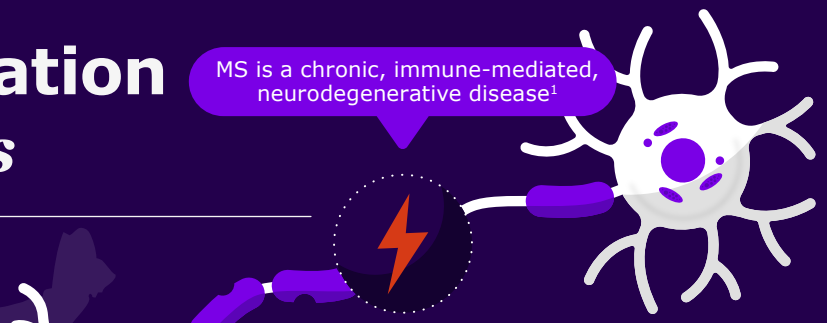
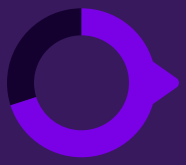
Disability Accumulation in *Multiple Sclerosis*

MS is a chronic, immune-mediated, neurodegenerative disease[1]



Up to
~1 million
adults have MS in the United States[2,3]



~70%
of patients say future disability is one of their greatest concerns[4a]

Inflammation and demyelination in the CNS lead to:[1]

- Irreversible axonal loss
- Brain volume loss
- Cognitive dysfunction
- Long-term disability

Our understanding of MS pathology is changing[5]

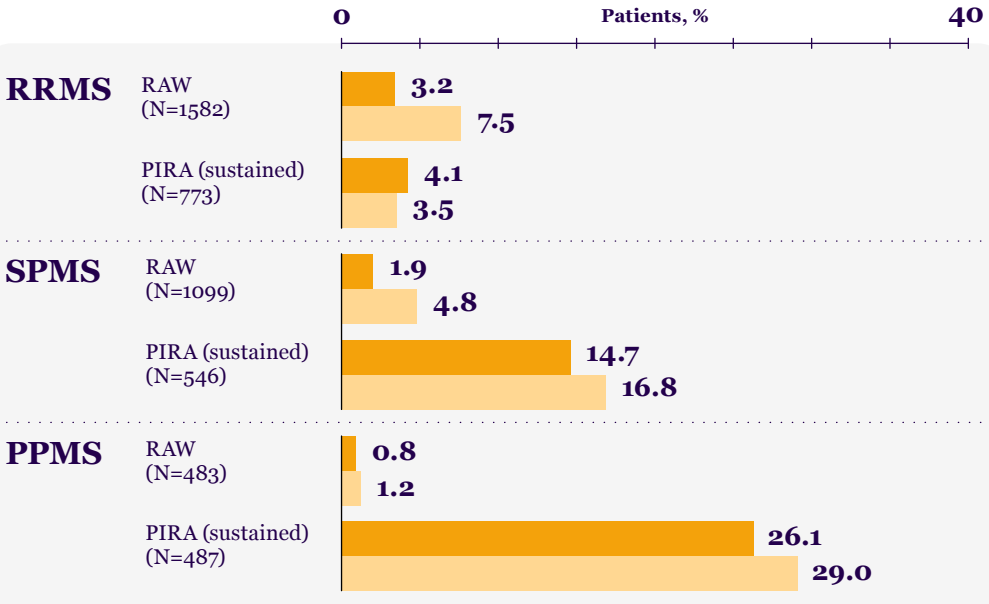
In natural history studies and clinical trials, **relapse activity** and **acute neuroinflammation** detected by MRI are **poor predictors of disability progression**, regardless of treatment status[5-7]

Progression independent of relapse activity (**PIRA**) starts early and continues throughout the disease course[5,6]

- In a recent cross-sectional survey of patients with MS, **62%–89%** of patients with RRMS reported continuous worsening of symptoms independent of relapses[8b]

In a study analysing the NO.MS dataset[c], patients across MS subtypes experienced substantial levels of PIRA even when inflammation was suppressed by DMTs[6]

Confirmed Disability Worsening (CDW) for Adult Patients With MS From Phase 3 Placebo-controlled Trials in the NO.MS Dataset (N=4970)[6c]



These observations may be explained by a diffuse smoldering pathological process that affects the entire CNS[5]

PIRA=progression independent of relapse activity; RAW=relapse-associated worsening (stepwise accrual of impairment due to incomplete recovery from a relapse).

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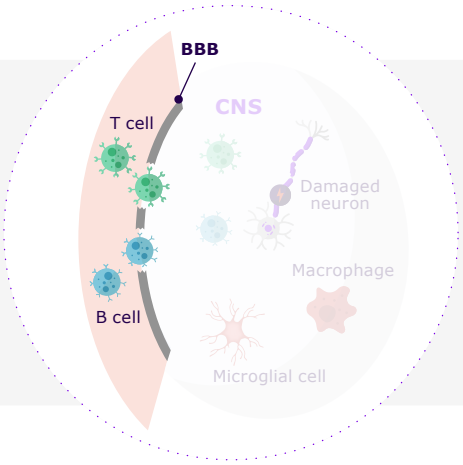
Smoldering disease is a key unaddressed component of MS driving disease progression[5]

Smoldering disease is an umbrella term characterizing chronic pathobiological processes in the CNS associated with neuroinflammation, neurodegeneration, and disability progression[5,9-11]

Acute focal inflammation



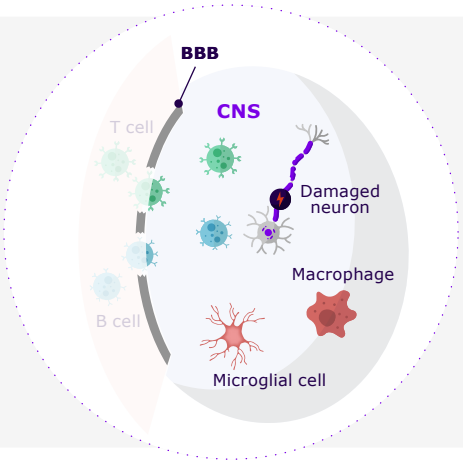
Relapse only[5,7,12]

- Acute neuroinflammation, focal lesions (T1, T2, Gd+ lesions)
- CNS penetration of immune B and T cells from the periphery

Perception[5]

- **Progression happens later**
- Relapse triggers progression

Smoldering disease



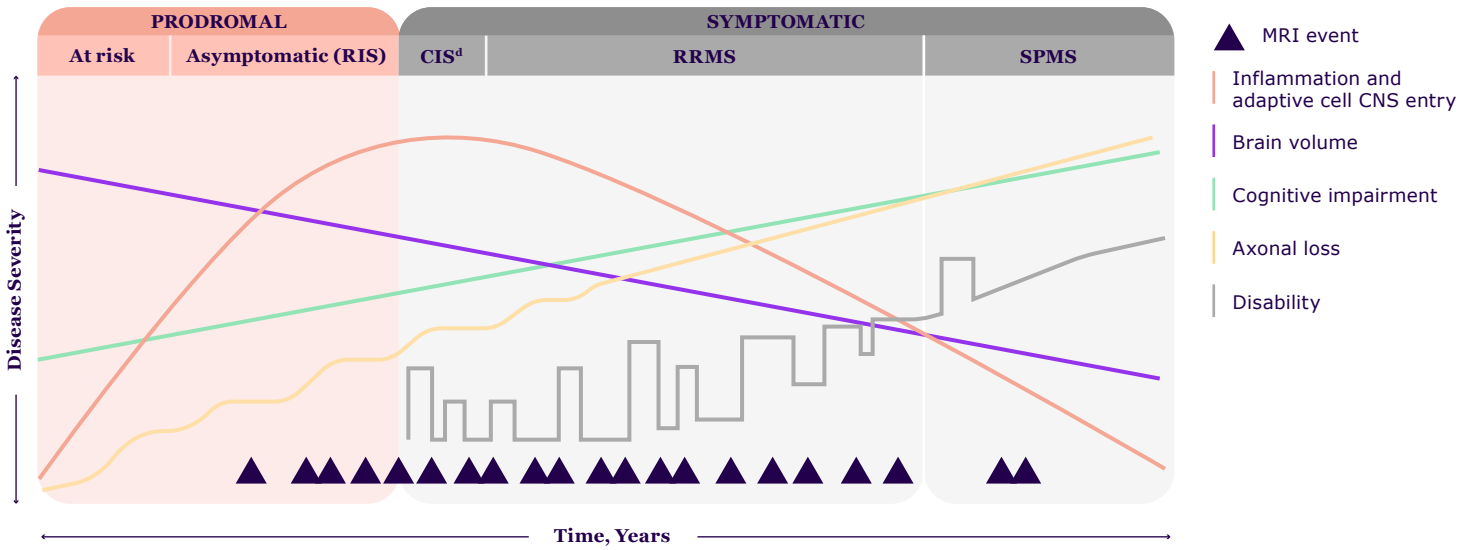
Relapse + progression[5,7,12]

- Neurodegeneration, chronic active lesions, brain volume loss
- Ongoing damage driven by innate immune processes (CNS resident immune cells, microglia)

Reality[5,6]

- **Smoldering disease starts EARLY** and throughout the disease course
- Progression happens independent of relapse

Smoldering disease starts early and continues throughout the disease course[5,13-16]



Activated microglia are important drivers of smoldering neuroinflammation[5,9,17]

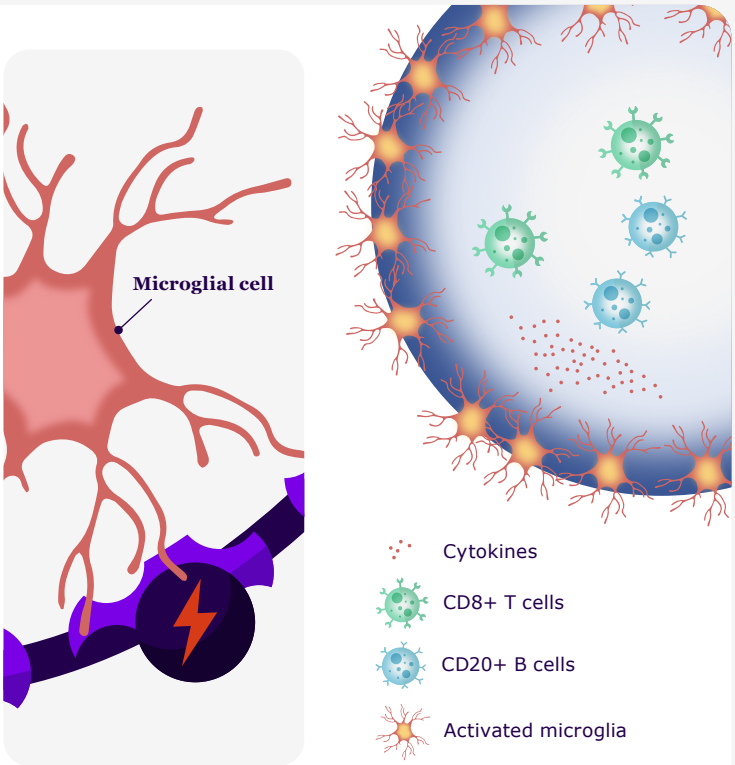
Microglia are the most abundant immune cells in the CNS[18]

In MS, microglia lose their homeostatic function and switch to a proinflammatory phenotype[19,20]

Activated disease-associated microglia are found at the lesion edge of chronic active lesions[9,17]

- Activated microglia take in iron released from damaged oligodendrocytes[17]
- Iron-rich microglia can be visualized as a paramagnetic rim around chronic active lesions using advanced MRI techniques[21]

Disability accumulation in MS is driven largely by smoldering disease from early in the disease course: therapeutic focus is now shifting with an aim to treat smoldering neuroinflammation[5]



Footnotes

[a]The vsMS survey was an international internet-based questionnaire completed by 1075 adult patients with RRMS in July and August 2015. The majority of participants (56%) were from the United States. The survey was funded by Sanofi.[4]
[b]MS Perspectives Survey is a cross-sectional online survey of patients with MS in Germany (N=4,555).[8]
[c]Analysis of 23 Novartis clinical trials. All CDW events were confirmed ≥6 months after the onset of the worsening. The "PIRA (sustained)" category included PIRA events that were confirmed ≥6 months after the onset of the worsening and sustained until the end of the follow-up period. A patient could experience sequential RAW and PIRA events.[6]
[d]CIS, if subsequently clinically active (one or more relapses) and fulfilling current MS diagnostic criteria, becomes RRMS.[13]

Abbreviations

BBB=blood–brain barrier; CDW=confirmed disability worsening; CIS=clinically isolated syndrome; CNS=central nervous system; DMT=disease-modifying therapy; MS=multiple sclerosis; NO.MS=Novartis-Oxford multiple sclerosis; PIRA=Progression independent of relapse activity; PPMS=primary progressive multiple sclerosis; RAW=relapse-associated worsening; RIS=radiologically isolated syndrome; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis.

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