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The onset location of multiple sclerosis predicts the location of subsequent relapses

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ABSTRACT

Background: Demyelinating events in relapsing-remitting multiple sclerosis (RRMS) can involve several locations in the central nervous system. We sought to determine if initial clinical demyelinating event (IDE) location predicts subsequent clinical relapse locations in early RRMS.

Methods: We identified all RRMS patients from two large MS clinics who were seen within 1 year of disease onset. Logistic regression was performed with the outcome defined as the second or third exacerbation location and the predictor defined as IDE \pm second event location.

Results: 195 patients with at least two clinical exacerbations were identified. There was an increased odds of a patient's second relapse occurring in the spinal cord if the IDE was in the spinal cord (odds ratio (OR) = 3.79, 95% CI 2.06 to 7.00, $p < 0.001$). There was more than a sixfold increase in the odds of a patient's second relapse occurring in the optic nerve if the IDE was in the optic nerve (OR = 6.18, 95% CI 2.90 to 13.18, $p < 0.001$). These associations remained similar after adjusting for treatment and patient characteristics. If the IDE and second event were both in the same location (spinal cord, optic nerve or brainstem/cerebellum), the third event was likely to remain in that location.

Conclusion: Patients with RRMS have relatively localised clinical relapses. It remains to be determined if genetic or biological processes are responsible for this pattern.

While many autoimmune diseases have the potential to affect more than one organ system, the phenotypic manifestations of these disorders often vary at the individual level. There may be several explanations for this variability. For example, in systemic lupus erythematosus (SLE), specific genetic polymorphisms influence which organs are affected by the disease¹⁻³ while simultaneously, a particular autoantibody may predict a unique set of clinical outcomes.⁴

Multiple sclerosis (MS) is also a heterogeneous disease. Although there are distinct pathological subtypes in early MS, one group found that within an individual patient, active lesions were of similar pathology.⁵ Relapse location may be one way to clinically characterise relapsing-remitting (RR) MS. If individual MS patients experience recurrent clinical exacerbations in a specific location of the central nervous system (CNS), one might hypothesise it could be due to genetic and/or biological processes. Such a propensity for relapses to occur in a given CNS location has been demonstrated within families.⁶

In a mostly retrospective study of patients with a long history of RRMS, we reported that patients who were treated with interferon beta (IFNB), as

compared with glatiramer acetate (GA), were more likely to have their next relapse in the spinal cord versus another CNS location, regardless of pretreatment relapse location.⁷ While pretreatment attack location did appear to predict the post-treatment event location, that the data were retrospective and were collected in a group of individuals with more advanced MS raised concerns that recall and/or misclassification bias (due to missed, subtle exacerbations, pseudoexacerbations or improper interpretation of relapse location) were threats to validity.

In this study, we sought to determine if patients tend to have clinical relapses in specific CNS locations independent of treatment in a prospective cohort of patients with RRMS who were seen within 1 year of their initial demyelinating event (IDE).

METHODS

This study was approved by the UCSF and Marseille Committees on Human Research. Each patient's relapses were coded as occurring in the spinal cord, brainstem/cerebellum, optic nerve or cerebrum; further, they were categorised as mono-regional (all symptoms could be explained by a single lesion) or polyregional. Demyelinating events were defined as new or recurring neurological symptoms referable to the CNS lasting for at least 48 h after a remission of 30 days or more since the previous event. Only patients who had at least two demyelinating events were included in the study. The severity of and recovery from each demyelinating event were determined by trained individuals (SD, EM) based on definitions that take into account the Functional Systems scores, Expanded Disability Status Scale scores and visual acuities of patients, as described in previous publications.⁷⁻⁹ Pseudo-exacerbations (transient, recurrent neurological symptoms in the context of infection or fever) and patients with neuromyelitis optica (NMO) were excluded.¹⁰

At UCSF, clinical and demographic information for all patients seen within 1 year of the IDE at the adult and paediatric MS Centers is prospectively entered into a Microsoft SQL server database.^{8, 11} Clinic visits usually occur every 6 months, and unscheduled visits occur if a patient has an exacerbation. At the MS Unit of the Pole de Neurosciences Cliniques, data from a prospective cohort of patients seen within 6 months of the IDE who participated in an MRI study of the natural history of MS were entered prospectively into the EDMUS database.^{11, 12} Clinic visits are typically scheduled every 3 months during the first year,

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every 6 months for the next 3 years and every year subsequently.

STATISTICS

We analysed whether IDE location predicted the second or third event locations and whether having the first and second relapses in the same location (eg, both in the spinal cord) versus having neither of the first two events occur in that location was predictive of having a third event in the same location. Multivariate logistic regression was performed, with the outcome defined as the second (or third) relapse location, and the two predictors defined as first (or first and second) relapse location and disease-modifying therapy (DMT). For example, for the optic nerve: outcome was second relapse location (optic nerve or not), and predictors were IDE location (optic nerve or not) and DMT. If the patient had a polyregional event, all involved locations were credited. A patient was considered as being on a given DMT if they had at least 3 months of continuous treatment before the subsequent relapse, since it is thought that there is a lag between initiation of therapy and the onset of therapeutic effectiveness.^{13 14}

To control for potential confounders, we then added covariates in turn to the multivariate model, including sex, ethnicity, age at IDE, polysymptomatic onset (yes or no), IDE severity and recovery, time to second event and disease duration at treatment initiation. When the third event was the outcome, we also added second event severity and recovery and time to third event. Finally, to further exclude the possibility of NMO or opticospinal MS, we tested whether IDE in the optic nerve or spinal cord predicted involvement of one another.

RESULTS

Baseline and exacerbation characteristics

We identified 195 RRMS patients (73% female) who had at least two clinical exacerbations and were seen within 1 year of the IDE. The average age at symptom onset was 32 (SD 11) years. There were 160 (82%) Caucasians, 14 (7%) African-Americans, 11 (6%) Asians, seven (3.5%) Hispanics or Latinos, and three (1.5%) of unknown/unreported race. The median time between IDE onset and the second relapse was 216 days (range 30 to 2052). There was at least 1 year of follow-up in 87% (n = 170) of patients, at least 2 years in 69% (n = 134) and at least 3 years in 54% (n = 105). Only 9% of patients had a normal initial brain MRI (n = 17). While 88 patients experienced a third event, only 80 were included in the analysis (eight patients had had the third event analysed in a prior study).⁷ The locations of the first, second and third attacks are detailed in table 1. There were too few cerebral events to analyse this location accurately.

Use of DMT

Thirty-eight patients (20%) initiated DMT before their second relapse, but only 29 (15%) were on treatment for at least 3 months before the second event (27 on IFNB and two on GA).

Of the patients who had a third relapse, 36 (45%) were on DMT for at least 3 months before that event (32 on IFNB and four on GA).

Predictors of second relapse location

There was a nearly fourfold increase in the odds of a patient's second relapse occurring in the spinal cord compared with the odds of it occurring in another location if the IDE was in the spinal cord (odds ratio (OR) = 3.79, 95% CI 2.06 to 7.00, $p < 0.001$). This effect was independent of treatment (table 2). As we controlled for the covariates of interest, there was never a clinically significant change in this association. Older age at IDE ($p = 0.03$) and less severe IDE ($p = 0.04$) were the only predictors that were independently associated with second event location in the cord.

There was a more than sixfold increase in the odds of a patient's second relapse being in the optic nerve compared with the odds of a second relapse in a different location if the IDE was in the optic nerve (OR = 6.18, 95% CI 2.90 to 13.18, $p < 0.001$). This association was not substantially impacted by adding DMT or any of the additional potential confounders to the model. Only Asian race was independently associated with second event location in the optic nerve ($p = 0.042$).

Brainstem/cerebellar IDE location tended to predict a second brainstem/cerebellar relapse (OR = 1.65; 95% CI 0.86 to 3.17, $p = 0.13$). Adding DMT to the model, with or without the other potential confounders, did not substantially alter this relationship. African-American race was the only covariate that was independently associated with second event location in the brainstem/cerebellum ($p = 0.033$).

Contrary to expectations for NMO or opticospinal MS, optic neuritis as the IDE was not associated with an increased odds of spinal cord involvement of the second event (OR = 0.47, 95% CI 0.24 to 0.91, $p = 0.025$); nor did IDE in the spinal cord predict an increased odds of optic neuritis during the second event (OR = 0.34, 95% CI 0.16 to 0.71, $p = 0.003$).

Predictors of third relapse location

IDE onset in the spinal cord was predictive of having a third relapse in the spinal cord (OR = 3.54; 95% CI 1.31 to 9.58, $p = 0.013$) (table 3). This relationship was not altered by adjustments for treatment but was mildly attenuated by adding IDE severity to the model. None of the potential confounders was independently associated with third event location.

When both the first and second events occurred in the spinal cord, the third relapse was more likely to involve the spinal cord (OR = 4.24; 95% CI 1.24 to 14.50, $p = 0.021$; table 4). This association was attenuated, albeit not markedly, by adjusting for use of DMT (OR = 3.14, 95% CI 0.87 to 11.27, $p = 0.079$) and IDE severity. Use of IFNB (vs no treatment) was associated with an increased odds of the third event being in the spinal cord, when adjusted for first and second event locations and disease duration at the time of treatment initiation ($p = 0.041$).

Table 1 Locations of the first, second and third events

	Initial demyelinating event n = 195	Second relapse n = 195	Third relapse n = 80
Spinal cord	106 (54%)	122 (63%)	54 (68%)
Brainstem/cerebellum	59 (30%)	58 (30%)	27 (34%)
Optic nerve	49 (25%)	39 (20%)	16 (20%)
Cerebrum	7 (4%)	2 (1%)	1 (1%)

This table demonstrates the actual number and the percentage of individuals who experienced involvement of each location during the first, second and third demyelinating events. The sum of the numbers and percentages in each column exceeds the total number of events (and 100%) because some people had polyregional relapses.

Table 2 Odds ratios (ORs) of second event occurring in the same location as the initial demyelinating event

Model	Spinal cord OR (95% CI)	Optic nerve OR (95% CI)	Brainstem/cerebellum OR (95% CI)
Unadjusted	3.79 (2.06 to 7.00)	6.18 (2.90 to 13.18)	1.65 (0.86 to 3.17)
Adjusted for treatment	3.75 (2.02 to 6.94)	6.07 (2.84 to 12.95)	1.75 (0.90 to 3.38)
Adjusted for treatment and most influential covariate	3.16 (1.67 to 5.99)	5.32 (2.42 to 11.71)	1.62 (0.83 to 3.16)

The ORs and confidence intervals of the prediction models for second event location are demonstrated. For each unadjusted OR, the predictor is initial demyelinating event location (spinal cord or not; optic nerve or not; brainstem/cerebellum or not, respectively). The outcome is second event location; the columns represent the three locations analysed. The most attenuated association obtained of all the models evaluated that were adjusted for treatment and the covariates of interest is shown in the third row. The initial demyelinating event severity was the covariate that weakened the measure of association most substantially in the spinal cord and optic nerve models; the time to second event was the covariate that did so in the brainstem/cerebellum models.

Optic neuritis as an IDE did not appear to strongly predict optic neuritis for a third event (OR = 1.62, 95% CI 0.48 to 6.02, $p = 0.43$) (table 3). However, if both the first and second events involved the optic nerve, the third relapse was more likely to include optic neuritis (table 4; OR = 3.67, 95% CI 0.93 to 14.45, $p = 0.063$). Unlike what we saw in the spinal cord model, this relationship was stronger when adjusted for use of DMT (OR = 5.21, 95% CI 1.15 to 23.68, $p = 0.033$). None of the covariates was independently associated with optic neuritis; nor did any of the covariates substantially attenuate the treatment-adjusted relationship between location of the third relapse and the first and second events (table 4).

Having an IDE with brainstem/cerebellar involvement again tended to predict brainstem/cerebellar location of the third relapse (OR = 1.97, 95% CI 0.76 to 5.08), $p = 0.16$) (table 3), which persisted when adjusted for DMT. Use of IFNB (vs no DMT; $p = 0.02$), when adjusted for IDE location and disease duration at treatment initiation), and older age, when adjusted for IDE location and DMT ($p = 0.016$), were independently associated with having a lower odds of the third event in the brainstem/cerebellum.

If the first and second events involved the brainstem/cerebellum, the odds of the third relapse affecting that region was nearly eight times the odds of it occurring in a different location (OR = 7.75, 95% CI 1.77, 33.95, $p = 0.007$) (table 4). This association was not substantially impacted when adjusted for DMT, and none of the covariates markedly changed the measure of association. Older age ($p = 0.016$) and use of IFNB versus no treatment ($p = 0.027$) were independently associated with a decreased risk of the third event location in the brainstem/cerebellum.

DISCUSSION

These results provide strong evidence that at the individual level, early clinical demyelinating events in MS tend to recur in the same anatomic location within the CNS. Since our cohort includes only patients with early RRMS, baseline disability is absent or very limited. Therefore, most clinical relapses are accounted for, whereas mild relapses could go unnoticed, and pseudoexacerbations would more likely occur in patients with more advanced disability. Furthermore, patients' descriptions of their IDEs were less likely to be influenced by recall bias, since the IDEs had occurred within the year prior to the first clinic

visit, and medical records were available to confirm most IDE descriptions. As such, we believe this cohort represents an unbiased group from which we accurately accounted for and correctly localised true relapses.

That the ORs are not the same across the various anatomic locations could have several explanations. First, there were more patients who had events in the spinal cord than in other locations in our cohort, allowing for a more precise estimate of the association; however, the ORs for the other location models were in the same direction. It is also possible that the predictors of event location are more complex for some regions of the CNS, such as brainstem/cerebellum, than for others.

That spinal cord and optic nerve IDEs predict involvement of the same locations in future events may raise the question of whether we inadvertently captured either NMO or opticospinal MS in this cohort. First, NMO is estimated to occur in less than 1% of patients in MS Centers in the United States, so only two patients would be expected to be affected in our group, even without screening. However, our cohort was rigorously evaluated for evidence of NMO, and patients who met criteria for NMO¹⁰ were excluded. Our patients also differ from those with opticospinal MS, in which most disease activity occurs in the optic nerve and spinal cord without clinical or subclinical involvement of the cerebrum or cerebellum.^{15–16} Opticospinal MS is considered a predominantly Asian disease; only 6% of our patients were Asian.¹⁷ Also, opticospinal MS is characterised by the absence or relatively small number of lesions in the cerebrum and cerebellum; only 9% of our patients had normal initial brain MRI. Finally, having an IDE in the spinal cord did not increase the odds of the second event occurring in the optic nerve, or vice versa.

While our cohort has conventional rather than opticospinal MS, that the two have been shown to differ at the genetic level supports that there are genetic determinants of MS relapse location.¹⁸ Data from the mouse model of MS, experimental autoimmune encephalitis (EAE), have demonstrated the importance of genetic as well as biological processes in determining lesion location.^{19–23} In EAE, the ratio of T_H17 to T_H1 appears to be critical in determining where inflammation occurs in the CNS. A T_H17:T_H1 > 1 leads to "atypical EAE," in which most disease activity occurs in the brain, while a T_H17:T_H1 ≤ 1 leads to "typical EAE," which is characterised by myelopathy.²³

Table 3 Odds ratios (ORs) of third event occurring in the same location as the initial demyelinating event

Model	Spinal cord OR (95% CI)	Optic nerve OR (95% CI)	Brainstem/cerebellum OR (95% CI)
Unadjusted	3.54 (1.31 to 9.58)	1.62 (0.48 to 5.45)	1.97 (0.76 to 5.08)
Adjusted for treatment	2.99 (1.07 to 8.35)	1.74 (0.51 to 6.02)	1.98 (0.75 to 5.27)
Adjusted for treatment and most influential covariate	2.48 (0.82 to 7.53)	1.48 (0.41 to 5.32)	1.65 (0.59 to 4.60)

Initial demyelinating event severity (spinal cord and optic nerve) and disease duration at time of treatment initiation (brainstem/cerebellum) were the covariates that weakened the measure of association most substantially.

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Table 4 Odds ratios (ORs) of third event occurring in the same location as the first two events

Model	Spinal cord OR (95% CI)	Optic nerve OR (95% CI)	Brainstem/cerebellum OR (95% CI)
Unadjusted	4.24 (1.24 to 14.50)	3.67 (0.93 to 14.45)	7.75 (1.77 to 33.95)
Adjusted for treatment	3.14 (0.87 to 11.27)	5.21 (1.15 to 23.68)	6.63 (1.46 to 30.01)
Adjusted for treatment and most influential covariate	2.16 (0.51 to 9.22)	4.66 (0.97 to 22.33)	5.82 (1.26 to 26.80)

The unadjusted ORs represent the odds of the third event occurring in the same location when the primary predictor was "first and second events in the same location" versus "neither event in the same location." Initial demyelinating event severity (spinal cord), initial demyelinating event recovery (optic nerve) and time to third event (brainstem/cerebellum) were the respective covariates that weakened the measures of association most substantially.

The research question addressed by this study was whether the location of the initial *clinical* demyelinating event predicted the location of future *clinical* events. While subclinical lesions are often detected by MRI in patients with MS, to have included these lesions would have been to ask a different research question, as presumably some unknown biological factors distinguish lesions that cause symptoms from those that do not. Furthermore, we only had access to a clinic-based cohort for whom standardised MRI protocols were not available; as such, including MRI features could introduce bias.

Few patients in our study initiated therapy, especially glatiramer acetate. Thus, we could not investigate our prior findings⁷ of a differential effect of treatment on the likelihood of relapse in a specific location. We have established, however, that adding DMT to the prediction models generally did not substantially change the strong association between IDE and second or IDE and third relapse locations. On the other hand, there was a marked increase in the association between the first and second events occurring in the optic nerve and the third event occurring in the optic nerve after adjusting for use of DMT; the OR increased from 3.67 to 5.21. Since most of the patients who received DMT prior to the third event were on IFNB, these findings suggest that IFNB might decrease the risk of recurrent optic neuritis. In contrast, in the spinal cord model, there was a slight attenuation of the association between the location of the first and second events and the third event location when adjusted for treatment. In this group, treatment (again, primarily IFNB) clearly was not protective against recurrent spinal cord relapses. Furthermore, when evaluating predictors of third event occurrence in the spinal cord, use of IFNB versus no therapy was independently, albeit modestly, associated with relapse in this location (after adjusting for first and second event locations and disease duration at the time of treatment initiation). Therefore, adding use of DMT to the spinal cord and optic nerve models led to different directions of change in the adjusted OR. Larger studies of patients with pre- and post-treatment relapses are needed to evaluate potential differential treatment effects.

We are currently following up on these results by identifying genetic polymorphisms that could correlate with the individual tendency for recurrent disease in specific CNS locations. Whether, in the human, MS relapse location is purely explained by genetics or by the genetic influence on biological interactions remains to be determined.

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