REVIEW ARTICLE

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Phases and Phenotypes of Multiple Sclerosis

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ABSTRACT

PURPOSE OF REVIEW: **This article describes the dynamic evolution of multiple sclerosis (MS) through its phases and the impact of this understanding on treatment decisions.**

RECENT FINDINGS: **MS consists of three phases: (1) the high-risk phase, (2) the relapsing-remitting phase, and (3) the progressive phase. Increasingly, subclinical disease activity is becoming an integral part of our definition of disease course in MS. In many patients, the relapsing-remitting phase starts as subclinical activity, likely long before they present with a clinically isolated syndrome. Differentiating progressive MS subgroups is also becoming less relevant. This is illustrated by comparing progressive MS that evolves from an asymptomatic state in individuals with radiologically isolated syndrome (primary progressive MS) and symptomatic individuals with relapsing-remitting MS (secondary progressive MS). In each case, the background disease activity and pathology can be indistinguishable. These phases evolve on a continuum and largely follow the aging process with little influence by the preceding clinical activity level. Recently, it also became evident that one or a few poorly recovered relapses at the beginning of clinical manifestations of MS predict much earlier progressive MS onset.**

SUMMARY: **These findings suggest that interventions to prevent progressive MS, when they become available for clinical practice, may need to be considered as early as when the asymptomatic radiologically isolated syndrome is detected. This early treatment approach is being evaluated with ongoing trials with available disease-modifying therapies. In contrast, continuing the use of disease-modifying therapy beyond a certain age may have little benefit. However, being in the progressive phase of MS is not, in itself, an argument against disease-modifying therapy use in active disease in younger patients.**

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INTRODUCTION

Heterogeneity in clinical, radiologic, biological, and pathologic presentations of multiple sclerosis (MS) has been well documented, beginning with Dr Charcot himself. Even the immunopathology of MS has significant heterogeneity.[1] This phenotypic variability is, at minimum, confusing and, at worst, leads to frustrating difficulties with interpreting and applying clinical trial results in the real world. This is

further complicated by the fact that early clinical trials of disease-modifying therapies largely focused on relapse reduction, whereas natural history studies completed before the advent of disease-modifying therapies showed that the progressive phase is the key determinant of poor long-term disability in MS.[2–5] These studies also documented that, other than progressive disease, determinants of worse long-term disability were male sex, older age at MS onset, spinal cord syndrome at MS onset, and high early relapse rate.[2–5]

Clinical definitions of MS phenotypes should be complemented by subclinical observations obtained with MRI. For example, in radiologically isolated syndrome, classic MS findings are detected on MRI studies in patients who have no typical symptoms of the disease. This situation was originally described as asymptomatic MS as it had also been observed in autopsy studies. This article discusses how understanding this asymptomatic phase of MS shed light onto MS phenotypes such as primary progressive MS. We have also learned that all progressive MS phenotypes, including primary progressive MS, have striking similarities in pathology, imaging, and clinical presentations. Aging, through yet-to-be-identified mechanisms, plays a major role in development of a progressive clinical phenotype of MS. Recent findings also document that gray matter atrophy in brain starts in the preclinical asymptomatic phase of MS, and spinal cord atrophy is already detectable at the time of clinical manifestation of progressive MS.[6,7]

Why does all this matter? The currently available disease-modifying therapies that work through immunomodulation seem to be mostly ineffective once the relapsing phase of MS is over. While mild to moderate disability in MS can be driven by clinical relapses and partial remissions, most of the moderate to severe disability in MS is associated with progressive disease. But, if the progressive gray matter and spinal cord atrophy started much earlier than the clinical manifestations, is it already too late to intervene with currently available disease-modifying therapies at the time of clinical MS diagnosis? It seems natural to think that when nervous system reserve is building earlier in life, it provides a better opportunity to actively intervene with a disease such as MS to prevent ensuing damage or harness the natural recovery process so that as one reaches an age where the reserve plateaus or starts declining, neurodegeneration is less likely to occur. While thinking about starting disease-modifying therapies earlier in life (not just earlier in clinically observable disease course), the decision is further complicated by the risks associated with prolonged exposure to disease-modifying therapies. The future potential of regenerative medicine approaches should also be considered. Understanding the clinical and radiologic phases of MS as they relate to pathology will be necessary to make the individualized treatment decisions of today and tomorrow.

KEY POINT

- **Current disease course classification in multiple sclerosis consists of three phases: the multiple sclerosis high-risk phase, the relapsing-remitting phase, and the progressive phase.**

PHENOMENOLOGY OF MULTIPLE SCLEROSIS

Interaction between two phenomena, relapses and progression, describe the disease course in MS. These phenomena can overlap at different stages in the disease. Current disease course classification in MS consists of three phases: the MS high-risk phase, the relapsing-remitting phase, and the progressive phase. About 80% of patients ultimately evolve to the progressive phase of the disease.[8] Each phase is further defined as active or inactive at any given time. Understanding how MS phenomenology is defined will help the reader follow the figures in this article. While diagnostic criteria are referred to in this

article, it is important for readers to recognize that diagnostic criteria are ever-evolving.

Relapses, Remissions, and Pseudorelapses

New events in a patient with MS are described as symptomatic or asymptomatic. A *symptomatic relapse* refers to a distinct, acute to subacute (peaking over hours to days), generally focal, sometimes multifocal and rarely diffuse, central nervous system (CNS) syndrome. However, a patient may also present with subclinical "activity" as new MRI lesions without symptoms, which is referred to as an *asymptomatic relapse*. Pathologically, whether symptomatic or asymptomatic, relapses reflect an acute inflammatory demyelination event with or without axonal injury. Currently, the biological basis of why some presentations remain asymptomatic in MS is unclear.

A symptomatic relapse generally plateaus over days to weeks, and a recovery phase ensues. *Remission* refers to this recovery phase, with some level of restoration of myelin and axonal integrity. Maximum clinical recovery after a relapse generally stabilizes within the first 3 months and rarely continues beyond 6 months following a relapse. Most patients clinically recover completely or almost completely back to baseline; some recover partially, but, rarely, patients may not recover at all.[9]

Recovery in MRI lesions (symptomatic or asymptomatic) can be defined as resolution of enhancement, restoration of diffusion characteristics, and shrinkage in size of the MS lesion(s) on MRI. Rapidly developing imaging technologies will likely give a better characterization of lesion recovery in the future, so the definition of subclinical recovery may change.

Clinicians should be aware of and able to identify a pseudorelapse. A pseudorelapse is a recurrence of symptoms from a previous clinical relapse or a subclinical lesion. A pseudorelapse likely indicates incomplete recovery from the previous CNS insult. Any stress to the nervous system (eg, heat, infection, exercise, fatigue) exceeding a threshold that the damaged nervous system can sustain can trigger a pseudorelapse. The sustained threshold is likely determined not just by the damage and limited recovery alone but also by the nervous system reserve. The latter is evident from many patients who may develop pseudorelapses years later in a CNS location previously affected by MS. The author of this article believes that this is due to aging and loss of reserve that affects the damaged nervous system areas disproportionally. Future studies looking into the age sensitivity of pseudorelapses can potentially provide indirect proof of this concept. Once the trigger is eliminated, symptoms are supposed to recover, often noted by the patients themselves (eg, self-limited worsening during a hot shower or during a urinary tract infection). If symptoms attributed to a pseudorelapse exceed the arbitrary cutoff of 24 hours or do not start improving within a few days despite identifying and intervening with a potential trigger (eg, treatment of a urinary tract infection), an MRI should be obtained to differentiate it from a symptomatic relapse recurrent in the same location or close vicinity on the same neural pathway. Two potential scenarios can otherwise arise that are problematic: (1) the patient is treated with steroids for a relapse because of strict adherence to the 24-hour rule when he or she actually has an ongoing infection or (2) the patient may be having a real relapse that cannot be differentiated from an existing deficit by history or examination alone (eg, a slight change in

sensory level due to a new transverse myelitis), and a delay in steroid treatment may ensue. This is one area in which the development of cost-effective precise serologic markers of a relapse in MS can significantly help clinical practice in the future.

Progression and Pseudoprogression

Progression is the insidious and irreversible worsening of neurologic function due to MS over years. The main corresponding pathology is one of progressive axonal injury or loss. Imaging technology is evolving, and in the future, detection of subclinical progression will be an important component of the treatment decision-making process in MS.

In some patients, the term *pseudoprogression* is used to describe accumulating insidious disability due to factors indirectly related or unrelated to MS. Examples are deconditioning, degenerative joint diseases, other concomitant medical illnesses associated with progressive fatigue, other causes of structural myelopathy (CASE 3-1), and other concomitant neurodegenerative diseases (eg, Parkinson disease) and peripheral nervous system disorders that can increase in frequency with age.

Active Versus Inactive Multiple Sclerosis

Operationally, MS activity is defined clinically and subclinically. *Active disease* is defined as new symptomatic relapses or asymptomatic MRI activity (contrast-enhancing T1-hyperintense lesions, new T2-hyperintense lesions, or enlarging T2-hyperintense lesions).[11] The absence of active disease for an arbitrarily determined time cutoff of 1 year or more[11] is referred as "no evidence of disease activity" (NEDA).[12] The NEDA definition also includes absence of any progression in MS; however, active status, as used in this article and supported by the author, implies what can be clinically and radiologically demonstrated as potential ongoing immunologic activation. In the author's opinion, because of the differing biological phenomena discussed below, inactive progression should be differentiated from an active progression within the NEDA definition.

Disability Worsening

Worsening disability can be due to the stepwise accumulation of neurologic deficit from partially recovered relapses, the insidious accumulation of neurologic deficit from progressive disease course, a combination of both, or other MS or non–MS-related factors.

Worsening disability sometimes is referred to as *disability progression*, but this term should be avoided. Disease-modifying therapies can impact disability worsening (the more appropriate term)[11] by preventing symptomatic relapses and asymptomatic subclinical activity. However, especially considering most recent studies of CD20-depleting monoclonal antibodies that interfere with disease activity (expectedly more so in younger individuals) without any clear impact on inactive progressive MS, caution should be exercised in setting patient expectations.[10] Hence, the term *progression* should only be used to indicate progressive MS and disease-modifying therapy should be described as decreasing the likelihood of disability worsening due to active MS in the setting of progressive MS. The concept of active versus inactive progressive MS is further discussed in the next section.

KEY POINTS

- **Progression is the insidious and irreversible worsening of neurologic function due to multiple sclerosis over years.**
- ***Active disease* in multiple sclerosis is defined as new symptomatic relapses or asymptomatic MRI activity (contrast-enhancing T1-hyperintense lesions, new T2-hyperintense lesions, or enlarging T2-hyperintense lesions).**
- **Worsening disability can be due to the stepwise accumulation of neurologic deficit from partially recovered relapses, the insidious accumulation of neurologic deficit from a progressive disease course, a combination of both, or other multiple sclerosis or non–multiple sclerosis-related factors.**

CASE 3-1

A 40-year-old left-handed woman presented for a neurologic consultation because of right-sided numbness and weakness. Three weeks earlier, she had the abrupt onset of right-sided lower extremity numbness and tingling below the upper chest wall, which peaked over the course of a week. Over the week before presentation, she had noticed the numbness had improved somewhat, but she had also developed weakness on that side. She stated that starting at about age 37, she had noticed right hip problems, which were thought to be mechanical in nature. She also noted right leg weakness and stiffness that was chronic at onset and had been insidiously progressive since. After hip surgery at age 39, she noticed a continued worsening and drag in her right lower extremity and experienced falls. She described heat-induced episodic worsening of her symptoms as well. She reported no bladder, bowel, or upper extremity problems. She had no other significant past medical history and no family history of neurologic disease or autoimmune disease. She had never smoked, drank, or used drugs and had always been athletic.

On examination, the patient was asymmetrically spastic and paraparetic with right lower extremity dominance with brisk right lower extremity deep tendon reflexes and an upgoing toe on the right side. She had a sensory level around T8 on the right. MRI of the brain and cervical and thoracic spinal cord showed cortical, juxtacortical, subcortical, cervical medullary junction, C2-C3, left C4-C5, and right C5-C6 spinal cord lesions, with mild atrophy associated with the right C5-C6 lesion without enhancement. She also had moderate cervical spondylosis, without central canal compromise, throughout most of the cervical spine. All lesions were at a location and orientation typical of multiple sclerosis (MS). She also had a faintly enhancing right anterolateral thoracic cord lesion at T6-T7 and a small nonenhancing left posterolateral T8 lesion. A lumbar puncture was performed, which showed 12 oligoclonal bands unique to CSF; IgG index was elevated to 2.3. In retrospect, an MRI of her brain obtained at age 35 for headaches reported similarly described brain lesions, although she did not have any other symptoms at that time. Although the images were not available for review, the report suggested a diagnosis of pre–radiologically isolated syndrome or radiologically isolated syndrome at that time.

The rest of the workup was negative for alternative diagnoses, and a diagnosis of clinically active primary progressive MS was established. Methylprednisolone 1 g/d IV for 5 days was given, but the patient failed to have sufficient recovery within the next 4 weeks. Her sensory level remained prominent, and, overall, her improvement from motor function was, at best, 50% from her peak deficit 4 weeks after treatment. She then received five plasma exchange treatments over the course of 10 days,

with rapid further recovery to 75% from the peak deficit overall. At the same time, subcutaneous interferon beta was initiated since the patient had active disease on top of a progressive course.

Over the next 3 years, the patient tolerated medications and stayed active, with mild progression in the right leg weakness and spasticity limiting her walking distance further, although she did not need any support. Yearly imaging revealed no new lesion formation, and she had no other new symptoms. The patient returned to clinic at age 44 with a 6-month history of progressively worsening bowel incontinence, increased spasticity, and symmetric upper extremity numbness from her midarms down that was provoked mainly by prolonged lying down and improved after standing or sitting up for a while. Examination revealed worsened right lower extremity spasticity compared to 1 year earlier. Repeat MRI of the brain, cervical spine, and thoracic spine revealed no evidence of new demyelinating lesions. However, the cervical central canal stenosis had worsened, with bilateral C5-C6 foraminal stenosis. She was referred to neurosurgery for intervention consideration.

COMMENT

This case illustrates the full spectrum of disease evolution, from asymptomatic findings on MRI to the development of progressive MS at a relatively early age complicated by ongoing active MS on a background of primary progressive MS. While a small percentage of patients with primary progressive MS can have active disease, this generally happens at a younger age. This patient would, in the old terminology, be described as having relapsing-progressive or progressive-relapsing MS. Disease-modifying treatments available for intervening with relapses would therefore be indicated with the caveat that they will not necessarily impact the insidious progression but may prevent any further cumulative deficits that could arise from incomplete recovery from relapses in the future. The progressive loss of nervous system reserve due to primary progressive MS also makes this patient even more prone to a life-altering cumulative deficit from a future relapse. In this author's opinion, as this patient is still at an age to have potentially active disease in the future (as discussed further in the next section), the preventive treatment was indicated. Indeed, most recent evidence from clinical trials with CD20-depleting agents clearly confirm this approach.[10] This case further illustrates a relatively rapid change in progressive phenotype that led to a suspicion of another neurologic problem. As the patient was monitored with cervical MRIs, it became clear that the cervical canal stenosis was leading to a pseudoprogression. After surgery, patient recovered back to her baseline of about a year prior and resumed an active lifestyle.

PHASES AND DISEASE COURSE IN MULTIPLE SCLEROSIS

FIGURE 3-1 illustrates the dynamic phases of MS and diagnostic categories as a patient evolves from one step to the other.[13] Each step where a patient can present is represented with a box outlining the diagnostic nomenclature. Some of these concepts will be familiar as they are used in MS diagnostic criteria and some not, such as the pre–radiologically isolated syndrome or solitary sclerosis concepts; these conceptually fill the missing links in our understanding of MS phases.

Relapsing-Remitting Phase

The relapsing-remitting MS diagnosis that most clinicians are familiar with requires the presence of multiple clinically distinct events affecting different parts of the CNS separated in time (arbitrarily defined as at least 1 month apart). This operational diagnostic rule, core to understanding the diagnosis of MS, is referred to as *dissemination in time and space*. All diagnostic criteria in MS (which have seen many iterations over the years) have been based on this core rule. However, in practice, one must see typical lesions in location, orientation, and shape on MRI. In the absence of these typical lesions, other diagnostic possibilities should be entertained. Also, in some patients with aggressive presentations, sequential lesions could develop in intervals shorter than 1 month. Activity status, as described above, is also used to further describe patients as having active or inactive relapsing-remitting MS during a specific time period (FIGURE 3-1).

After a first-ever or "singular" clinical event, the term *clinically isolated syndrome* applies (FIGURE 3-1). When a patient experiences another clinical relapse (clinically active disease),[14] clinically isolated syndrome evolves into clinically definite relapsing-remitting MS.[15] According to the 2016 Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) and the 2017 McDonald criteria updates, MRI activity can fulfill dissemination in time and space criteria without the need for another clinical relapse.[16,17]

Clinically isolated syndrome can be further subgrouped into two categories (FIGURE 3-1). The term *solitary sclerosis* is used to define patients whose imaging findings at the time of clinically isolated syndrome do not fulfill the minimum MRI requirement for an MS diagnosis (at least three of the four imaging criteria),[18] but the existing "multiple" additional CNS lesions are unexplained by other pathology and are typical of MS in location, orientation, and shape. When a patient with solitary sclerosis proceeds to fulfill the minimum MRI requirement for an MS diagnosis (at least three of the four imaging criteria),[18] the diagnosis of *single-attack MS* may be used. While the ever-evolving diagnostic criteria have included parts of clinically isolated syndrome with relapsing-remitting MS, keeping clinically isolated syndrome separated as such into two subgroups has three uses in real-world practice. First, all the original clinical trials in clinically isolated syndrome were done without this division, but many patients represented high-risk groups more like single-attack MS than solitary sclerosis by the MRI criteria of dissemination in time and space used today. When the single-attack MS category is categorized together with relapsing-remitting MS, the application of these trials in current practice becomes limited to the solitary sclerosis group for which they were not specifically designed to be enriched. Until these subgroups are separated, it is clear from clinical practice and the original clinically isolated syndrome trials that efficacy of preventing a second

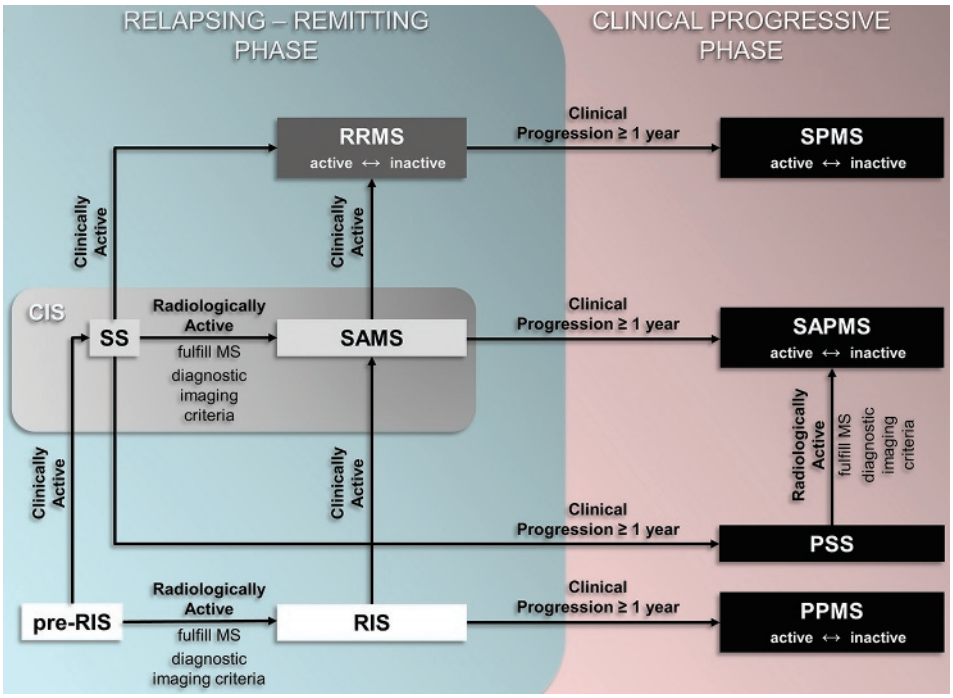

FIGURE 3-1

Evolution within and between phases of multiple sclerosis (MS).

CIS = clinically isolated syndrome; PPMS = primary progressive multiple sclerosis; PSS = progressive solitary sclerosis; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SAMS = single-attack multiple sclerosis; SAPMS = single-attack progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis; SS = solitary sclerosis.

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KEY POINTS

- **The relapsing-remitting multiple sclerosis diagnosis that most clinicians are familiar with requires the presence of multiple clinically distinct events affecting different parts of the central nervous system separated in time (arbitrarily defined as at least 1 month apart). This operational diagnostic rule, core to understanding the diagnosis of multiple sclerosis, is referred to as *dissemination in time and space*.**
- **When a patient presents with symptoms not typical of multiple sclerosis (MS) and an MRI is obtained that fulfills the diagnostic imaging criteria, a diagnosis of radiologically isolated syndrome is given. When these patients develop their first MS symptom, they fulfill the criteria for single-attack MS (30% in 5-year follow-up). This evolution is significantly faster in pediatric radiologically isolated syndrome (60% in 1-year follow-up).**

relapse was greatest in patients with high lesion loads. Therefore, caution should be exercised in discussion of disease-modifying therapy initiation with patients with solitary sclerosis as evidence of efficacy has not been explicitly studied. Second, each of these categories can evolve into a specific progressive phenotype of progressive solitary sclerosis (FIGURE 3-1) that is not covered by the classic definitions of primary progressive MS or secondary progressive MS. Third, as the asymptomatic presentations discussed below evolve, this subcategorization allows for a diagnosis to be established. Otherwise, the physician is left with trying to fit the diagnosis into a category that does not really fit any diagnostic criteria and there are gaps in the diagnostic continuum of phases of MS.

When a patient presents with symptoms not typical of MS and an MRI is obtained that fulfills the diagnostic imaging criteria,[18] a diagnosis of radiologically isolated syndrome is given.[19–21] When these patients develop their first MS symptom, they fulfill the criteria for single-attack MS (30% in 5-year follow-up).[22–26] This evolution is significantly faster in pediatric radiologically isolated syndrome (60% in 1-year follow-up).[27]

Many asymptomatic individuals present with lesions typical for MS but do not fulfill the diagnostic imaging criteria, so, technically, a radiologically isolated syndrome diagnosis cannot be established.[18] The term *pre–radiologically isolated syndrome* is used by some to define such cases. Currently, it is unclear how many of these individuals with pre–radiologically isolated syndrome will evolve to

having radiologically isolated syndrome when they fulfill the imaging criteria or evolve into having solitary sclerosis when they develop their first clinical event.

Progressive Phase

The progressive phase of MS is assumed to be established after 1 year of clinical progression is documented. During this phase, patients can continue to have active disease with symptomatic relapses or asymptomatic MRI activity because of temporal overlap between the relapsing and progressive phases. The patient is then further described as having active progressive or inactive progressive MS. This is independent of the further progressive MS subgroup definition as described below.

The progressive phase is classified into subgroups based on the presence or absence of preceding clinical relapses before the onset of a progressive disease course (FIGURE 3-1). Primary progressive MS refers to radiologically isolated syndrome followed by the progressive phase (although, in most cases, this is inferred, as discussed below when patients present with progression),[23] single-attack progressive MS refers to single-attack MS followed by the progressive phase,[8,28] and secondary progressive MS refers to relapsing-remitting MS followed by the progressive phase. If solitary sclerosis leads to a progressive phase, it is described as progressive solitary sclerosis.[29,30] Special consideration should be given to understanding the primary progressive MS diagnosis as, in most cases, patients have evidence of MRI activity compatible with a previous radiologically isolated syndrome at the time of primary progressive MS presentation, although a formal diagnosis of radiologically isolated syndrome had not been previously established. It is, however, natural to assume that if these patients had been imaged earlier, they would be compatible with a radiologically isolated syndrome diagnosis.

The differences between the progressive MS subtypes do not seem to be because of different progression mechanisms but rather because of why disease activity remains subclinical in some individuals. This argument is specifically supported by the following:

- The progressive phase of all subtypes of progressive MS seems to become symptomatic, on average, in the mid-fifth decade (FIGURE 3-2)[8,31,32]
- Subclinical MRI activity in patients with radiologically isolated syndrome who develop primary progressive MS cannot be reliably differentiated from subclinical MRI activity in patients with relapsing-remitting MS who develop secondary progressive MS (FIGURE 3-3[33])[23]
- Even a single critically located lesion is enough to set up a patient for a progressive disease course[29,30]
- The pathologic signatures of progressive MS, such as appearance of "smoldering plaques," are also age-dependent processes that are not strongly impacted by disease activity during the preprogressive phase (FIGURE 3-4)[34]

Among patients with secondary progressive MS, once the progressive MS course is set and patients reach moderate disability levels, any further disability worsening is linear and follows a similar slope regardless of how long it took to get to moderate disability levels in the first place (FIGURE 3-5).[35] It almost seems as if the disease has forgotten about the preprogression phase. Therefore, onset of the progressive phase of MS seemingly is age dependent but agnostic to disease duration and preprogressive phase.[13] While the mechanisms of such an age

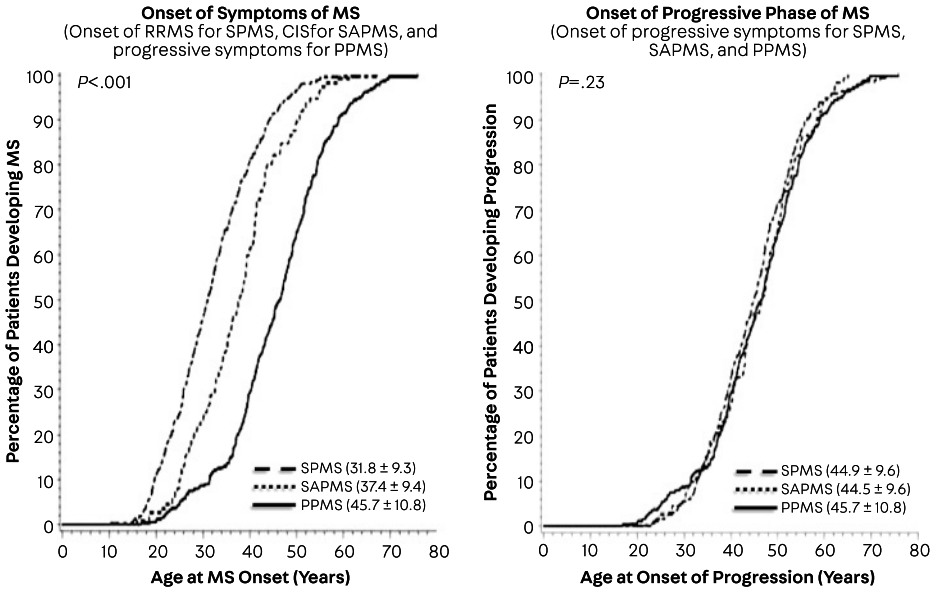

FIGURE 3-2

Age at onset of clinically progressive multiple sclerosis (MS) is preprogression disease course agnostic and does not differ between primary progressive MS, single-attack progressive MS, and secondary progressive MS. The progressive phase of all subtypes of progressive MS seems to become symptomatic, on average, in the mid-fifth decade. Therefore, age at onset of clinically progressive MS is preprogression disease course agnostic and does not differ between primary progressive MS, single-attack progressive MS, and secondary progressive MS.

CIS = clinically isolated syndrome; PPMS = primary progressive multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SAPMS = single-attack progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

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KEY POINT

- **Onset of the progressive phase of multiple sclerosis seemingly is age dependent but agnostic for disease duration and preprogressive phase.**

dependence of progressive MS onset are yet to be fully understood, any future (eg, regenerative) intervention to halt progressive MS should be applicable to any progressive MS subtype regardless of what happened before the onset of the progressive phase.

Whether a patient has none, one, or multiple clinical relapses before the onset of progressive MS does not alter the age when clinically obvious progression ensues.[8,28,31,32,36] However, the potential imaging markers of subclinical progression (eg, whole brain, thalamic, or spinal cord atrophy) likely starts long before clinical progression is evident. Deep or cortical gray matter atrophy can present as early as radiologically isolated syndrome.[6] Patients with secondary progressive MS have detectable spinal cord atrophy before or at the time of progressive MS onset more than age- and sex-matched patients with radiologically isolated syndrome and relapsing-remitting MS.[7] Additionally, limited recovery from the relapse(s) as early as the first relapse seems to accelerate the progressive MS evolution regardless of later disease course (FIGURE 3-6).[9] The combined conclusion from these studies is that mechanisms of the progressive phase of MS are set in motion long before it is clinically evident. Hence, future repair interventions targeting better recovery from relapses that are more frequent early on may help delay the progressive MS phenotype. One caveat is that spontaneous recovery potential from relapses is higher when patients are younger and declines with age (FIGURE 3-7).[37] Therefore, experience in a 2018 recovery trial has found a higher magnitude of effect in older patients with

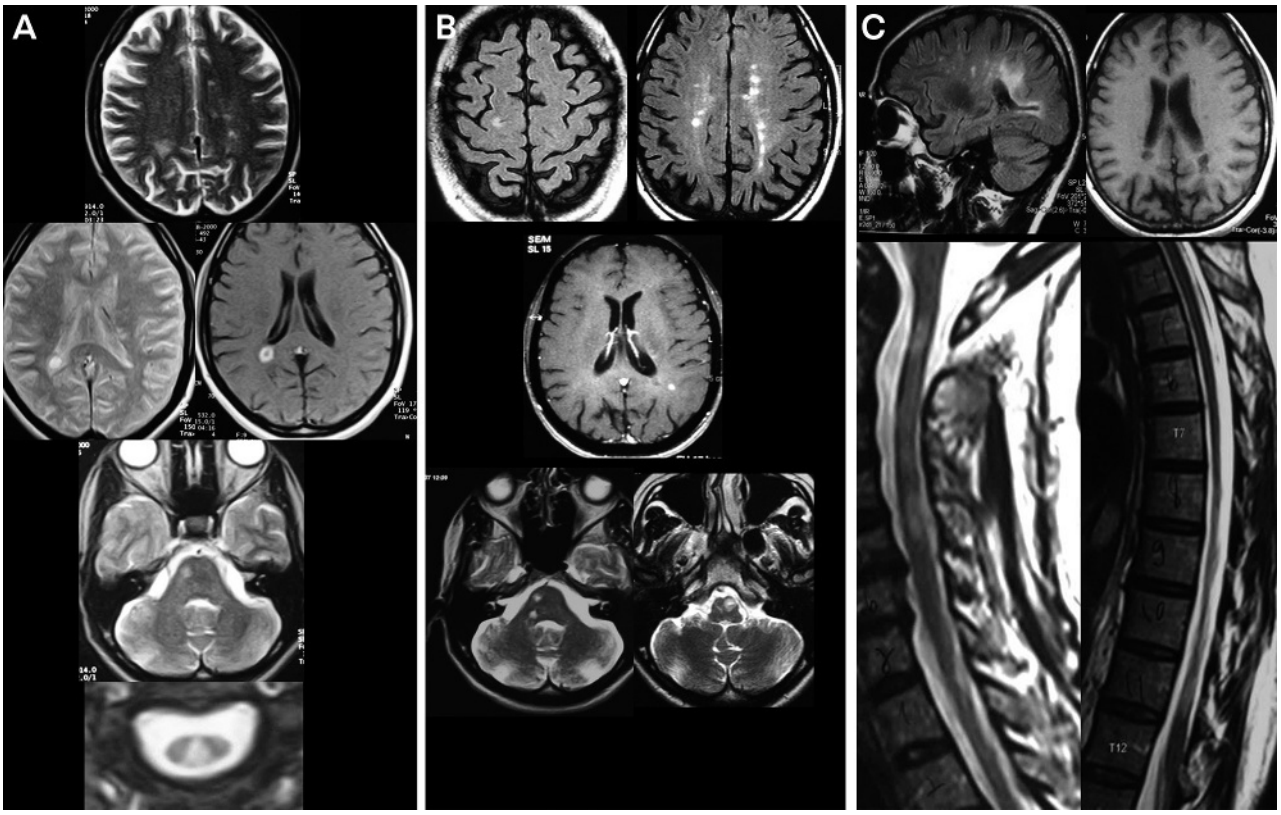

FIGURE 3-3

Imaging of a patient with radiologically isolated syndrome that evolves into primary progressive multiple sclerosis. *A*, At age 33, the patient is experiencing tension headaches and the MRIs at the diagnosis of radiologically isolated syndrome reveal active and inactive lesions: three periventricular lesions, one of which is gadolinium-enhancing; three juxtacortical lesions; three infratentorial lesions; and one cervical spinal cord lesion at C3-C4. *B*, At ages 36 through 38, MRIs at the follow-up of radiologically isolated syndrome reveal new active and inactive juxtacortical and cortical lesions, periventricular lesions, subcortical lesions (gadolinium-enhancing), and infratentorial lesions. *C*, At age 43, the patient presented with progressive myelopathy. MRIs reveal an extensive lesion load, including T1-weighted dark lesions; thoracic spine atrophy; and new inactive periventricular, subcortical, cervical spinal cord, and thoracic spinal cord lesions.

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limited recovery potential than in younger patients with spontaneous and strong recovery potential.[38] Also, it seems plausible to prevent even the first relapse in the form of clinically isolated syndrome using currently available disease-modifying therapies if one is to impact the future disease course in MS. Such clinical trials in radiologically isolated syndrome are under way.

Several clinically useful predictors of evolution to progressive MS (other than age) are having spinal cord lesions, being male, consuming tobacco, being obese, and having a low serum 25-hydroxyvitamin D_3 level.[22–26] Even in the absence of specific medications targeting progression alone in MS, some of these factors are modifiable and, together with an active lifestyle and physical therapy, can potentially help build nervous system reserve and resistance to injury.

Once the progressive phase starts, the relapse-based disability accumulation gives secondary progressive MS and single-attack progressive MS a head start over primary progressive MS at the time of progressive MS onset, leading to a

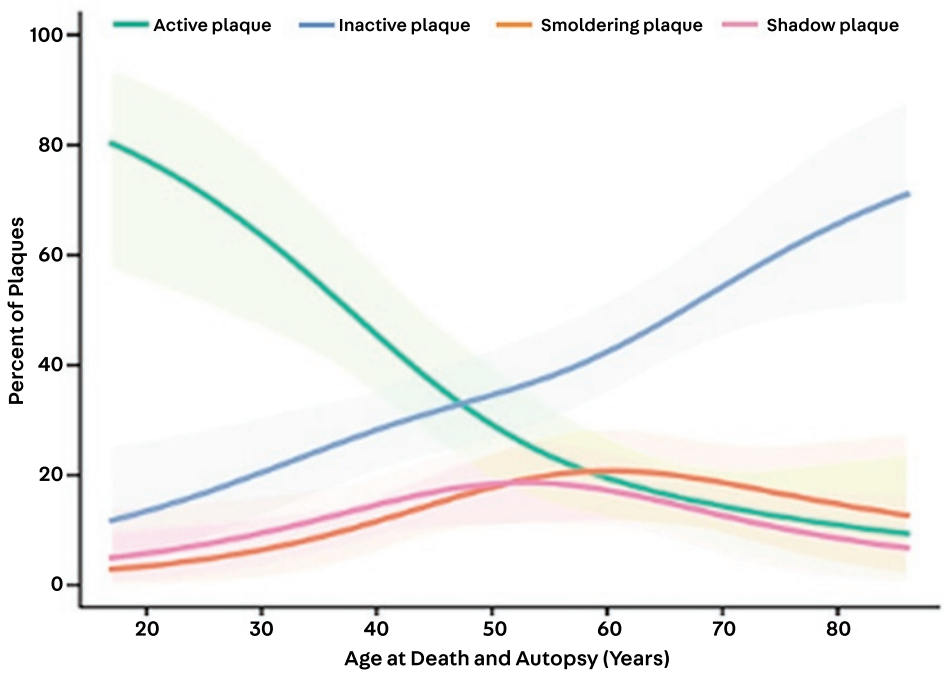

FIGURE 3-4
The pathologic phenotype of multiple sclerosis is age dependent.
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KEY POINTS

- **Several clinically useful predictors of evolution to progressive multiple sclerosis (other than age) are having spinal cord lesions, being male, consuming tobacco, being obese, and having a low serum 25-hydroxyvitamin D_3 level. Even in the absence of specific medications targeting progression alone in multiple sclerosis, some of these factors are modifiable and, together with an active lifestyle and physical therapy, can potentially help build nervous system reserve and resistance to injury.**
- **Disease-modifying therapies are efficacious early in multiple sclerosis, but the utility of continuing them in patients older than age 60 should be considered on an individual basis.**

higher starting point of disability.[31,39] Also, mirroring the preprogressive phase, patients with secondary progressive MS or single-attack progressive MS have a higher tendency for clinically active MS than patients with primary progressive MS.[39] Clinically active progressive MS reaches severe disability milestones faster than inactive progressive MS (FIGURE 3-8[40]), but this clinically active phase has an age limit, with chances of having a relapse decreasing to less than 5% in the last part of the sixth decade and less than 1% after the sixth decade (FIGURE 3-9[41]).[31,39]

The relevance of these observational data is seen in the context of currently available disease-modifying therapies. FIGURE 3-9 shows that when considering the overlap between onset of relapses and onset of progression, clear age periods can be defined when available relapse prevention strategies would be the most impactful. Interestingly, disease-modifying therapy trials have mostly included more patients in the average impact period of 27 to 46 years of age rather than the potentially more impactful period of earlier ages. In a 2017 meta-analysis of all trials, disease-modifying therapy efficacy was found to be lower in older patients compared to younger patients (FIGURE 3-10),[42] likely reflecting the decrease in relapses and increase in progressive MS with age. Disease-modifying therapies are efficacious early in MS, but the utility of continuing them in patients older than age 60 should be considered on an individual basis.

Pathologic Basis for Age Dependence of Phase Switches in Multiple Sclerosis

Further research into understanding progression mechanisms and why some patients never manifest clinical relapses in MS is needed. Pathologic studies have

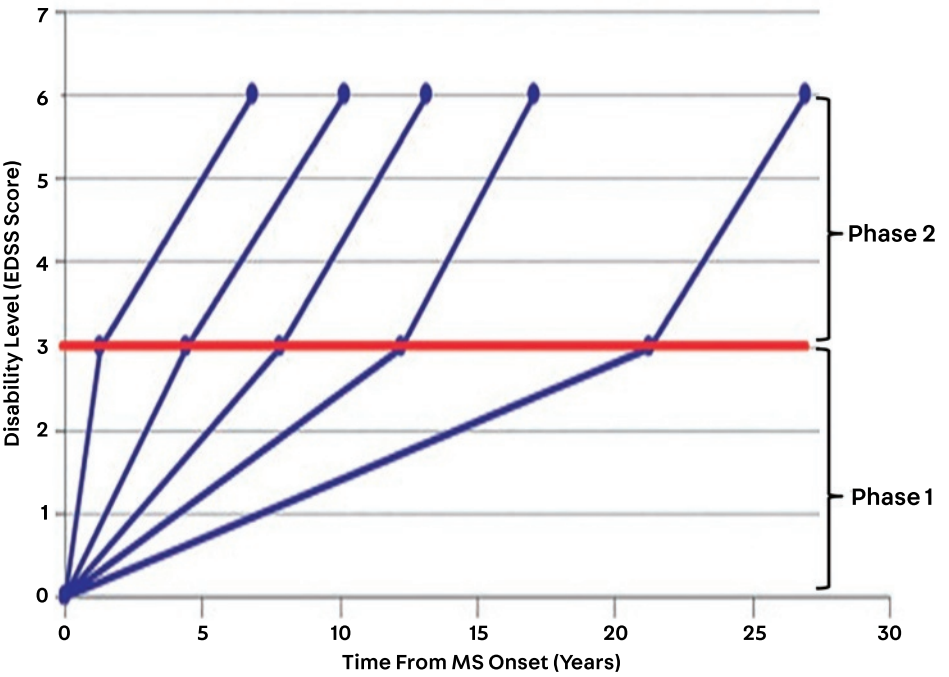

FIGURE 3-5

The two-phase model of disability worsening in multiple sclerosis (MS) illustrates that while it may take longer to reach moderate disability levels for different individuals, after that point the disability worsening slope is linear and similar among different patients.

EDSS = Expanded Disability Status Scale.

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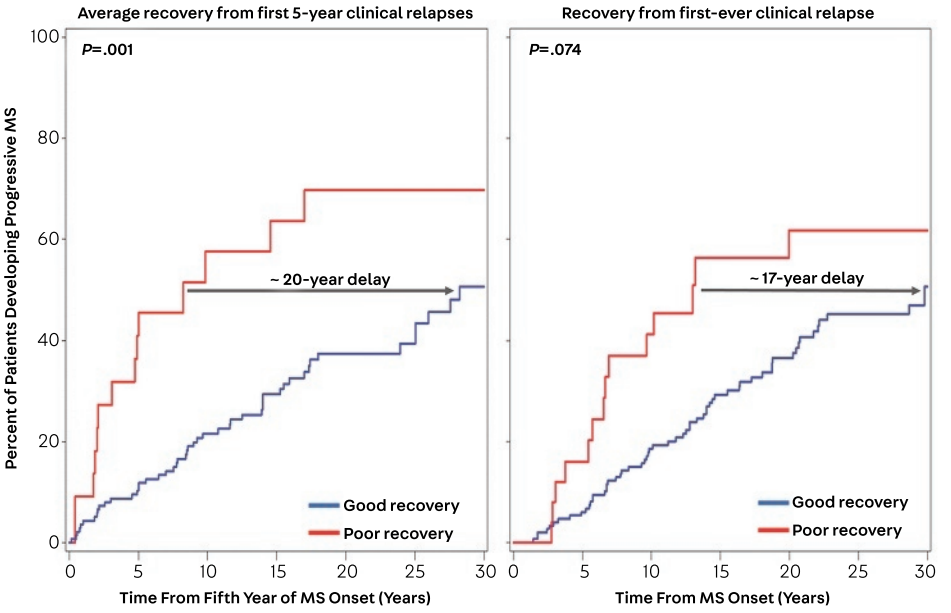

FIGURE 3-6

Recovery from early relapses and progressive multiple sclerosis (MS) onset. Good recovery from early relapses in MS delays the onset of progressive MS by decades.

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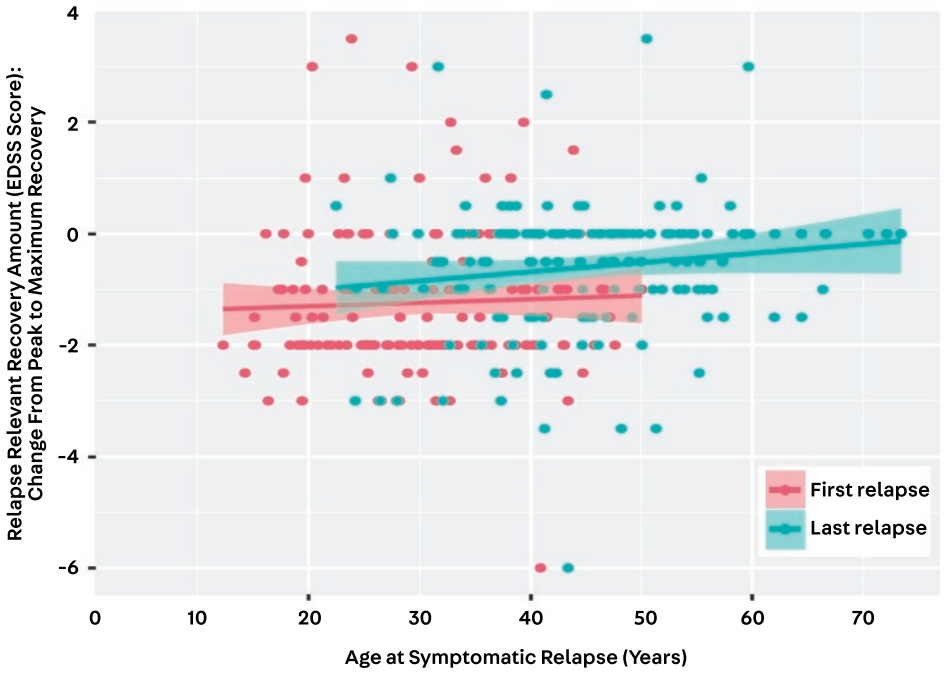

FIGURE 3-7

Recovery from first-ever and last-ever relapses from the same individuals. In a paired analysis of first-ever or last-ever relapse in patients from a population-based cohort, evidence of linear decline is seen in relapse recovery potential by age expressed as the amount of recovery from Expanded Disability Status Scale (EDSS) score at the peak of a relapse to maximum recovery attained. *Pink dots* represent the recovery from the first-ever relapse. *Green dots* represent last-ever relapse in the same individuals, separated on average by about 15 years. As recovery is measured by a drop of points from the peak deficit, negative numbers indicate better recovery. It is clear that patients whose first-ever relapses happen at an earlier age recover better than those whose first-ever relapses happen later in life or whose last-ever relapses happen later in life. This is true for ages between 20 and 60, but beyond these extremes, confidence intervals do not allow us to deduce a reliable conclusion. Between these limits, however, an individual loses approximately a full point of recovery potential in EDSS score and relatively linearly.

Modified from Conway BL, et al, Mult Scler.[37]

provided partial but critical understanding of some of the mechanisms involved in phase switches in MS.

A cascade of tissue injury occurs in progressive MS that follows the general order of demyelination, oligodendrocyte loss, thin axonal damage, astrocytic gliosis, and absence of remyelination.[43,44] Once the functional axonal threshold (a factor of both axonal number and individual axonal function) is exceeded, the progressive phase likely starts.[45–47] When and how to interfere in this cascade is not yet clear. The aging nervous system might simply be losing the trophic support[48] and myelin maintenance capacity to preserve the reserve that was developed earlier in life.[49,50] Oxidative stress followed by mitochondrial injury due to higher levels of iron in the aging oligodendrocytes may contribute to the age dependence of progressive MS onset.[1] Trapped, compartmentalized inflammation may also be a potential mechanism in the progressive phase of MS, limiting anti-inflammatory access.[1] Most recent studies also indicate a potential role of changes in microglial activity by aging that impact the local immune system response, leading to limited recovery and neurodegeneration.[51,52]

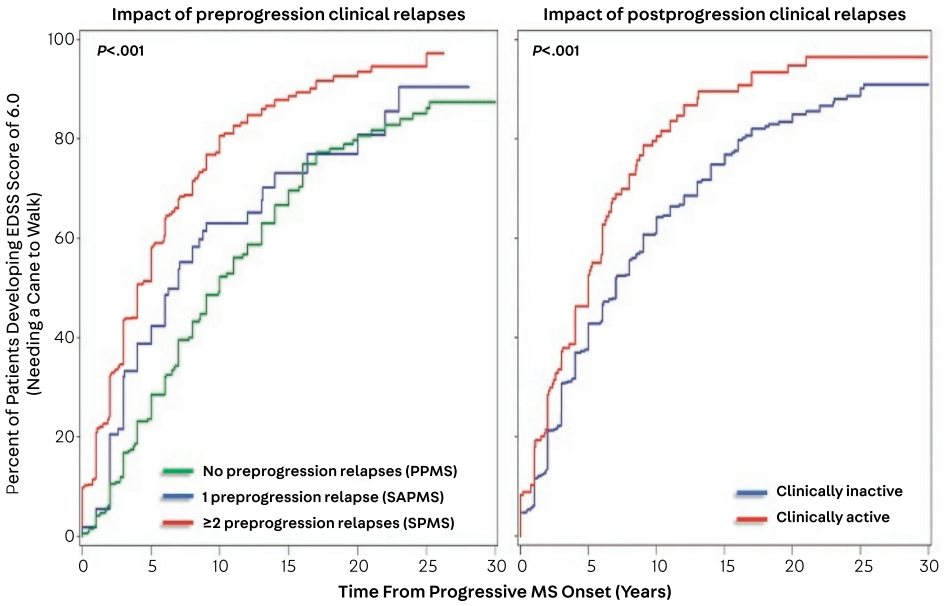

FIGURE 3-8

Impact of preprogression-onset relapses and postprogression-onset relapses on disability accumulation in multiple sclerosis (MS).

EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; SAPMS = single-attack progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

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MS pathology occurs on a continuum. Different MS plaque types (ie, active, inactive, shadow, and smoldering)[43,53] are present to different degrees at various stages of disease. Some of this is predictable from clinical phase descriptions of MS. Active plaques correlate with symptomatic relapses or asymptomatic MRI activity.[54] Inactive plaques with limited numbers of activated microglia are present mainly in inactive progressive MS. Shadow plaques with full remyelination capacity[55] are present across all phases of MS.[34] Smoldering plaques are associated with both secondary progressive MS and primary progressive MS and have a slowly expanding active rim of microglia with an inactive center.[34,43,56] Seemingly a pathologic hallmark of progressive MS, these smoldering plaques peak in frequency at around the fifth decade, a time when the dominant plaque type also switches from active to inactive plaques[34] (FIGURE 3-4), mirroring the independent epidemiologic observation of established mean age of progressive MS onset of 45 years (FIGURE 3-2).[8] The compact myelination in human brain terminates by the fourth decade, and white matter integrity as measured by MRI is slowly lost in the following years.[57,58] As the white matter reserve starts to decline in the fifth decade when all these pathologic changes are happening, this likely forms the "perfect storm" for progressive MS to manifest clinically.

CONCLUSION

The age of a patient seems to be highly relevant to the predicted phase of MS he or she is in. While clinical milestones help define phases of MS, subclinical disease processes have likely long been active, making imaging an integral part of

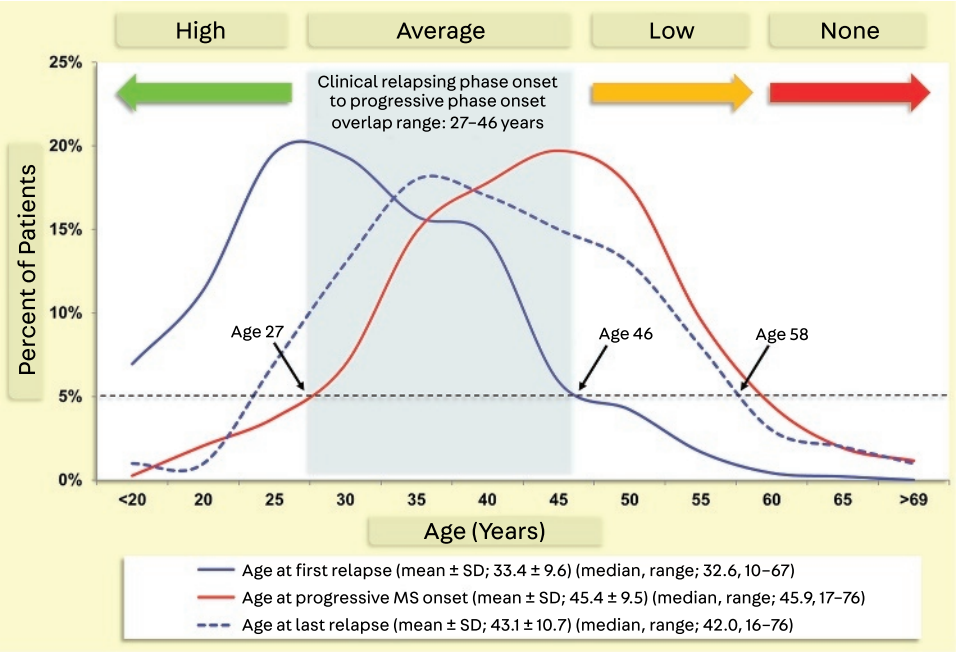

FIGURE 3-9

Overlapping age-dependent relapsing-remitting and progressive phases of multiple sclerosis (MS) and their impact on potential treatment decisions. The 5% *dotted line* marks the point below which there are only 5% of the patients crossing the line. Therefore, in this superimposed image, 95% of individuals have their first relapse before age 46, while 95% of individuals develop progressive MS after age 27. The *dashed blue line* represents last-ever relapse, but this would be impacted by treatment as the others are not. (Patients do not get treated before first-ever relapse and existing disease-modifying treatments are not known to change progressive MS onset age as is). The conclusion would be if one aimed to prevent the critical lesion(s) leading to progressive MS in 95% of individuals, one needs to treat the patients at an age earlier than 27 with disease-modifying treatments (ie, "high impact chance"). The other natural conclusion is that after the second half of the fifth decade, continuing treatment will be nonproductive for most patients (ie, "no impact chance").

SD = standard deviation.

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KEY POINT

- **Seemingly a pathologic hallmark of progressive multiple sclerosis, smoldering plaques peak in frequency at around the fifth decade, a time when the dominant plaque type also switches from active to inactive plaques, mirroring the independent epidemiologic observation of established mean age of progressive multiple sclerosis onset of 45 years.**

understanding the disease course in MS. All patients start with a high-risk period that is determined by genetic and environmental factors. This phase is followed by the presymptomatic active phases of MS, followed by the relapsing-remitting phase and, finally, in most patients, a progressive phase of MS. Therefore, MS is a dynamic continuum of phenotypic phases. Each phase is linked to a change in disability worsening that can result from poorly recovered relapses, progression, and non-MS–related factors. Thus, it is evident that optimal windows of opportunity exist for different types of interventions, such as the available disease-modifying therapies, future reparative or regeneration therapies, or even preventive strategies. For example, the optimal window for existing disease-modifying treatments is earlier in life when the disease is more likely to be active. However, our current strategy of treatment with escalation from weaker to strong drugs may indeed be the opposite of what we should do. This author believes that we will likely see an evolution of concepts toward more aggressive early treatment with maintenance approaches later in life, especially in patients with relatively active disease. As the definition of active MS is evolving, as is our understanding

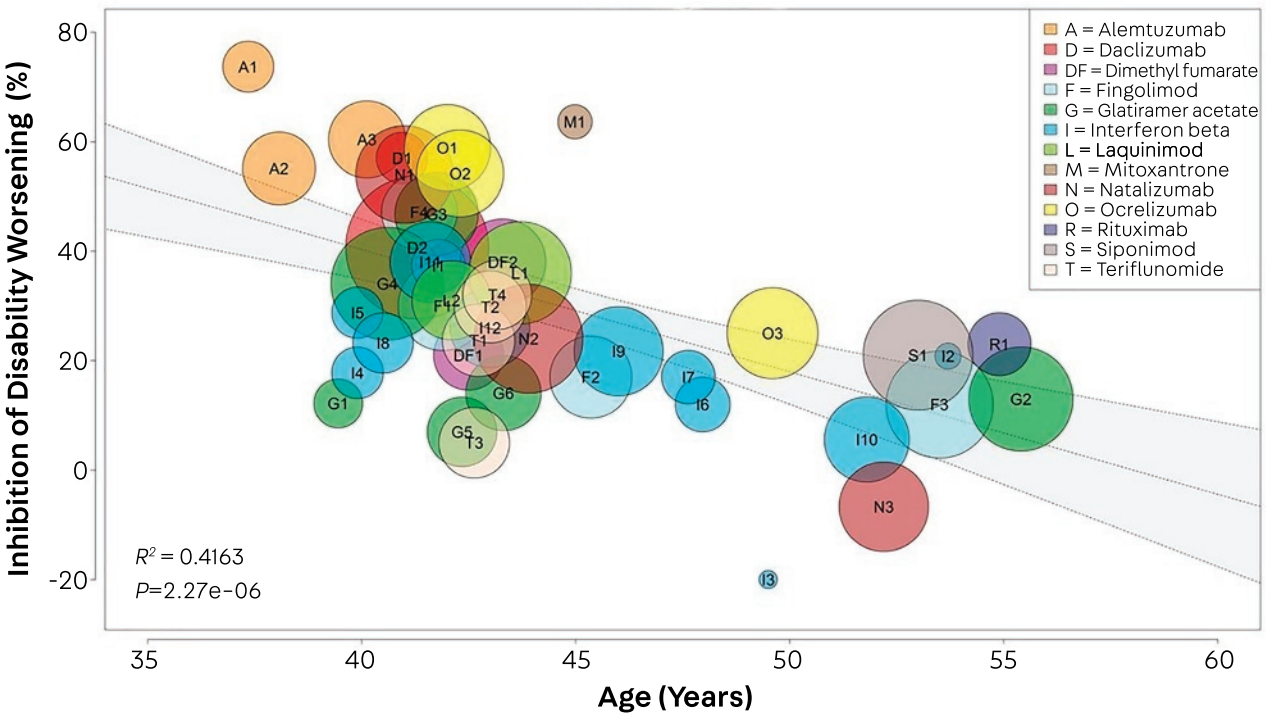

FIGURE 3-10

Impact of age on disability worsening outcome in multiple sclerosis (MS) clinical trials. This figure illustrates that, accounting for the size of individual clinical trials with disease-modifying therapies, when placed against the age axis, their impact on reduction of disability worsening (mainly due to active MS) declines with age. Same agents, such as the example with ocrelizumab, utilized in different age groups for different trial constructs illustrate this point better as an age effect that is seemingly true across the board.

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of the safety of disease-modifying drugs, we will be able to make better individualized decisions in the future. Aging and the loss of ability to maintain nervous system reserve must be kept in context when making these decisions.

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