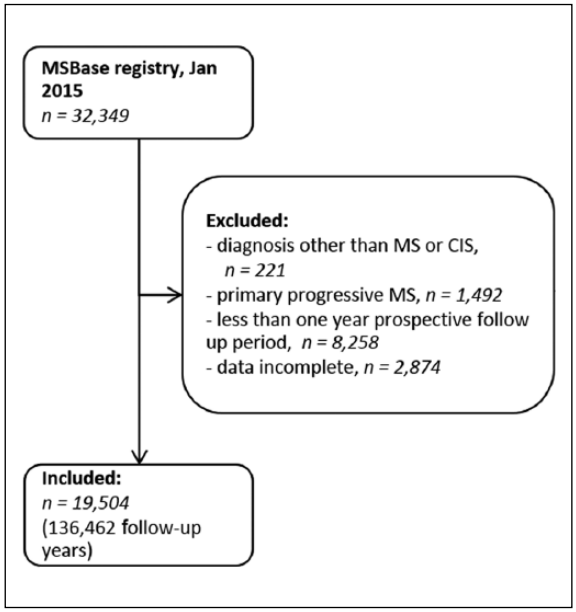

Figure 1. CONSORT flowchart of patient disposition. The patients excluded due to incomplete data had at least one of the following information missing: MS course at inclusion and censoring, disease-modifying therapy, relapse-related information (relapse onset, phenotype).

Table 2. The included patients experienced 34,858 relapses, with a median of 1 (interquartile range: 0–2) relapse per patient. In total, 53% were treated with steroid therapy and 52% had occurred while the patient was on disease-modifying therapy. Of the 28,310 relapses with phenotype information, patients experienced mostly relapses that included sensory and/or pyramidal symptoms/signs (50% and 42%, respectively). The majority (68%) of relapses with phenotype information were monosymptomatic. Relapse characteristics are outlined in Table 1.

Relapse frequency and change in EDSS

The multivariable regression model used in step 1 showed that higher relapse frequency was associated with an increase in EDSS, independent of the duration of the prospective follow-up period ($\beta = 0.16$, 95% confidence interval (95% CI): 0.13–0.19; Table 2). In addition, a longer follow-up period, older age, male sex, longer disease duration and a diagnosis of secondary progressive MS at inclusion were associated with a greater increase in EDSS, while a higher EDSS score at baseline, greater persistence on disease-modifying therapy and a diagnosis of CIS at inclusion were associated with a smaller increase in EDSS score. An interaction term demonstrated that the effect of relapse frequency on EDSS change decreased with longer

Table 1. Patient and relapse characteristics.

	At inclusion	At censoring
Patients		
Patient number (female)	19,504 (72%)	
Age (years)[a]	37.6 (11.2)	44.6 (11.7)
Follow-up period (years)[b]		5.9 (3.1–9.8)
Disease duration (years)[b]	3.8 (1–10.2)	11.9 (6.7–19)
EDSS[b]	2 (1–3.5)	2.5 (1.5–4.5)
Change in EDSS[b]		0.5 (0–1.5)
Number of relapses[b]		1 (0–2)
Proportion of follow-up time on DMT[b]		65% (0%–97%)
Disease course		
CIS	4167 (21%)	1513 (8%)
RRMS	13,829 (71%)	14,992 (77%)
SPMS	1508 (8%)	2999 (15%)
Relapses		
Total relapses		34,858
Relapses treated with steroids		18,431 (53%)
Relapses while on DMT		18,109 (52%)
Relapse phenotype recorded		28,310 (81%)
Monosymptomatic relapses		19,362 (68%)
Polysymptomatic relapses		8948 (32%)
Pyramidal[c]		11,962 (42%)
Bowel/bladder[c]		1602 (6%)
Cerebellum[c]		2959 (10%)
Visual[c]		4030 (14%)
Brainstem[c]		4397 (16%)
Cerebral[c]		375 (1%)
Sensory[c]		14,279 (50%)

EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy; CIS: clinically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
[a]Mean (standard deviation).
[b]Median (interquartile range).
[c]The number of relapses with the specific phenotypes includes both mono- and polysymptomatic relapses.

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follow-up period. Relapses with polysymptomatic presentation showed a relatively stronger association with disability accrual than monosymptomatic relapses (β=0.20, 95% CI: 0.17–0.23 vs β=0.06, 95% CI: 0.04–0.09, respectively). Relapses treated with corticosteroids were more likely to result in disability accrual than the untreated relapses (β=0.06, 95% CI: 0.04–0.08). An analysis of patients with at least 10-year prospective follow-up (n=4709) confirmed the above results (see Online Supplementary Table 3).

Relapse phenotype and change in EDSS

Of the 19,504 patients who met the inclusion criteria, 16,052 had complete available phenotypic information for all relapses experienced and were included for analysis in step 2. Outcomes of seven multivariable models, each of which included only one relapse phenotype, are summarised in Table 3. All of the relapse phenotypes were associated with an increase in EDSS score. Change in EDSS disaggregated for relapse count and phenotype is visualised in Figure 2.

A model encompassing all seven relapse phenotypes was designed to compare their mutually independent associations with EDSS change. The model showed that the positive associations of pyramidal (0.27 (0.25 to 0.30)), cerebellar (0.17 (0.12 to 0.22)) and bowel/bladder (0.12 (0.04 to 0.19)) relapses with the increase in EDSS were relatively more pronounced than those of brainstem (0.03 (−0.02 to 0.07)), visual (−0.03 (−0.07 to 0.01)), sensory (−0.08 (−0.10 to 0.05)) and cerebral (−0.17 (−0.3 to −0.02)) relapses (coefficient (95% CI)).

Table 2. Multivariable model of the associations between relapse number and EDSS change.

	Beta coefficient (95% CI)	*p* value
Number of relapses (per one relapse)	0.16 (0.13 to 0.19)	<0.001
Age (per year)	0.03 (0.03 to 0.03)	<0.001
Sex (male)	0.18 (0.14 to 0.23)	<0.001
Follow-up period (per year)	0.06 (0.05 to 0.07)	<0.001
Disease duration (per year)	0.01 (0.01 to 0.02)	<0.001
Baseline EDSS (per one point)	−0.29 (−0.31 to −0.28)	<0.001
DMT treatment proportion (per 10%)	−0.01 (−0.02 to −0.00)	0.004
Disease course (RRMS)	Reference	
CIS	−0.16 (−0.22 to −0.10)	<0.001
SPMS	0.86 (0.77 to 0.96)	<0.001
Number of relapses by follow-up period (interaction term)	−0.01 (−0.01 to 0.00)	<0.001

EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy; CIS: clinically isolated syndrome; SPMS: secondary progressive multiple sclerosis; CI: confidence interval; RRMS: relapsing-remitting multiple sclerosis.
The multivariable regression coefficients represent the estimated mean change in EDSS score per relapse after the effect of the confounding variables has been taken into account.

Table 3. Change in EDSS according to relapse phenotype.

Relapse phenotype	Beta coefficient (95% confidence interval)	*p* value
Pyramidal	0.27 (0.25–0.29)	<0.001
Sensory	0.05 (0.03–0.07)	<0.001
Bowel/bladder	0.42 (0.35–0.49)	<0.001
Cerebellar	0.35 (0.30–0.39)	<0.001
Brainstem	0.15 (0.11–0.19)	<0.001
Visual	0.06 (0.02–0.10)	0.008
Cerebral	0.25 (0.12–0.39)	<0.001

EDSS: Expanded Disability Status Scale.
The results of seven multivariable models (for details of the models, see Table 2). For each model, only the association for the corresponding relapse phenotype is shown. The multivariable regression coefficients represent the estimated mean change in EDSS score per relapse of the given phenotype after the effect of the confounding variables has been taken into account.
p values adjusted according to the Benjamini–Hochberg method.

Relapse phenotype and change in KFS scores

Finally, we designed a series of multivariable models to evaluate associations between relapse phenotype and changes in disability in each functional domain (step 3). Of the 19,504 included patients, between 14,199 and 14,277 patients had sufficient phenotypic information for the studied KFS changes. Outcomes of 49 multivariable models, each of which included only one relapse phenotype and change in one KFS score (adjusted for patient and disease characteristics as in step 1) are summarised in Table 4. For each of the seven functional domains, relapses with the respective phenotype predicted an increase in the corresponding KFS score. We also observed associations between certain relapse phenotypes and accumulation of disability in anatomically related domains (such as the long descending and ascending fibres and the infra-tentorial region). For example, pyramidal relapses led to an increase in the bowel/bladder KFS score, and vice versa, while brainstem relapses led to an increase in the cerebellar KFS score, and vice versa. In addition, the number of cerebellar relapses was associated with changes in the pyramidal and bowel/bladder KFS scores. In contrast, the magnitude of the associations between visual or sensory relapses and visual or sensory KFS score change was relatively low.

Sensitivity analyses

The first sensitivity analysis, which assessed the effect of relapse phenotype among patients who

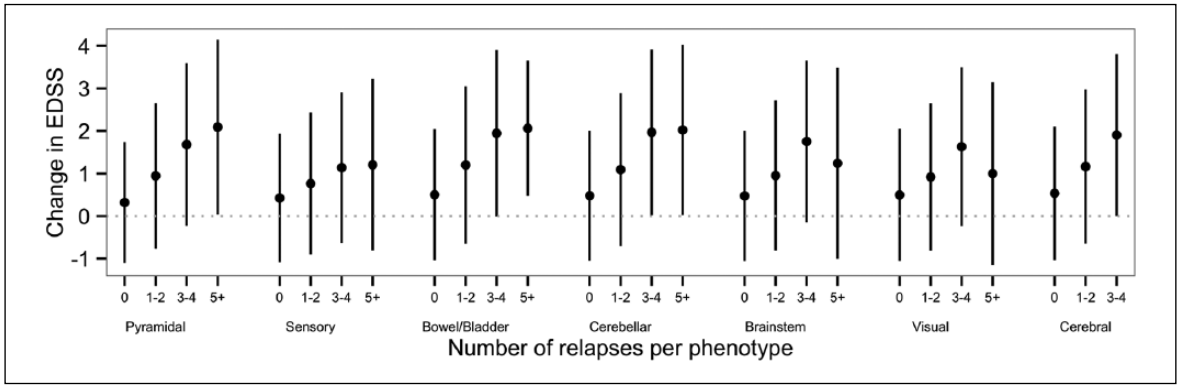

Figure 2. Change in EDSS according to number of relapses experienced per phenotype. Markers indicate the mean change in EDSS for patients who experienced 0, 1–2, 3–4 or more than 5 relapses of each phenotype. Error bars indicate standard deviation.

Table 4. Multivariable models of the associations between relapse phenotypes and likelihood of change in KFS scores.

Relapse phenotype	Pyramidal KFS score	Sensory KFS score	Bowel/bladder KFS score	Cerebellar KFS score	Brainstem KFS score	Visual KFS score	Cerebral KFS score
Pyramidal	0.16 (0.15–0.18)	0.10 (0.09–0.12)	0.10 (0.09–0.12)	0.11 (0.10–0.13)	0.05 (0.04–0.06)	0.02 (0.01–0.03)	0.03 (0.02–0.04)
Sensory	0.05 (0.03–0.06)	0.07 (0.05–0.08)	0.04 (0.02–0.05)	0.03 (0.02–0.04)			
Bowel/ bladder	0.29 (0.24–0.34)	0.22 (0.17–0.26)	0.28 (0.24–0.33)	0.19 (0.14–0.23)	0.09 (0.06–0.13)	0.08 (0.03–0.12)	0.07 (0.04–0.11)
Cerebellar	0.18 0.15–0.22)	0.10 0.07–0.13)	0.15 (0.12–0.18)	0.22 (0.19–0.25)	0.12 (0.10–0.15)	0.04 (0.01–0.07)	0.07 (0.05–0.09)
Brainstem	0.09 (0.07–0.12)	0.08 (0.05–0.10)	0.05 (0.02–0.07)	0.11 (0.09–0.14)	0.09 (0.07–0.11)		0.05 (0.03–0.07)
Visual	0.05 (0.02–0.08)	0.05 (0.03–0.08)	0.04 (0.01–0.06)	0.05 (0.03–0.08)	0.04 (0.02–0.06)	0.07 (0.05–0.10)	
Cerebral	0.18 (0.08–0.28)			0.19 (0.10–0.28)	0.09 (0.01–0.16)		0.18 (0.11–0.25)

KFS: Kurtzke Functional System.
Coefficients from 49 adjusted multivariable models of associations between relapse phenotype and change in KFS scores are shown (coefficient (95% confidence interval)). The multivariable regression coefficients represent the estimated mean change in EDSS score per relapse of the given phenotype after the effect of the confounding variables has been taken into account. Only the coefficients significantly different from 0 are shown ($p < 0.05$ after the Benjamini–Hochberg correction).

experienced at least one relapse during follow-up (Online Supplementary Tables 4–6), included 11,290 patients with 95,809 patient-years follow-up and a median of 2 (interquartile range: 1–4) relapses. This analysis confirmed the association between relapse frequency, as well as pyramidal, bowel/bladder, cerebellar, brainstem and cerebral relapse frequency and increased disability accumulation. However, in this cohort, sensory ($p = 0.40$) and visual ($p = 0.59$) relapses were not associated with an increase in EDSS.

The second sensitivity analysis ($n = 10{,}562$) confirmed that the higher relapse frequency as well as pyramidal, bowel/bladder and cerebellar relapses were associated with the increase in EDSS confirmed over ⩾12 months. On the other hand, the associations between visual, sensory, brainstem and cerebral relapse phenotypes and disability outcomes were not confirmed (Online Supplementary Tables 7 and 8).

Finally, the sensitivity analysis evaluating the effect of relapse phenotype among patients with long-term prospective follow-up from disease onset (the MSBASIS study) included 3093 patients with 15,609 patient-years follow-up, a median time from the first symptom of 4.8 (interquartile range: 2.4–9.6) months, and a median of 1 (interquartile range:

0–2) relapse per patient. This analysis confirmed all results from the primary analysis, with stronger associations between relapse number and disability accumulation (Online Supplementary Tables 9–11). The sensitivity analyses confirmed that relapses with the respective phenotype predicted an increase in the corresponding KFS score.

Discussion

In this study conducted in almost 20,000 patients from the observational MSBase cohort, we have demonstrated that the overall association of MS relapses with accumulation of neurological disability varies depending on the relapse phenotype and is most pronounced for pyramidal, bowel/bladder and cerebellar relapses. We have shown that the phenotype of the accumulated disability corresponds to the phenotype of the preceding relapses. An association between disability phenotypes and relapses involving anatomically related functional systems is strongest for pyramidal, bowel/bladder and cerebellar relapses. In addition, we have observed that relapses involving multiple neurological functions are more likely to associate with increase in disability. Finally, acute treatment with corticosteroids is typically reflective of more severe relapses, which is demonstrated by their positive association with disability accrual.

We confirmed the results of several previous studies that showed that higher relapse frequency promotes disability accumulation.[1–3,23,24] Using data from 524 relapses, Hirst et al.[1] showed that a half of relapses resulted in an EDSS increase of at least 0.5 points, with nearly a third of relapses resulting in an increase of 1.0 EDSS points. Another study demonstrated that, in 224 patients, each relapse was associated with an average increase of 0.24–0.57 EDSS points.[2] Similarly, in our study, a relapse was independently associated with an increase in EDSS by 0.16 steps. In a cohort followed prospectively from early after disease onset, we observed a mean adjusted increase in EDSS by 0.28 steps per relapse, an effect whose magnitude is comparable to that reported by Lublin et al.[2]

While all relapse phenotypes were associated with disability accumulation, pyramidal, cerebellar and bowel/bladder relapses were the most influential predictors of unfavourable disability outcomes, whereas sensory and visual phenotypes were the least influential. These outcomes extend the results of other studies which demonstrated that motor,[5–9] cerebellar[5–9,23] and/or bowel/bladder[4–7] symptoms at MS onset are associated with less favourable disability outcomes compared to sensory and/or visual symptoms.[7,9]

While pyramidal relapses appeared to have the greatest effect on disability accumulation, it must be noted that the EDSS is weighted towards motor disability, particularly at the higher scores. However, pyramidal relapses were associated with an increased disability in all neurological domains as determined by their effect on all KFS scores, in particular, the bowel/bladder, sensory and cerebellar KFS scores. This confirms that the effect of pyramidal relapses on EDSS change is not solely determined by their effect on locomotion, but an interaction with multiple neurological domains.

It was also found that disability accumulation within specific neurological domains varied according to relapse phenotype. The number of relapses of each phenotype was positively associated with increase in the KFS score of the corresponding domain. While a similar phenomenon was described in the visual system,[25] this is the first study to examine this association for all seven functional domains. This finding is compatible with the observation of domain-specific relapse recurrence, which may potentially reflect anatomical, immunological or structural determinants of the topography of autoimmune inflammation.[14,26,27]

We have also shown that relapses of certain phenotypes are associated with accumulation of disability within neurological domains which are anatomically closely related to the domains directly affected by relapses. These domains correspond to two anatomically distinct systems: the long descending and ascending fibres (with observed associations among pyramidal, sensory and bowel/bladder relapses and their KFS scores) and the infra-tentorial structures (with associations between cerebellar and brainstem relapses and their KFS scores). Interestingly, bowel/bladder, pyramidal and cerebellar relapses, which have the largest impact on the overall disability change, were also associated with an increase in the KFS scores of all other neurological domains. One may therefore speculate that the relapses with a more widespread effect on the central nervous system may lead to a more pronounced accumulation of permanent disability. Furthermore, sensory and visual relapses, which are associated with a relatively lower change in disability, tend to occur in younger age.[14] It was shown that regenerative capacity within the central nervous system is greater in younger patients,[28] which may underline the relatively higher recovery rate of sensory and visual relapses.[14]

All relapse phenotypes were associated with an increase in the pyramidal or cerebellar KFS scores, with the pyramidal domain being the most susceptible to damage associated with relapses. It is possible that

this high susceptibility is proportional to the extensive length of the pyramidal pathways, in keeping with the hypothesis that the MS-related damage is a deterministic process where the risk of axonal damage depends on the axonal length. Against this hypothesis is the observation that sensory and bowel/bladder domains were relatively less susceptible to damage compared to the pyramidal domain, which would imply the role of other, tract- or region-specific factors in the overall susceptibility to permanent damage.

Several known MS prognostic factors were included in the statistical models used in this study. In agreement with the previous studies, older age,[29] male sex,[14,29] longer disease duration[23] and secondary progressive MS[20,30] were associated with an increased probability of disability accumulation. The inverse relationship between the baseline EDSS score and the probability of disability accrual was likely determined by several factors: (a) the asymmetry of the EDSS (where the scale is less stable towards the lower end of the disability spectrum, with a greater probability of transition between EDSS steps) and (b) a ceiling effect (where the range of nominal EDSS change among the patients with lower EDSS scores is greater than in those with higher EDSS scores.[20,31,32]

The main limitation of this study lies inherent in the method of measuring disability accumulation in patients with MS. The EDSS is a non-linear scale, thus a change of one EDSS point between lower scores and higher scores does not equate to the same proportional change in disability or functional status. While observational studies may be susceptible to recall bias, we have minimised its impact by only analysing information that was recorded between the first and the last recorded visits with full neurological assessment. We have tested the possible effect of reporting bias with sensitivity analyses, including only patients followed from early after disease onset (the MSBASIS cohort) and also by only assessing patients with at least one relapse recorded during the follow-up period. Both sensitivity analyses confirmed the results of the primary analyses. The intra- and interrater variability of the EDSS assessments may have contributed to some of the recorded changes in EDSS. We have minimised this error by conducting a sensitivity analysis that required confirmation of the EDSS scores over $\geqslant$12 months. This analysis has shown that the associations involving visual, sensory, cerebral and brainstem relapses could at least in part be attributed to the assessment error but has confirmed the effect of pyramidal, bowel/bladder and cerebellar relapses on disability change. Finally, selection bias inherent in the observational study may limit generalisability of the presented conclusions.

Conclusion

Using a large, representative MS cohort, this study has demonstrated that relapses are associated with disability accumulation. Furthermore, it has shown that relapse phenotype constitutes an additional prognostic marker readily accessible to clinicians and their patients. Therefore, prevention of relapses, in particular those presenting with pyramidal, cerebellar and bowel/bladder signs, represents an important therapeutic goal. Whether relapse phenotype should contribute to treatment initiation or switch decisions remains to be determined.

Acknowledgements

The list of MSBase Study Group co-investigators and contributors is given in the online supplement. Vilija Jokubaitis and Tomas Kalincik contributed equally to the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Tamasine Stewart did not declare any competing interests. Tim Spelman received compensation for travel from Biogen. Eva Havrdova received speaker honoraria and consultant fees from Biogen, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen, Merck Serono and research grants from Charles University in Prague (PRVOUK-P26/LF1/4) and Czech Ministry of Health (NT13237-4/2012). Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck Serono, Teva and Novartis, as well as support for research activities from Biogen and research grants from Charles University in Prague (PRVOUK-P26/LF1/4) and Czech Ministry of Health (NT13237-4/2012). Maria Trojano received speaker honoraria from Biogen Idec, Bayer Schering, Sanofi Aventis, Merck Serono, Teva, Novartis and Almirall; has received research grants for her Institution from Biogen Idec, Merck Serono and Novartis. Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck Serono and Teva. Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD Serono. Dr Girard has also received a research grant from Canadian Institutes of Health Research. Pierre Duquette did not declare any competing interests. Alexandre Prat did not declare

any competing interests. Alessandra Lugaresi is a Bayer, Biogen, Genzyme, Merck Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck, Novartis, Sanofi and Teva, research grants from Bayer, Biogen, Merck, Novartis, Sanofi and Teva, travel and research grants from the Associazione Italiana Sclerosi Multipla. Pierre Grammond is a Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis. Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals. Patrizia Sola received travel grants and speaking honoraria from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi/Genzyme and Teva. Vahid Shaygannejad did not declare any competing interests. Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck Serono, Biogen, Genzyme Sanofi and Teva, research funding from Merck Serono and Biogen, and speaker honoraria from Sanofi-Genzyme and Novartis. Raed Alroughani received honororia from Biologix, Biogen, Bayer, Genpharm, Genzyme, Merck Serono, GSK and Novartis and served on advisory board for Biologix, Biogen, Bayer, Genpharm, Genzyme, Novartis, Genzyme, Merck Serono and Novartis. Celia Oreja-Guevara received honoraria as consultant on scientific advisory boards from Biogen, Bayer Schering, Merck Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis. Eugenio Pucci served on scientific advisory boards for Genzyme and Biogen; he has received honoraria and travel grants from Sanofi Aventis, UCB, Lundbeck, Novartis, Bayer Schering, Biogen, Merck Serono, Genzyme and Teva; he has received travel grants from Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche. Cavit Boz received conference travel support from Biogen, Novartis, Bayer Schering, Merck Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. Jeannette Lechner-Scott has accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment and also clinic support from Bayer Health Care, Biogen, CSL, Genzyme Sanofi, Merck Serono and Novartis. Roberto Bergamaschi received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi Aventis, Teva; research grants from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi Aventis, Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi Aventis, Teva. Vincent Van Pesch has served on advisory boards for Biogen, Novartis Pharma and Sanofi-Genzyme; has received travel grants and consultancy fees from Biogen, Bayer Schering, Sanofi Aventis, Merck Serono, Sanofi-Genzyme and Novartis Pharma; has received research grants from Bayer Schering. Gerardo Iuliano had travel/accommodations/meeting expenses funded by Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi Aventis, and Teva. Cristina Ramo-Tello received research funding, compensation for travel or speaker honoraria from Biogen, Novartis, Genzyme and Almirall. Ricardo Fernandez-Bolanos received speaking honoraria from Biogen, Novartis, Merck Serono and Teva. Bruce Taylor has received funding for travel and speaker honoraria from Bayer Schering Pharma, CSL Australia, Biogen and Novartis. Mark Slee has participated in, but not received honoraria for, advisory board activity for Biogen, Merck Serono, BayerSchering, Sanofi Aventis and Novartis. Daniele Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer Schering, Novartis and Sanofi Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck Serono. Franco Granella has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall. Freek Verheul is an advisory board member for Teva Biogen Merck Serono and Novartis. Pamela McCombe has received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi and travel grants from Novartis, Biogen and Bayer Schering. Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering. Maria Pia Amato received honoraria as consultant on scientific advisory boards by Biogen, Bayer Schering, Merck Serono, Teva and Sanofi Aventis; has received research grants by Biogen, Bayer Schering, Merck Serono, Teva and Novartis. Steve Vucic did not declare any competing interests. Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck Serono and Novartis; has received travel grants from Biogen, Merck Serono and Novartis; has participated in clinical trials by Biogen and Merck Serono. Edgardo Cristiano received honoraria as consultant on scientific advisory boards by Biogen, Bayer Schering, Merck Serono, Genzyme and Novartis; has participated in clinical trials/other research projects by Merck Serono, Roche and Novartis. Michael

Barnett has served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck Serono and Novartis. Erik van Munster received served on scientific advisory boards for Merck Serono, Novartis, Biogen, De Baar Solutions BV, and Genzyme Sanofi. Maria Laura Saladino did not declare any competing interests. Javier Olascoaga serves on scientific advisory boards for Biogen, Genzyme and Novartis; has received speaker honoraria from Biogen, Bayer Schering, Genzyme, Merck Serono, Novartis and Teva and research grants from Biogen, Merck Serono, Novartis and Teva. Julie Prevost has accepted travel compensation from Novartis, Biogen, Genzyme, Teva and speaking honoraria from Biogen, Novartis, Genzyme and Teva. Norma Deri received funding from Bayer, Merck Serono, Biogen, Genzyme and Novartis. Cameron Shaw received travel assistance from Biogen and Novartis. Bhim Singhal received consultancy honoraria and compensation for travel from Biogen and Merck Serono. Fraser Moore has participated in clinical trials sponsored by EMD Serono and Novartis. Neil Shuey has received travel compensation from Bayer Schering, Novartis and Biogen Idec. Csilla Rozsa has received speaker honoraria from Bayer Schering, Novartis and Biogen, congress and travel expense compensations from Biogen, Teva, Merck Serono and Bayer Schering. Olga Skibina did not declare any competing interests. Ilya Kister served on scientific advisory board for Biogen and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen, Serono and Novartis. Tatjana Petkovska-Boskova received congress and travel expense compensations from Biogen Idec and Teva. Radek Ampapa has received conference travel support from Novartis, Teva, Biogen, Bayer and Merck Serono and has participated in a clinical trials by Biogen, Novartis, Teva and Actelion. Allan Kermode has received speaker honoraria and scientific advisory board fees from Bayer, BioCSL, Biogen, Genzyme, Innate Immunotherapeutics, Merck Serono, Novartis, Sanofi, Sanofi Aventis and Teva. Helmut Butzkueven has served on scientific advisory boards for Biogen, Novartis and Sanofi Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis and has received research support from Merck Serono, Novartis and Biogen. Vilija Jokubaitis has received conference travel support from Novartis. Tomas Kalincik has served on an advisory scientific board for Novartis, Merck and Biogen and has received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi, Genzyme, Teva, BioCSL and Merck and has received research support from Biogen.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financially supported by National Health and Medical Research Council (practitioner fellowship 1080518, project grants 1083539 and 1032484 and centre for research excellence 1001216) and University of Melbourne (Faculty of Medicine, Dentistry and Health Sciences research fellowship). The MSBase Foundation is a not-for-profit organisation that receives support from Merck, Biogen, Novartis, Bayer Schering, Sanofi Aventis and BioCSL. The study was conducted separately and apart from the guidance of the sponsors.

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