



Predictors of Multiple Sclerosis Relapse Location

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J. Neurol. Neurosurg. Psychiatry published online 25 Jan 2008;
doi:10.1136/jnp.2007.136440

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Title: Predictors of the Location of Multiple Sclerosis Relapse

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Words in Abstract: 253

Words in Body: 1491

Disclosure:

Serina Deen, Dr Peter Bacchetti and Andrew High have no conflict of interest. Dr Waubant has received research support from Biogen Idec, Genentech Inc, Pepgen and Sanofi-Aventis, and honoraria for one patient educational presentation from Teva.

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Keywords: Multiple sclerosis, Spinal Cord, Location, Exacerbation, Optic Nerve

Abstract:

Background: While clinical relapses are the defining feature of relapsing-remitting multiple sclerosis (RRMS), their characteristics vary widely from patient to patient. We sought to identify predictors of MS relapse location. Based on current literature, two potential predictors were identified: treatment with interferon beta (IFNB), and location of previous relapse.

Methods: RRMS patients were identified from the UCSF MS Center database who underwent at least 3 months of IFNB or glatiramer acetate (GA) treatment. The relapse immediately preceding the initiation of treatment (pre-treatment relapse), and the first relapse occurring after the initiation of treatment (on-treatment relapse) were coded as affecting the spinal cord (SC), optic nerve (ON), brainstem/cerebellum (BC), or cerebrum. Logistic regression was performed to identify independent predictors of on-treatment relapse location.

Results: The 134 IFNB and 56 GA patients did not differ in gender, race, age at symptom onset (30.3 years), or disease duration at treatment start (5.7 years). Patients with pre-treatment SC relapses had increased odds of having on-treatment SC compared to non-SC relapses (OR=2.31, p=0.013); the same tendency for localization occurred with BC (OR=3.05, p=0.013), and ON relapses (OR=3.63, p=0.011). Additionally, patients who relapsed on treatment had a higher SC (but not ON or BC) relapse risk when they were on IFNB compared to GA (OR 2.05, p=0.041), independent of pre-treatment relapse location.

Conclusion: Our results show a tendency for patients to have localized exacerbations, which could be mediated by genetic or immunological factors. In addition, and to be confirmed in subsequent studies, IFNB treatment may influence SC relapse risk.

Introduction

While clinical relapses are the defining feature of relapsing-remitting multiple sclerosis (RRMS), their characteristics vary widely from patient to patient. It is unknown whether there is less within-patient variability. Several demographic and clinical measures might predict certain relapse characteristics.^{1,2}

We propose that the location of a relapse within the central nervous system (CNS) may be a predictor of future relapse location. Relapse location may be partially genetically determined. In the murine model of MS, different genetic loci have been identified for controlling the distribution and severity of brain versus spinal cord lesions.³ Alternatively, animal studies suggest that the location of lesions within the CNS may be partially determined by the nature of the target autoantigen.^{4,5,6}

Disease modifying treatment (DMT) could also influence the location of subsequent relapses. There is a striking discrepancy in interferon beta (IFNB)'s efficacy when looking at the prevention of new lesions on brain MRI scans versus the prevention of clinical relapses.^{7,8,9} No real explanation has been found for this gap. This discrepancy is not seen with glatiramer acetate (GA), which prevents similar amount of new brain MRI lesions and clinical relapses.^{10,11} One possible explanation for the discrepancy seen with IFNB is that it prevents a higher percentage of lesions in the brain versus the spinal cord. This would explain the higher efficacy of IFNB when looking at brain MRI scans, reflecting only brain involvement, versus looking at clinical relapses, reflecting both brain and spinal cord involvement.

The aim of this study is to determine if demographics, location of previous relapse and/or treatment with IFNB compared to GA predicted location of subsequent MS relapse.

Methods

This study was approved by the UCSF Committee on Human Research. Clinical and demographic information for all patients seen at the UCSF MS Center is entered into a Microsoft SQL server database (retrospectively when the patient is first seen in clinic, and then prospectively as the patient returns for visits).¹² The authors queried the database for RRMS patients who underwent at least three months of continuous IFNB or GA treatment as their first disease-modifying therapy (DMT) and had at least one well-documented pre-treatment and on-treatment exacerbation (e.g. that could be attributed to specific CNS locations). Three months was used because it is an accepted time period in which IFNB and GA reach therapeutic effectiveness.^{13,14} Patients who had initiated another DMT treatment in the past, who discontinued treatment for greater than one month, or who were being treated concurrently with another DMT or pulse steroids were excluded. Relapses were defined clinically by the patient's usual MS neurologist according to standard definitions (new or recurrent symptoms lasting for 48 hours or more, in a patient stable for at least 30 days, excluding pseudo-exacerbations). The majority of relapses were documented during clinic visits. For each patient, a pre-

treatment relapse was defined as the last relapse preceding DMT initiation, and an on-treatment relapse as the first relapse occurring after DMT initiation. Relapses were coded as involving the spinal cord (SC), optic nerve (ON), brainstem/cerebellum (BC), cerebrum, or polyregional.

To determine if previous relapse location predicted subsequent relapse location, logistic regression was performed, with the outcome defined as on-treatment relapse location (e.g. positive outcome: relapse involving the ON, negative outcome: relapse not involving the ON), and the two predictors defined as pre-treatment relapse location, and treatment type (IFNB or GA; to control for the effect of treatment on relapse location).

To test our hypothesis of a differential effect of IFNB vs GA on the spinal cord, logistic regression was performed with positive outcome defined as on-treatment relapse involving the SC and negative outcome as on-treatment relapse not involving the SC. The two predictors were defined as type of treatment (IFNB versus GA) and pre-treatment relapse location (SC versus non-SC). Pre-treatment relapse location was included in order to control for its effect on on-treatment relapse location.

Secondary analysis was performed by adding demographic and disease characteristic covariates to create three-predictor models (see Table 2 for specific covariates).

Results

We identified 134 RRMS IFNB and 56 GA recipients seen at the UCSF MS center between January 2000 and June 2007 who received at least 3 months of continuous treatment, and had both a well-defined pre-treatment and on-treatment exacerbation. The two cohorts appeared similar (Table 1). The rate of on-treatment SC relapses for IFNB and GA are shown in Figure 1. 35 patients had a pre-treatment ON relapse, of these 11 also had an ON on-treatment relapse. The on-treatment ON relapse was ipsilateral compared to the pre-treatment relapse in 36%.

Table 1: Clinical and demographic characteristics of patients

	IFN n=134	GA n=56	mean difference and 95%CI	p value
Age at Onset (mean ± SD)	30.0 ±7.6 yrs	31.0 ±9.6 yrs	-1.34 [-3.94-1.25]	0.31
Race	115 C 6 HIS 5 AA 1 ASI 7 UNK	44 C 3 AA 4 HIS 5 UNK		0.68
Sex (%Female)	69%	71%		0.71
Disease duration at treatment start (mean ± SD)	5.6 ± 6.4 yrs	5.9 ± 8.3 yrs	-0.25 [-2.44-1.95]	0.82
Time from Pre-DMT relapse to DMT start (mean ± SD)	138 ± 152 days	169 ± 166 days	-30.60 [-79.55-18.36]	0.22
Time from DMT start to on- DMT relapse (mean ± SD)	1.8 ± 1.8 yrs	1.4 ± 1.4 yrs	0.42 [-0.12 -0.96]	0.13
EDSS at DMT start (median, range)	1.0 (0.0-5.0)	1.5 (0.0-5.0)		0.73
Pre-Tx Relapse Location	51% SC 20% B/C 19% ON 10% Poly	54% SC 21% B/C 18% ON 7 % Poly		0.34

DMT= disease modifying therapy, C= Caucasian, AA= African American, HIS=Hispanic/Latino, ASI= Asian, UNK= Unknown

SC= Spinal Cord, B/C= Brainstem/Cerebellum, ON= Optic Nerve, Poly= Polyregional

Thirty-six percent of patients had available EDSS scores at treatment start (n=44 for IFNB, n=24 for GA).

Of the 134 IFNB recipients, 71% received Avonex, 17% Betaseron, and 11% Rebif. The results of multivariate analysis are shown in Table 2. There was a greater than three-fold increased odds of ON relapse for patients whose pre-treatment relapse was ON (OR 3.63, 95%CI 1.35-9.77, p=0.011), and also a three-fold increased odds for BC relapse given pre-treatment BC relapse (OR 3.05, 95%CI 1.27-7.31, p=0.013). There was a greater than two-fold increased odds of a SC relapse for patients whose pre-treatment relapse was SC compared to non-SC (OR 2.31, 95%CI 1.20-4.46, p =0.013). These findings were independent of treatment type (IFN or GA)(Table 2).

Table 2: Logistic regression models for on-treatment relapse location

Predictors	Odds Ratio	95% CI	<i>p</i>
Outcome: On-treatment spinal cord relapse			
Pre-treatment relapse location (sc vs non-sc)	2.31	1.20-4.46	0.013
Treatment type (IFNB vs GA)	2.05	1.03-4.08	0.041
Pre-treatment relapse location (sc vs non-sc)	2.31	1.19-4.50	0.013
Treatment type (IFNB vs GA)	2.04	1.03-4.07	0.042
Age at symptom onset	0.99	0.96-1.04	0.91
Pre-treatment relapse location (sc vs non-sc)	2.31	1.20-4.48	0.013
Treatment type (IFNB vs GA)	2.07	1.04-4.13	0.038
Gender (Male vs Female)	0.74	0.37-1.50	0.41
Pre-treatment relapse location (sc vs non-sc)	2.48	1.26-4.90	0.009
Treatment type (IFNB vs GA)	1.99	1.00-3.98	0.050
Ethnicity (Caucasian vs Other)	1.58	0.66-3.82	0.31
Pre-treatment relapse location (sc vs non-sc)	2.56	1.30-5.03	0.007
Treatment type (IFNB vs GA)	1.96	0.98-3.92	0.058
Time from pre-treatment relapse to treatment start	0.52	0.25-1.09	0.084
Pre-treatment relapse location (sc vs non-sc)	2.34	1.21-4.53	0.012
Treatment type (IFNB vs GA)	2.04	1.03-4.07	0.042
Disease duration at treatment start	1.00	0.95-1.04	0.68
Pre-treatment relapse location (sc vs non-sc)	2.30	1.19-4.44	0.013
Treatment type (IFNB vs GA)	2.07	1.03-4.14	0.040
Time from treatment start to during-treatment relapse	0.98	0.81-1.18	0.83
Outcome: On-treatment brainstem/cerebellar relapse			
Pre-treatment relapse location (spinal cord reference)			
- brainstem/cerebellum	3.05	1.27-7.31	0.013
- optic nerve	1.26	0.44-3.60	0.66
- polyregional	1.92	0.54-6.76	0.31
Treatment type (IFNB vs GA)	0.71	0.32-1.55	0.39
Outcome: On-treatment optic nerve relapse			
Pre-treatment relapse location (spinal cord reference)			
- optic nerve	3.63	1.35-9.77	0.011
- brainstem/cerebellum	1.01	0.30-3.46	0.98
- polyregional	1.23	0.24-6.23	0.80
Treatment type (IFNB vs GA)	0.60	0.25-1.45	0.23

Note: horizontal lines separate different models.

Table 2 also shows that there was a two-fold increased odds of a SC exacerbation on-treatment for patients treated with IFNB compared to GA (OR 2.05, 95%CI 1.03-4.08, $p=0.041$). The interaction between the predictors of pre-treatment location and treatment type did not approach statistical significance ($p=0.43$), but its confidence interval was too wide (OR 0.14 to 2.30) to provide strong evidence against substantial interaction in either direction. In the three-predictor models, no covariates strongly attenuated the findings related to treatment type (Table 2).

Discussion

Our results suggest a tendency for patients with SC relapses to have further SC compared to non-SC relapses (OR=2.31). Similarly, patients with BC relapses appear to have further BC relapses (OR=3.05), and patients with ON relapses further ON relapses (OR=3.63). This tendency for a patient to develop relapses in the same location has not yet been represented in published literature. The tendency for localized exacerbations could be genetically predetermined, or different immunological mechanisms of myelin destruction could lead to preferential spinal cord versus brain lesion development.^{15,16}

Our results also suggest that patients treated with IFNB who experience a relapse on therapy have twice the odds of having their first on-treatment relapse be in the SC as patients treated with GA (OR=2.05). This effect appears to be independent of the pre-treatment relapse location and other factors such as demographic and disease course characteristics. No such finding is reported for ON and BC relapses (Table 2). The discrepancy in efficacy at the SC locations in patients who continue to have MS relapse while on therapy could be mediated by IFNB having a different effect at the blood-brain barrier (BBB) versus the blood-spinal-cord barrier (BSCB). The BBB differs in several ways from the BSCB. The BSCB has been shown to be more permeable than the BBB to various compounds.^{17,18} In addition, in the murine model of MS, disruption of the blood-CNS barrier is more prominent and occurs earlier in the spinal cord than the brain,¹⁹ and a lower number of encephalitogenic T cells are needed to induce an inflammatory reaction in the spinal cord than in the brain²⁰. Given all of these differences in the two locations, it is conceivable that IFNB has different levels of efficacy at these sites. Our study has several limitations. First, this is not a prospective randomized experiment. We used three predictor models to evaluate the impact of each of six additional covariates, and none of the covariates strongly impacted the effect of treatment type, suggesting little potential confounding due to non-randomized treatment choice. EDSS could have been a useful covariate to indicate disease severity, but this data was not available for all patients at treatment initiation. A second limitation pertains to the relatively limited number of GA recipients, which led to fairly wide confidence intervals. Our main results nevertheless reached statistical significance. A third limitation is that we only take into account clinical relapses, and therefore did not account for patients who have not had further clinical relapses during the time of observation, but may have had new silent lesions detectable by MRI. Finally, pseudo-exacerbations were excluded from the analysis, and hence should not have confounded the results.

These findings have prompted us to investigate whether specific genetic polymorphisms or biological processes underlie specific types of MS exacerbations. This ultimately could help identifying sub-groups of patients who may need earlier DMT initiation or more aggressive preventive therapies. We have started to investigate the correlation of clinical characteristics between first, second and third demyelinating events using a larger cohort of patients seen within one year of their disease onset. Finally, a prospective study is needed before confirming that GA does not show a regional preference in relapse prevention compared to IFNB, ideally using MRI to compare the location of lesions.

Disclosure:

Serina Deen, Dr Peter Bacchetti and Andrew High have no conflict of interest. Dr Waubant has received research support from Biogen Idec, Genentech Inc, Pepgen and Sanofi-Aventis, and honoraria for one patient educational presentation from Teva.

Acknowledgement:

The authors would like to acknowledge the National Multiple Sclerosis Society for its generous support of this project.

Legends:

Table 1 provides baseline characteristics of patients on IFNB and GA.

Table 2 provides the results of multivariate logistic regression analyses according to treatment group (IFNB versus GA) and pre-treatment relapse location.

Figure 1 displays the proportions of patients who experienced on-treatment spinal cord relapses according to location of pre-treatment relapse and treatment group (IFNB versus GA).

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