Relapsing MS patients treated with DMTs exhibit highly variable disease progression; a New Natural History

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Abstract

Background: Patterns of disease progression in the "treatment era" of Relapsing MS (RMS) remain to be defined.

Objective: To examine three patterns of progression in RMS patients using recently proposed definitions[1] which categorize patients according to whether or not rapidly worse aggressive disease occurred at any time and whether or not EDSS 4.0 was reached.

Methods/setting: In a single center we retrospectively examined data collected since 1995 on patients newly diagnosed with RMS. Group 1 patients were termed “aggressive MS” (AMS) and experienced rapid progression defined as an increase of 2 or more EDSS points in 2 or less years to result in an EDSS of 4.0 or more. Group 2 patients reached EDSS 4.0 with a slower rate of change. Group 3 patients did not reach EDSS 4.0. Groups were compared for progression of EDSS.

Results: Of the 204 patients followed during an average of 12.1 years, 13.9% became aggressive in 1st five years and 12.6% the next decade. Disease modifying treatments (DMTs) were used by 98% of patients.

Conclusions: A transition from relatively mild MS to an aggressive course may begin at any time in the first 15 years, despite DMTs. Our definition for AMS is unique and identifies a group of patients who become permanently disabled over a course of less than 2 years after a variable amount of time spent in a benign phase, and this group comprises the majority of all severely disabled patients seen in the first 15 years of RMS.

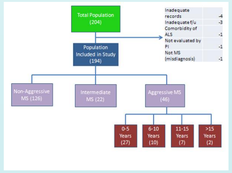
Methods

Inclusion Criteria:

- Attended the Allegheny MS Treatment Center (AMSTC); evaluated within 12 months of 2nd attack (disease defining) or serial MRI changes
- Met the McDonald criteria for a diagnosis of MS. (n=204)

Exclusion Criteria:

- Less than 2 years of MS symptoms from onset until final follow up
- Fewer than 2 examinations, ≥ 6 months apart at AMSTC
- 2 or more possible attacks of demyelinating disease occurring more than 1 year prior to presentation to our clinic



AMS: Reached at any point, EDSS ≥4.0 (sustained for at least 6 months) during an advancement ≥2 EDSS points within 2 years.
IMS: Attained EDSS 4.0 (sustained for at least 6 months) less rapidly, not by progressing 2 or more EDSS points within 2 years.
MMS: Never reached a sustained EDSS 4.0.

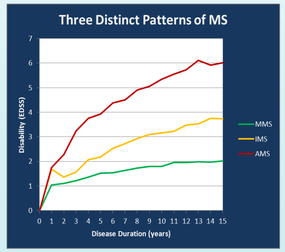
5-year Epochs
-AMS group was stratified into 5-year epochs (0-5, 6-10, 11-15 >15 years from onset) based on disease duration period.

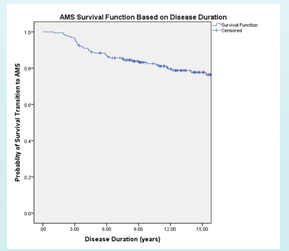
EDSS
The lead investigator solely determined EDSS. EDSS scores resulted from formal measurements routinely performed in our clinic and were available from all visits, as ascertained by a retrospective review of patient charts.

Results

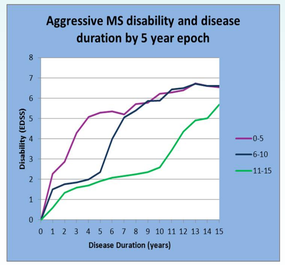
MS grouping	% Female	Age at MS onset, mean (SD) yrs	Disease Duration at last exam (SD) yrs	Follow-up years at last exam, mean (SD)	Sustained EDSS at last exam, mean (SD)
MMS (n =126)	79%	34.5 (8.4)	13.4 (5.0)	11.6 (4.2)	2.00 (0.9)
IMS (n = 22)	73%	37.3 (9.0)	16.4 (3.7)	15.0 (3.3)	4.46 (1.0)
AMS (n =46)	67%	36.4 (9.9)	13.7 (4.8)	12.0 (4.8)	6.19 (1.5)
Total (n =194)	76%	35.2 (8.8)	13.8 (4.9)	12.1 (4.4)	3.27 (2.1)

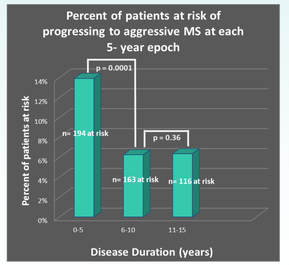
- AMS (*m* rank 41.89) remained more disabled at last exam (sustained EDSS) than IMS (*m* rank 19.05) p < 0.001
- Only variable to predict whether patient remained at EDSS ≥ 4.0 was group membership (AMS vs. IMS) p = 0.006





	% Remained EDSS ≥ 4.0 at sustained last exam	Age in yrs reached EDSS 4.0 (SD)	Disease duration, yrs (SD) when reached EDSS 4.0	% Reaching EDSS 6.0
AMS	96%	42.11 (10.82)	5.75 (4.68)	78%
IMS	68%	49.27 (7.09)	11.95 (5.14)	14%
p value	p = 0.004 (OR= 10.27, 95% CI 1.92-54.93)	(t(59) = 3.26 p = 0.002)	(t(66) = 4.96, p < 0.001)	p < 0.001 (OR =22.80, 95% CI 5.42-93.59)





Discussion

- We are among the first to describe a “New Natural History” of MS, with 98% of our patients being followed before and after early intervention with DMTs.
- Onset of relatively rapid worsening MS can occur any point in first 2 decades of RMS; somewhat less likely over time.
- Our model of AMS vs. IMS divides progressive patients into 2 distinct patterns, suggesting more heterogeneity than allowed by some previous models. The fact that a relatively large number of patients fell into each group, and that progression patterns remained distinctly different over many years, lends plausibility to our model as a useful tool for understanding the variability in disease course.
- The pattern of disease progression seen in our analysis might have been predicted by examining the previously described findings, that patients tend to spend a relatively short time at EDSS levels 4 and 5 versus other levels[2,3]; however, one could also hypothesize that patients with aggressive disease might pursue an entirely different course of progression after exposure to DMTs.

Conclusion

As we describe patterns of progression in the era of DMTs (a “new natural history”), we see that most patients who experience disabling disease do so during a period of relatively rapid decline surrounding the EDSS level of 4.0, as was previously reported in MS populations who were relatively untreated. We also propose that our definition of AMS works well as a simple EDSS-based tool for clinicians and researchers, identifying a group of patients who have declined fairly rapidly and have a need for more efficacious treatments.

References

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