

# Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis

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## Abstract

Secondary progressive multiple sclerosis (MS) is typically defined as deterioration independent of relapses for  $\geq 6$  months following an initial relapsing–remitting course; however, this definition is not always easily applied in clinical practice and the declaration of the change in clinical phenotype is often delayed. To identify the length of time required to re-classify relapsing–remitting MS (RRMS) patients whom have clinically transitioned to secondary progressive MS (SPMS) in clinical practice. We reviewed 123 patients with long-term follow-up and identified a sub-group whom transitioned from RRMS to SPMS, then characterized this transition period. There were 14/20 patients who transitioned during the follow-up period that had visits with uncertainty related to the clinical phenotype characterized by possible, but not definitive progression. The mean duration of this period of uncertainty was  $2.9 \pm 0.8$  years. A period of diagnostic uncertainty regarding the transition from RRMS to SPMS existed in many of our patients. Potential reasons included the subtle nature of early progressive disease and caution in applying a progressive label, in light of the lack of evidence-based treatments as well as third-party payer concerns. Delay in definitive identification of an SPMS phenotype has a variety of implications related to patient care and research.

## Keywords

Diagnosis, disease progression, multiple sclerosis, relapsing–remitting multiple sclerosis, secondary progressive multiple sclerosis, transition

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## Introduction

The diagnostic categories of relapsing–remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) have been widely used for clinical trial design, regulatory approval and therapeutic decisions. While these categories were originally conceived as descriptions of clinical phenotypes, they are widely construed to reflect distinct disease course entities. On the individual level, it has become common to field the question from the well-informed patient, “What kind of MS do I have?” More generally, modern clinical trials are typically designed to evaluate MS patients from only one clinical subtype, such as RRMS, rather than an admixture. Consequently, regulatory agencies have approved disease-modifying therapies (DMTs) for specific MS disease

subtypes and not others, as though they reflect distinct diagnoses. As such, in this paper we use the phrase ‘diagnose’ SPMS, though we recognize that the original spirit of the disease course descriptions would have these as ‘categorizations,’ rather than separate diagnoses. SPMS is typically defined as deterioration independent of relapses for  $\geq 6$  months, following an initial RRMS course.<sup>1</sup> In clinical

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practice, this definition of SPMS is not always easily applied, and a period of diagnostic uncertainty often characterizes the clinical transition from RRMS to SPMS. This can result in a delay in SPMS diagnosis.

## Methods

To maximize internal consistency, we reviewed 123 patients with a long-term clinical follow-up of  $\geq 8$  years, using a single academic MS specialist. We identified patients whom transitioned from RRMS to SPMS during the follow-up period. We characterized the cohort of patients, focusing on this clinical transition period. We recorded the dates of the last definitive RRMS and first definitive SPMS diagnoses and closely examined the intervening visits for diagnostic uncertainty. These visits were characterized by ambiguous diagnostic labels that were suggestive of progression (“MS, slightly worse,” “RRMS versus SPMS” or similar labels) in the absence of relapse. This study was approved by the Mount Sinai Medical Center’s Internal Review board (IRB).

## Results

Of the 123 patients included in the long-term cohort, 88 began the follow-up period with a diagnosis of CIS or RRMS. One patient was excluded because of incomplete information. Of the remaining 87 patients, 20 (23%) were identified as having transitioned from RRMS to SPMS (Figure 1). We found that 14/20 (70%) patients had medical visits with some level of diagnostic uncertainty related to the clinical phenotype; thus, they were characterized by possible, but not definitive, progression. The duration of this period of uncertainty, from the first visit with a suggestion of progression to the visit that was definitively labeled as SPMS, was  $2.9 \pm 0.8$  years. The duration between the last visit the patient was definitively labeled as having RRMS and the first labeled as SPMS was  $4.3 \pm 0.8$  years. A total of 14/20 (70%) patients reached an Expanded Disability Status Scale (EDSS) of  $\geq 6$  by the time of their SPMS diagnosis (Figure 2).

## Discussion

A period of diagnostic uncertainty regarding the transition from RRMS to SPMS existed in many of our patients. Several potential reasons may account for the delay in the diagnosis of SPMS. The earliest indicators of SPMS may be subtle; if a patient reports worsening, but little change occurs in the neurological examination, a period of true diagnostic uncertainty may exist in the clinician’s mind. The clinician is also likely to be appropriately cautious in labeling a patient as having SPMS, given the lack of available evidence-based treatments for this condition and patients’ anxieties regarding its prognosis. In addition, a

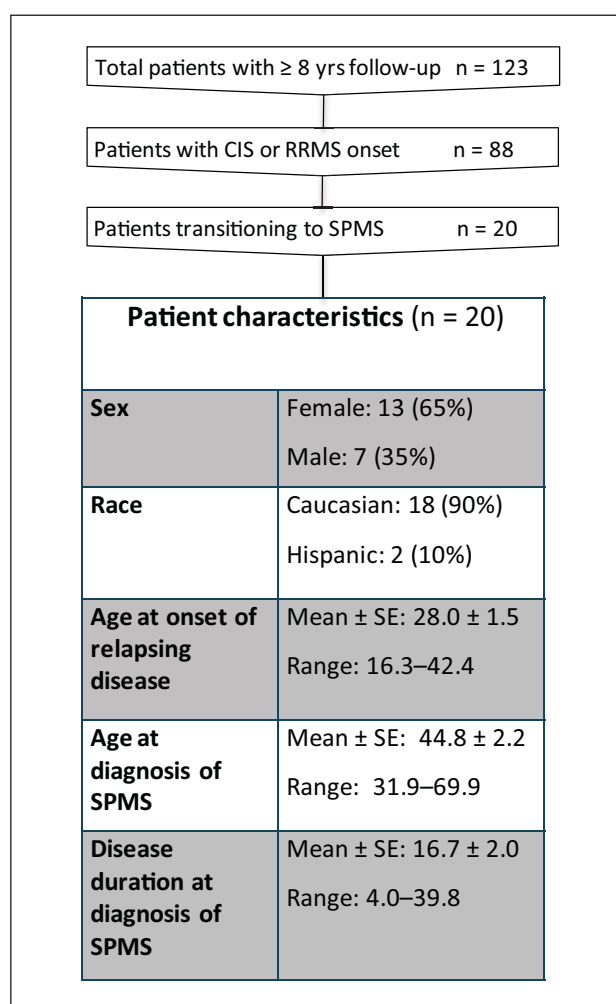


**Figure 1.** Inclusion criteria and demographics for patients transitioning from RRMS to SPMS.

RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

SPMS label may raise concerns regarding coverage for treatments by a third party.

Delay in definitive identification of a SPMS phenotype has a variety of implications related to patient care and research. During this delay, patients may remain on therapies for RRMS that are ineffective at slowing SPMS, and that may result in unnecessary adverse effects and costs. As new therapies are introduced, especially those with potential neuroprotective effects, early SPMS may represent a window of opportunity for intervention. In addition, patients with SPMS represent a difficult population to study; the identification of a larger patient group with early SPMS could improve recruitment for clinical trials. Though limited by its retrospective design and single-provider patient group, this study suggested that better tools are required to identify early SPMS, and the clinical subtypes could be revised to better encompass a transitional MS spectrum.

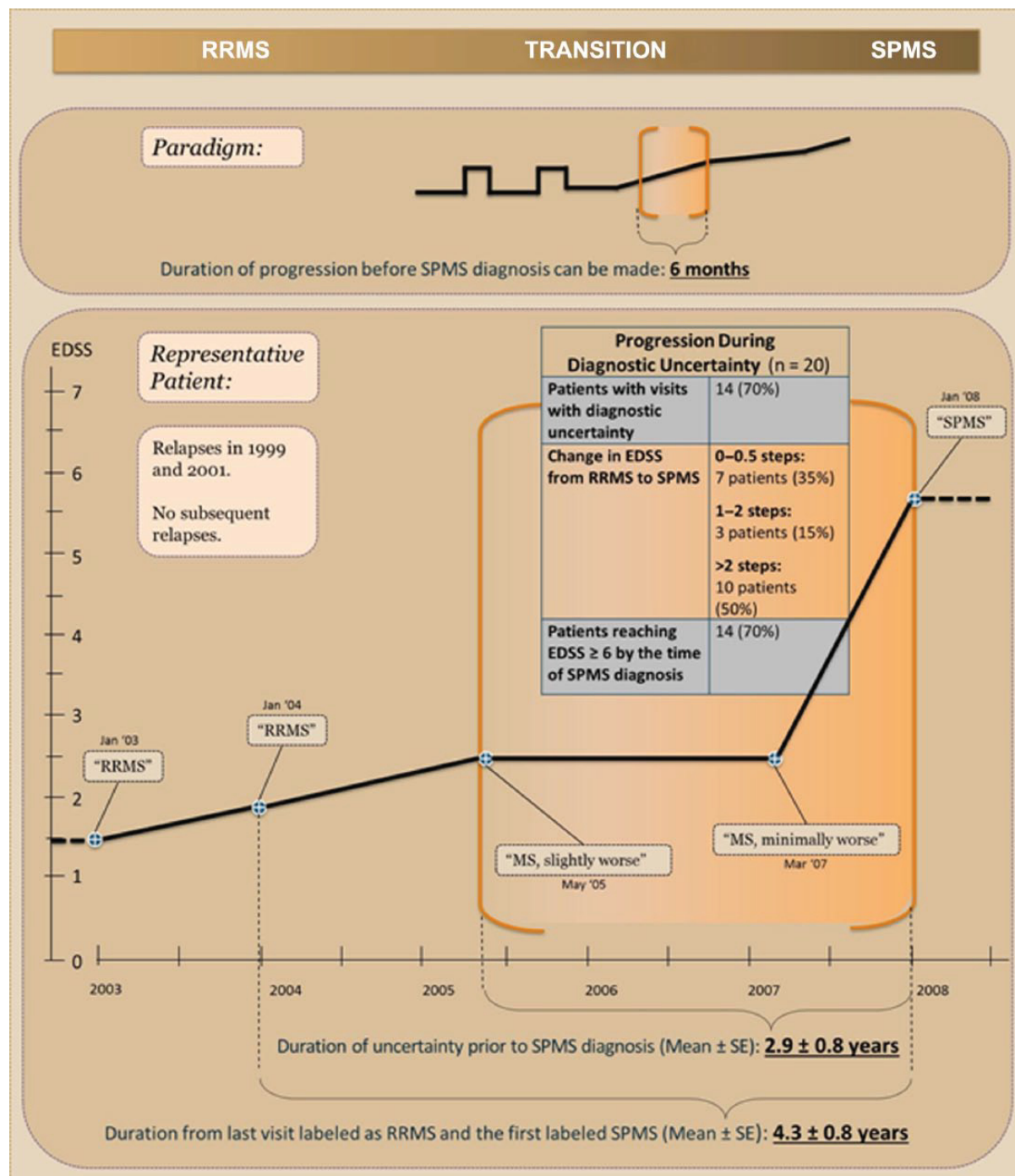


**Figure 2.** Disability change over time as measured by EDSS during the transition to SPMS: the paradigm, a representative patient and data from this cohort.

EDSS: Expanded Disability Status Scale; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

**Conflict of interest**

Author C Farrell had nothing to disclose. I Katz Sand's fellowship was supported in part by the National Multiple Sclerosis Society. Katz Sand also received research support from the Guthy Jackson Charitable Foundation and Acorda Therapeutics. S Krieger received research funding from Bayer HealthCare Pharmaceuticals; had consulting agreements or advisory board positions with Acorda Therapeutics, Bayer HealthCare Pharmaceuticals, Biogen Idec, Genzyme, Questcor and Teva Neuroscience; and had Speakers' Bureau Honorarium Agreements with Teva Neuroscience. AE Miller has received research support from Acorda, Novartis, Genentech, Genzyme, Sanofi-Aventis, Biogen Idec, Roche, Osmotica and Questcor; and was a consultant for Genzyme/Sanofi-Aventis, Biogen Idec, Glaxo Smith Kline, EMD Serono (Merck Serono),

Novartis, ONO, Acorda, Nuron Biotech and Accordant Health Services.

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**Reference**

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