Increased Relapse Rate in Pediatric-Onset Compared With Adult-Onset Multiple Sclerosis

Mark P. Gorman, MD; Brian C. Healy, PhD; Mariann Polgar-Turcsanyi, MS; Tanuja Chitnis, MD

Objective: To investigate whether or not the disparity in disease progression in those with pediatric-onset compared with adult-onset multiple sclerosis (MS) is due to differences in relapse rates.

Design: Inception cohort. Mean follow-up times were 3.67 (standard deviation, 1.64) and 3.98 (standard deviation, 1.17) years in the pediatric and adult groups, respectively.

Setting: Comprehensive MS centers.

Patients: Patients with relapsing-remitting MS who were seen at the pediatric and adult MS centers at Massachusetts General and Brigham and Women’s Hospitals, respectively, 12 months or less from onset of first symptom in July 2001 or later and were followed up for 12 months or longer. One hundred ten patients with adult-onset and 21 patients with pediatric-onset MS were included. Three eligible patients with adult-onset MS were excluded owing to incomplete records.

Main Outcome Measure: Annualized relapse rates were compared between pediatric-onset and adult-onset patients using the proportional means model.

Results: The annualized relapse rate in the pediatric-onset group was significantly higher than that in the adult-onset group (1.13 vs 0.40; \(P < .001\)) with an adjusted rate ratio of 2.81 (95% confidence interval, 2.07-3.81). When we controlled for time spent undergoing disease-modifying treatment in the analysis, the difference between the groups remained highly significant (adjusted rate ratio, 2.82; 95% confidence interval, 2.08-3.83; \(P < .001\)). When age at disease onset was treated as a continuous variable, a highly significant association between age and relapse rate was observed \((P < .001)\).

Conclusions: Relapses are more frequent in patients with pediatric-onset compared with adult-onset MS in the disease-modifying treatment era. This finding suggests that patients with pediatric-onset MS experience a more inflammatory disease course than patients with adult onset of the disease.

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Although the clinical onset of multiple sclerosis (MS) typically occurs between ages 20 and 40 years, 2.7% to 10.5% of patients have been reported to develop their first symptoms before their 18th birthday. By comparing patients in the same geographic region, 3 studies have demonstrated that initial disease progression is slower in patients with pediatric-onset MS compared with those with adult-onset MS. In one such study, there was a nonsignificant trend toward a higher relapse rate in the first 2 years of disease in the pediatric group. However, in another study, there was a significant inverse relationship between age at onset and relapse rate at 10 years from disease onset, while the third study did not report the relapse rate in the adult-onset group. Thus, it is unclear whether or not the disparity in disease progression is due to differences in relapses between these groups.

To investigate this question, we compared relapse rates and location in patients with pediatric-onset and adult-onset MS in a cohort evaluated in our pediatric and adult MS centers, during the disease-modifying treatment era, shortly after first symptom onset. Based on our clinical observations and limited existing literature, we hypothesized that patients with pediatric-onset MS paradoxically have more frequent relapses than patients with adult-onset MS during the early phase of the disease.

METHODS

PATIENTS

Data were collected from February 2000 to December 2007 in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s Hospital at the Partners Multiple Sclerosis Center. This is an ongoing longitudinal cohort study investigating the natural history of MS in the disease-modifying treatment era. Patients are monitored with semi-annual neurological examinations. At each visit, clinicians generate a detailed electronic note and also enter information on patients’ age, sex, race, ethnicity, residence, date of MS symptom onset, date
of MS diagnosis, relapses, treatment, and Extended Disability Status Scale score into a computerized database. Patients self-report race and ethnicity on an intake form using the following choices: “Race—American Indian or Alaska Native, Black or African American, More than one race, Native Hawaiian or Other Pacific Islander, White, and Unknown or Not Reported; Ethnicity—Hispanic or Latino, Not Hispanic or Latino, Unknown.” Data are collected retrospectively at the first visit and prospectively thereafter. The same database was used to collect information on patients examined at the Partners Pediatric Multiple Sclerosis Center at Massachusetts General Hospital from June 2004 to December 2007. Patients with pediatric-onset MS who met inclusion criteria were included from both the adult and pediatric MS centers. A board-certified pediatric neurologist with MS fellowship training validated all database entries with retrospective review of the electronic clinical notes of included patients. The study was approved by the Partners Human Research Committee.

CLINICAL DEFINITIONS

Patients were classified as having pediatric-onset MS if the onset of disease symptoms occurred before their 18th birthday, according to the International Pediatric MS Study Group consensus definitions.6 Relapses were defined as the appearance of a new symptom or worsening of an old symptom that lasted longer than 24 hours, could be attributed to MS in the absence of fever or intercurrent illness, and was preceded by stability or improvement in the preceding 30 days. Relapses reported at routine visits were included. Whether or not relapses were confirmed by examination was recorded. Relapse localization at routine visits were included. Whether or not relapses were confirmed by examination was recorded. Relapse localization

CLINICAL DEFINITIONS

The database was queried with an automated process for eligible patients based on the following predetermined inclusion criteria: (1) diagnosis of relapsing-remitting MS by McDonald criteria,7 (2) first MS symptoms in July 2001 or later to coincide with McDonald criteria publication, (3) first visit to the centers within 12 months of first MS symptoms, and (4) minimum follow-up of 12 months from first symptoms. Patients with recurrent or multiphasic acute disseminated encephalomyelitis were excluded.5

STADISTICAL ANALYSIS

Annualized relapse rates were calculated by dividing the total number of relapses by the total number of person-years at risk. The primary focus of analysis was the overall annualized relapse rate, but pre–disease-modifying treatment and post–disease-modifying treatment annualized relapse rates were also estimated to allow comparisons with prior articles. Eight patients with adult-onset MS chose not to receive disease-modifying treatment and contributed data only to the pre–disease-modifying treatment calculation. To be inclusive of currently available treatments, we regarded interferons, glatiramer acetate, chemotherapy, monoclonal antibodies, and oral immunosuppressants, regardless of treatment duration, as disease-modifying treatment. The proportion of total disease duration during which disease-modifying treatment was used was calculated in each group by dividing the amount of time undergoing disease-modifying treatment by total disease duration.

The annualized relapse rates in pediatric and adult patients were compared using a proportional means model.8,9 For analyses that included the first attack, this attack was assumed to occur very shortly after enrollment, as these 2 events (enrollment and first attack) cannot occur at the same time in the model. In addition, annualized relapse rates excluding the first attack were compared using negative binomial regression, which is similar to Poisson regression but relaxes the assumption that the mean and variance of the outcome are equal. All models controlled for sex and race. To control for time undergoing disease-modifying treatment, treatment was included as a time-dependent covariate in the proportional means model, and the proportion of time on treatment was included in the negative binomial model. Each of these models was also fit with age at first symptom as a continuous covariate.

The secondary aims of the study were to compare demographics, relapse localization, and treatment in patients with pediatric-onset and adult-onset MS. Comparisons were completed using a Wilcoxon test, Fisher exact test, or log-rank test as appropriate. Finally, the first interattack intervals in the groups were compared using a Cox model controlling for sex and race. All statistical analyses were completed in the statistical package R (R Foundation for Statistical Computing, Vienna, Austria); functions from the Modern Applied Statistics with S-PLUS and survival libraries were used.11

RESULTS

The database query identified 113 patients with adult-onset and 21 patients with pediatric-onset MS. Three adult-onset patients were excluded owing to inadequate documentation of relapses.

Demographic and clinical data for included patients are summarized in Table 1. The proportion of white/Caucasian patients in the pediatric-onset group was significantly lower than in the adult-onset group (P < .001). In the pediatric-onset group, there were 4 African American (19%) and 3 Hispanic (14%) patients. There were no significant differences in sex, distance from the centers, basis for dissemination in time for MS diagnosis, interval between first symptom and evaluation at the centers, duration of observation, and Extended Disability Status Scale score at last follow-up.

The relapse rate results are summarized in Table 2. The cumulative number of relapses, excluding the first attack, over the course of observation is shown in the Figure. The overall annualized relapse rate was significantly higher in patients with pediatric-onset MS in the proportional means model (adjusted rate ratio, 2.81; 95% confidence interval [CI], 2.07-3.81) and negative binomial model (adjusted rate ratio, 2.93; 95% CI, 1.93-4.46). The results were similar with both inclusion and exclusion of the first attack. When we controlled for disease-modifying treatment use, the difference between the groups remained highly significant (proportional means model: adjusted rate ratio, 2.82; 95% CI, 2.08-3.83; negative binomial model: adjusted rate ratio, 3.02; 95% CI, 2.00-4.57). When age at MS onset was treated as a continuous variable, a highly significant association between age and annualized relapse rate was observed in both models (P < .001). When disease duration was divided into pretreatment and posttreatment intervals, the
The annualized relapse rate in patients with pediatric onset was significantly higher than in patients with adult onset in the proportional means model (pretreatment: adjusted rate ratio, 1.75; 95% CI, 1.13-2.72; posttreatment: adjusted rate ratio, 3.14; 95% CI, 2.19-4.5) and negative binomial model (pretreatment: adjusted rate ratio, 2.13; 95% CI, 1.12-4.06; posttreatment: adjusted rate ratio, 3.26; 95% CI, 1.94-5.48) for both periods. None of the results significantly changed when the first attack was included or when patients with adult-onset MS treated with disease-modifying treatment following clinically isolated syndromes (CISs) were excluded.

The relapse clinical localizations are summarized in Table 3. Although transverse myelitis was more common in adult-onset MS, there were no significant differences (P = .40, Fisher exact test).

Treatment characteristics of the groups are summarized in Table 4. No patients with pediatric onset and 28.2% of patients with adult onset were given disease-modifying treatment following CISs (P = .004). Although the proportion of time spent undergoing treatment was significantly different in the 2 groups, this difference was not significant after patients with adult-onset MS who were treated following CISs were removed (P = .19). There were no significant differences between the groups in the time from first symptom onset to treatment onset or the total treatment duration, even when patients with adult-onset MS who were treated fol-
lowing CIS were included. The percentage of patients treated with scheduled steroid pulses, chemotherapy, monoclonal antibodies, oral immunosuppressants, and/or combination therapy was similar between the groups.

We have demonstrated that relapses are significantly more common during the early stages of MS in patients with pediatric onset compared with those with adult onset. These findings persisted in multivariate regression models when controlling for sex, race, and proportion of disease spent undergoing disease-modifying treatment and when age at onset was treated as a continuous variable.

Prior studies have demonstrated mixed results regarding the effect of age at onset of MS on relapse rate. In the era before magnetic resonance imaging (MRI) and disease-modifying treatment, most studies suggested that relapse rates were not affected by age at onset,12-15 though 1 study reported higher relapse rates in patients with earlier onset.14,16 In the post-MRI era, a study of 821 patients given placebo found a significant inverse relationship between age at MS onset and relapse rate in the univariate analysis but not in the multivariate analysis.17 Another study found a nonsignificant trend between younger age at MS onset and the occurrence of relapses in 117 patients given placebo.18 However, all of the patients in these 2 recent studies were older than 18 years at the time of study entry; therefore, these studies do not represent a true comparison between pediatric-onset and adult-onset MS.

Studies in the post-MRI era that included patients with pediatric-onset MS provide conflicting information. In an Italian cohort, relapses in the first 2 years of disease were twice as frequent in those with adult-onset MS at 1.0 per year compared with 0.5 per year in those with pediatric-onset MS, though the difference was not significant.2 However, in another study of a larger number of patients from the same center, the authors reported a significant trend toward higher mean relapse rates 10 years after disease onset in younger patients.4 Unlike the current study, none of these studies attempted to control for disease-modifying treatment.

Discrepancies in these studies may be due to 2 factors. First, it has been suggested that relapse rates determined prospectively are consistently higher than those determined retrospectively.19,20 In most of these studies, the time in between the patients’ first symptoms and their presentation to neurological attention was not reported. It is plausible that patients with pediatric-onset MS have longer disease duration before their inclusion in observational studies, particularly when the studies are conducted at adult MS centers. If this is the case, relatively more of a patient’s history will be obtained retrospectively at the first visit, which could falsely lower their relapse rates. In addition, patients who have had MS diagnosed in adulthood may be affected by recall bias in interpreting earlier experiences during childhood and may erroneously attribute transient symptoms to MS. This situation could lead to inaccurate inclusion of patients in the pediatric-onset group and would again bias this group to have a longer retrospective period.

We addressed these 2 issues by limiting our included patients to those who were examined in our centers within 12 months of their first MS symptoms. This limited the amount of retrospective recall and made this amount of time similar in the pediatric- and adult-onset groups. In addition, the onset of symptoms could be more accurately timed and the universal use of MRI in our cohort could definitively ascribe the symptoms to MS. Although our use of strict inclusion criteria led to a rela-
tively small pediatric sample size, the very high level of significance demonstrates that it was adequate. We actively discussed and chose not to recruit more patients because the study was sufficiently powered to observe the effect of interest.

An additional advantage to our approach is the higher quality of documentation of relapses using prospective methods compared with retrospective methods that were reliant on patients’ recall over years, particularly as some patients may not present to medical attention for many years after disease onset.20 This approach may also minimize referral bias, as patients early in the course of the disease are unlikely to have significant disability, which was true for our cohort.20

There was a lower percentage of white/Caucasian patients in the pediatric-onset group of our New England cohort compared with the adult-onset group, consistent with previous findings from Canada and the southeastern United States.21,22 Although some articles have reported a more aggressive disease course in African American patients with MS,23 controlling for race in our cohort did not significantly alter the results. Additional studies are needed to determine the genetic and environmental influences that underlie the different racial and ethnic compositions of pediatric- and adult-onset MS groups and their potential effects on disease course.

Although this study was designed to compare patients with pediatric-onset and adult-onset MS and not the effects of treatment, the pretreatment and posttreatment relapse rates in both groups were assessed to allow comparisons with previous studies. With the first attack included, the pretreatment relapse rate of 2.76 in our study is nearly identical to the rate of 2.8 in a study of 81 Italian patients with pediatric-onset MS,24 which also included the first attack (personal communication, Angelo Ghezzi, MD, 2008). With the first attack excluded, the rate of 1.2 in our study is lower than the rate of 1.9 in a study of 51 German patients with pediatric-onset MS25 and 1.8 in an Argentinian study of 24 patients with pediatric-onset MS,26 both of which excluded the first attack (personal communication, Daniela Pohl, MD, and Silvia Tenembaum, MD, 2008). Based on these comparisons, we conclude that we did not select an unusually active group of patients with pediatric-onset MS. In the current study, the posttreatment relapse rate of 1.12 in patients with pediatric-onset MS was higher than the rates of 0.5 and 0.8 in the Italian and German cohorts, respectively.24,25 All of these rates are strikingly higher than the on-treatment relapse rates of 0 to 0.25 in the Argentinian study.26 In light of the known decrease in relapse rates with increasing disease duration,13,14,16,17 these discrepancies may be partly due to differences in the disease duration at treatment onset, with our study having the shortest duration (7.6 months) and the Argentinian study having the longest (40.3 months).20 However, we did not formally assess compliance in our study and cannot rule out poor compliance as a contributing factor.

In our study, the pretreatment and posttreatment relapse rates in the adult-onset group were lower than the rates reported in the pivotal clinical trials of the disease-modifying agents.27-30 However, the use of the Poser criteria and the requirement that patients must have had at least 2 relapses in the 2 years before entry in the pivotal trials likely biased inclusion toward patients with a greater number of relapses. In general, relapse rates in patients in clinical trials have been steadily declining since the initial pivotal trials. Although differences in methodology preclude comparisons of the pretreatment relapse rates, the posttreatment relapse rate of 0.35 in our study was very similar to the rates in the recent Rebif vs Glatiramer Acetate in Relapsing MS Disease (0.3)31 and Betaseron vs Copaxone in MS with Triple-Dose Gadolinium and 3-T MRI Endpoints (0.25 and 0.32)32 trials. Thus, based on comparisons with contemporary reports, it does not appear that we selected an unusually inactive group of adult MS patients.

Despite the similarities between our data and previously published data, it remains possible that patients with more severe pediatric-onset MS were selectively evaluated at our centers. However, distance from the center, a proxy measure for referral bias, which has been shown to influence clinical characteristics in prior articles in the neurology33 and oncology34 literature, was not different between our pediatric-onset and adult-onset groups. Thus, the 2 groups were recruited from overlapping regions, making referral bias a less likely explanation for our findings.

One clear difference between the 2 groups in our study was that 28% of adult-onset and 0% of pediatric-onset patients were treated with disease-modifying treatment following CIs. It is not clear a priori whether inclusion of such patients would bias the adult group to have a higher or lower relapse rate. On one hand, such patients are being treated earlier, while on the other hand, they may comprise a more severe group whom clinicians elected to treat aggressively. We therefore included them in the main analysis but performed additional analyses excluding them, which yielded the same conclusion.

In general, the disease course of MS has been divided into a relapsing-remitting phase, during which inflammatory mechanisms predominate, and a secondary progressive phase, during which neurodegenerative mechanisms predominate.35 Acute relapses are the clinical hallmark of the inflammatory phase of MS. The higher relapse rate in the pediatric-onset group in our study may therefore suggest that patients with pediatric-onset MS are coming to medical attention closer to the true biological onset of their disorder than patients with adult onset during a more inflammatory phase, as has been previously suggested.36

Several studies have demonstrated that individuals with pediatric-onset MS have slower disease progression than their adult-onset counterparts, particularly during the early stages of the disease.2-4,37 It is unclear if this same pattern applies to our cohort given the relatively short disease duration. However, if individuals with pediatric-onset MS have slower disease progression despite more relapses than individuals with adult onset, as suggested in 1 study,4 this discrepancy may suggest greater plasticity, less neurodegeneration, and potentially more repair and remyelination in the younger nervous system. Further study of the biological basis for this discrepancy may yield insight into the apparent disconnect between relapses and long-term disability progression.38
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Correspondence: Tanuja Chitnis, MD, Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, ACC–708, 55 Fruit St, Boston, MA 02114 (tchitnis@partners.org).

Author Contributions: Study concept and design: Gorman, Healy, and Chitnis. Acquisition of data: Gorman, Polgar-Turcsanyi, and Chitnis. Analysis and interpretation of data: Gorman and Healy. Drafting of the manuscript: Gorman, Healy, and Chitnis. Critical revision of the manuscript for important intellectual content: Gorman, Healy, Polgar-Turcsanyi, and Chitnis. Statistical analysis: Healy. Obtained funding: Chitnis. Administrative, technical, and material support: Polgar-Turcsanyi. Study supervision: Chitnis.

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REFERENCES