HHS Public Access

Author manuscript

Nat Rev Neurol. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Nat Rev Neurol. 2021 August ; 17(8): 515–521. doi:10.1038/s41582-021-00519-3.

The multiple sclerosis prodrome

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Abstract

A prodrome is an early set of signs, symptoms or other findings that occur before the onset of typical symptoms of a disease. Prodromal phases are well recognized in several neurological and inflammatory diseases, but the possibility of a prodrome in multiple sclerosis (MS) has received relatively little attention until the past few years. In this Perspective, we summarize what is currently known about the MS prodrome, including its possible duration, clinical features and potential biomarkers. We also consider what insights and lessons can be learned from knowledge of and research into the prodromal phases of other diseases. A better understanding of the MS prodrome could have profound clinical implications as it could enable earlier recognition of MS and earlier initiation of treatments that reduce relapse rates and long-term disability. Knowledge of the MS prodrome could also affect research into the causes of MS, and putative risk factors must be re-evaluated in light of the MS prodrome. We conclude by outlining the major knowledge gaps and propose future initiatives.

Multiple sclerosis (MS) is a chronic neuroinflammatory and neurodegenerative disease that is a leading cause of neurological disability in young adults. MS most commonly occurs in a relapsing–remitting form, in which the clinical course is characterized by acute neurological symptoms (relapses) separated by periods of relative quiescence (remission). According to the diagnostic criteria for MS, its diagnosis requires the occurrence of at least one clinical episode consistent with CNS demyelination (known as clinically isolated syndrome (CIS)) plus clinical, MRI or laboratory evidence of lesions within the CNS that are disseminated in space and time[1]. Typical acute neurological symptoms include (but are not limited to) visual, sensory and motor deficits. Recovery from relapses can be incomplete and disability typically increases over time. Consequently, the ability to identify individuals with MS early in their disease course is of great interest as it would enable the prompt initiation of interventions designed to prevent relapses and long-term disability.

The presence of a so-called latent period between the initiation of disease pathobiology and the onset of typical clinical symptoms in MS has been generally accepted for some time[2]. However, a newer concept is that of an MS prodrome — an early set of signs and symptoms

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Author contributions

Both authors contributed to all aspects of the manuscript.

that occur before the onset of the typical clinical symptoms, presumably during the latent period[3–7]. Clinical onset of MS usually occurs between the ages of 20 and 50 years[1,8], but the prodromal phase could begin many years earlier and its characteristics are likely to vary between individuals[4,6,9–13].

In this Perspective, we discuss the concept of the MS prodrome and what is currently known about its features and duration. We focus on recent studies that have examined the period before the onset of typical MS symptoms or a CIS rather than on MS diagnosis itself — use of the date of diagnosis to demark the end of the prodromal phase is problematic because this time point is susceptible to changes in the diagnostic criteria[1,14]. We draw parallels between MS and other neurological and immune-mediated diseases with better-defined prodromal phases. We also consider the known risk factors for MS and the need for careful evaluation of these in light of the possibility that they are also features of the MS prodrome. Finally, we propose that a better understanding of the MS prodrome could have profound implications for the prevention, earlier recognition and diagnosis of MS, particularly regarding interventions to prevent MS or delay the onset of typical clinical symptoms and/or disability, and we consider the key challenges remaining.

Clinical features of the MS prodrome

A prodrome can be defined as an early set of signs or symptoms that indicates the onset of a disease and precedes the more obvious or typical symptoms that enable diagnosis. Historically, a prodromal phase was not thought to exist in MS[15]. However, studies that suggest the existence of a prodromal phase in MS have begun to emerge in the past decade. Initial studies were limited by small numbers of participants and/or recall bias and often involved select groups of individuals, yet they provided much needed insight into this overlooked area[13,16–18] and led to further studies and accumulating evidence.

Increased health-care usage.

Population-based studies have emerged in the past 5 years[4–6,9–13,19–23] and suggest a trend of deteriorating health before clinical onset of MS. For example, in one study conducted in Canada, analysis of health administrative data linked with MS-specific clinical data from >14,000 people with MS and >72,000 controls from the general population matched for age, sex, region and socioeconomic status revealed that the use of health-care services by patients with MS was higher in the 5 years leading up to their first clinical demyelinating event (based on physician-derived diagnostic codes in administrative data) or MS symptom onset (determined by an MS neurologist) than that of controls. In the year before the first clinical demyelinating event, hospitalizations and physician visits were 78% and 88% higher, respectively, for people with MS than for matched controls. Similarly, dispensed prescription medications were 49% higher among patients who went on to develop MS[6]. In a subsequent study conducted in the UK, analysis of primary care data from >10,000 people with MS and nearly 40,000 matched controls revealed more visits to general practitioners among those with MS up to 10 years before their MS was diagnosed (based on codes for MS or CIS recorded in general practitioner records)[19].

The observed higher rates of health-care usage resulted from a myriad of issues. Use of mental health services by people who developed MS was high[6,9,11] — visits to psychiatrists in the 5 years before MS symptom onset were 50% higher than among controls[9]. Fatigue, pain, fibromyalgia, migraine, bowel issues, bladder issues, sleep disturbances and anaemia were also more common among people who developed MS than among controls in the years leading up to MS symptom onset[9,11,19]. Women with MS were also less likely to have become pregnant and were more likely to fill a prescription for a hormonal preparation (such as an oral contraceptive) than controls in the 5 years before onset of typical MS symptoms, observations that suggest a behavioural change before the clinical onset of MS[9]. When faced with a range of health complaints as part of the MS prodrome, women may have opted — whether consciously or subconsciously — to delay pregnancy[9]. Though fewer pregnancies might lead to a greater risk of a first clinical demyelinating event[24], the potential for reverse causation must be carefully considered.

Cognitive impairment.

Low cognitive performance before onset of typical MS symptoms has been reported in a nested case–control study of >20,000 Norwegian men who entered the mandatory national military service at the age of 18–19 years[20]. Among the 924 individuals diagnosed with MS, cognitive performance was lower than among the 19,530 healthy controls up to 2 years before MS onset. Among the <50 individuals who developed primary progressive MS (rather than relapsing–remitting), cognitive performance was lower than among the controls up to 20 years before clinical onset of MS[20]. However, whether these observations are generalizable to the wider population, including women, remains undetermined.

Age and sex effects.

Sex and age seem to affect features of the MS prodrome, although these and other population demographics, such as ethnicity, are underexplored[10,11]. In a study conducted in Canada that included 6,863 people with MS and 31,865 matched controls, the odds of anaemia were higher among men with MS than among men in the general population (OR 2.40, 95% CI 1.68–4.29), whereas the increase in odds for women with MS were more modest (OR 1.23, 95% CI 1.04–1.45). Pain was more likely in older adults than in younger adults in the 5 years before a first demyelinating event — the odds ratio increased from 1.76 at <30 years of age to 2.14 at 30–50 years of age and to 2.35 at ≥50 years of age[11]. All odds ratios were adjusted for socioeconomic status, index year, age and sex. Further work is warranted to delineate the impact of age, sex and other patient demographics on features of the MS prodrome.

Disease course and dermatological complaints.

Another study conducted in Canada identified visits to dermatologists as a prodromal feature of MS that might differentiate the two main disease courses. Visits were more common among those who developed relapsing–remitting MS (n = 1,887) than among those who developed primary progressive MS (n = 171) in the 5 years before onset of typical MS symptoms. These skin-related issues could conceivably reflect an early inflammatory manifestation of MS[10].

Other features.

Further possible features of the MS prodrome have been identified in a systematic review of MS morbidities. The review included 29 studies published before February 2019; in these studies, the period before MS diagnosis or clinical MS onset was examined[13]. Broadly, the review identified consistent evidence that anxiety, depression and migraine as well as a low cognitive performance are all part of the MS prodrome[13].

Biomarkers of the MS prodrome

Radiologically isolated syndrome.

MRI findings that are characteristic of MS are sometimes detected incidentally in individuals with no typical symptoms of MS but who underwent MRI for other reasons (for example, head trauma). These findings are referred to as the radiologically isolated syndrome (RIS), a formal definition of which was proposed in 2009 (REF.[25]). In the diagnostic criteria for MS, RIS is distinguished by a lack of typical MS symptoms. RIS was first described in adults but has also been reported in children[26].

The exact prevalence of RIS is unknown. One large, hospital-based study in Sweden indicated a prevalence of 0.05% (0.15% among those aged 15–40 years) among 2,105 individuals who underwent MRI for any reason during a 1-year period[27]. A meta-analysis that included 15,559 individuals with no history of neurological symptoms determined that 0.06% had MRI findings that were suggestive of demyelination[28].

Whether all individuals with MS develop abnormalities that are detectable on MRI before they develop typical MS symptoms is unknown. However, studies of individuals with a first clinical demyelinating event have revealed multiple lesions on MRI at first clinical presentation[29–32], suggesting that asymptomatic brain lesions predate the first clinical demyelinating event in a substantial proportion of individuals. Carefully designed prospective MRI studies of individuals prior to the onset of typical MS symptoms are therefore warranted to establish whether RIS overlaps with the prodromal phase and, if so, how.

Furthermore, RIS could itself be a marker of the MS prodrome. This possibility is suggested by the finding that the majority of individuals with RIS have a variety of subtle or non-specific symptoms, most commonly headache[25,33]. This observation raises the possibility that some people have clinical symptoms that are part of the prodromal phase of MS.

Regardless of whether RIS is a biomarker of the prodrome, individuals with RIS are at substantial risk of a subsequent clinical demyelinating event and a diagnosis of either relapsing–remitting MS or primary progressive MS[34]. Consequently, markers that are associated with later development of MS in individuals with RIS are of interest in the context of the MS prodrome, as they could also be markers of prodromal MS. Several studies have been conducted to identify such markers. One large, multicentre, retrospective study included 451 individuals from the USA and Europe who fulfilled the 2009 criteria for RIS[25]. Of these individuals, 34% developed clinical symptoms of MS within 5 years of their first abnormal MRI, increasing to 51% after 10 years (among 257 participants with 10-year

follow-up)[33,35]. Factors associated with an increased risk of a clinical demyelinating event were a younger age at development of RIS, male sex, the presence of asymptomatic infratentorial or spinal cord lesions on MRI, and abnormal cerebrospinal fluid (CSF) findings (a high IgG index or the presence of two or more unique oligoclonal bands)[33,35]. These factors might also warrant exploration as potential biomarkers of the MS prodrome.

Cognitive impairments have also been reported in individuals with RIS. In a study conducted in France that included people with RIS, MS or neither (26 in each group, matched for age, sex and educational level), individuals with MS or RIS had a lower performance than the controls in a range of cognitive assessments, including the Paced Auditory Serial Addition Test (PASAT), phonemic fluency, the digit-symbol subtest of the Weschler Adult Intelligence Scale, digit span (direct and indirect), cross-tapping and the Go-No-Go test[36]. Cognitive profiles were generally similar in the RIS and MS groups, although performance was lower among those with MS on the direct digit span and cross-tapping tests. A study conducted in Italy resulted in similar findings — 28% (8 of 29) of individuals with RIS and 35% (9 of 26) of those with MS were classified as having cognitive impairment on the basis of failure in at least two tests. Performance on the PASAT2 and word-list generation were lower among those with MS than among those with RIS[37]. Similarly, a study conducted in Israel showed that the performance on all cognitive tests was lower than expected (based on age and education) for 30 individuals with RIS who were assessed up to 3 months after diagnosis[38]. Together, these findings in RIS reinforce the idea that impaired cognition could be a measurable feature of the MS prodrome.

Advanced neuroimaging.

Advanced neuroimaging techniques — beyond those that are used in clinical practice — have been used to assess the characteristics of RIS and the findings could indicate features of the MS prodrome. The results of several studies (mainly case–control studies) of modest size suggest that whole-brain volume and regional brain volumes (for example, thalamic and cerebellar volumes) are lower in individuals with RIS than in healthy controls[39–41]. In one study conducted in Italy, normalized whole-brain and cortical volumes were similar in 26 individuals with MS and 19 with RIS but lower in both groups than in 21 healthy controls of similar age and sex[37]. In this study, lower cortical volumes were associated with poorer performance in a cognitive battery among individuals with RIS.

Advanced MRI also identified cortical lesions in 40% of 15 individuals with RIS[42] and diffusion tensor imaging revealed microstructural changes in white matter tracts in 18 individuals with RIS compared with 20 healthy controls[43]. In addition, proton magnetic resonance spectroscopy has shown that *N*-acetylaspartate and creatine levels are lower in people with RIS than in healthy controls, suggesting abnormalities in brain metabolic pathways[44]. These early studies suggest that advanced neuroimaging could be helpful for identifying biomarkers of the prodromal phase of MS, though further studies are needed to determine their value in this context.

Serum and CSF biomarkers.

In addition to neuroimaging, biomarkers in the blood and/or CSF could be of value in the MS prodrome. Several studies have identified potentially useful markers.

In one nested case–control study, analysis of stored serum samples from 30 US military personnel who went on to develop MS and 30 healthy matched controls showed that serum levels of neurofilament light chain (NfL; a marker of neuro-axonal injury) were higher among individuals who went on to develop MS than among controls at a median of 6 years before the onset of MS symptoms[45]. The results of this small but compelling study, which involved a predominantly non-Hispanic white (60%), male (77%) population, suggest that neuro-axonal injury occurs years before onset of the typical clinical symptoms of MS.

In a study of 75 individuals with RIS, 23 of whom developed CIS during follow-up, high CSF levels of NfL and the presence of unique CSF oligoclonal bands were associated with earlier development of CIS[46]. A high IgG index and the presence of two or more unique oligoclonal bands in the CSF have been reported as risk factors for a clinical demyelinating event in adults and children with RIS[26,33,46,47]. These CSF markers could therefore be similarly helpful for the risk stratification of individuals with clinical symptoms of possible prodromal MS even if they do not have RIS. Future studies are needed to address this possibility.

Novel techniques, such as single-cell analyses, could also produce biomarkers of prodromal MS[48]. For example, single-cell RNA sequencing of the CSF from six clinically healthy individuals who were monozygotic twins of patients with MS revealed clonal expansion of $CD8^+$ T cells and B cells, indicating early adaptive immune activation[49]. Whether these asymptomatic but high-risk individuals will transition to clinical MS remains to be determined, but the findings illustrate the potential of single-cell analysis to identify very early pathological changes.

Insights from specific groups

Paediatric-onset MS.

The typical clinical symptoms of MS usually emerge in early adulthood but 3–10% of individuals with MS develop neurological symptoms before the age of 16–18 years[50,51]. The existence of paediatric-onset MS suggests that the pathobiology of MS begins early in life and that the MS prodrome could be detectable as early as childhood.

A prodrome for paediatric-onset MS has been suggested by the findings of a study conducted in Canada, which involved the analysis of administrative data from 659 children (age <18 years) with MS and 3,294 population controls matched (up to 1:5) for sex, age and region of residence[22]. The proportion of children who were hospitalized in the year before their first clinical demyelinating event was greater among those with MS than among controls. Similarly, the median number of physician visits was greater among the children with MS over the same period.

In a second study in Canada, administrative data were compared with health-care usage data for mothers with and without a child with MS[21]. In comparison with 624 mothers of children without MS, the 156 carefully matched mothers of children with MS had a higher rate of physician visits for any mood or anxiety disorder up to 5 years before the child's first demyelinating event. One possible explanation for this observation is that children with MS experienced prodromal symptoms in the years before their first demyelinating event, leading to increased stress and higher mental health service use by their mothers[21]. Taken together, these studies suggest that an MS prodromal phase occurs in paediatric-onset MS, but the clinical features of this prodromal phase are yet to be determined.

As in adults, RIS could be a neuroimaging correlate of the MS prodrome in children. RIS in children seems to be relatively uncommon (for example, only one child had RIS in a population-based study of 3,966 children aged 8–11 years)[25,52] but does seem to be associated with an increased risk of developing clinical symptoms of demyelination when it occurs. In a multicentre international study of 38 children with RIS (defined according to the 2010 criteria for dissemination in space on MRI)[53], 42% developed a first clinical event after a median of 5 years on the basis of Kaplan–Meyer analyses and an absolute median of 2 years[26]. The presence of two or more unique oligoclonal bands in the CSF and asymptomatic spinal cord lesions on MRI were associated with an earlier first clinical event, in agreement with findings in adults, again raising the possibility that these findings are biomarkers of the MS prodrome.

First-degree relatives of people with MS.

Studying first-degree family members of individuals with MS, who are at higher risk of MS than the general population, could yield important insights into prodromal features of MS. In one prospective study of 65 first-degree relatives, vibration sensitivity testing of the distal extremities revealed a poorer performance among participants who were at the highest risk of MS than among those at the lowest risk on the basis of a weighted genetic and environmental risk score[54]. This observation suggests that subtle neurological findings can precede the onset of typical MS symptoms. Among the participants of this study, five (8%) fulfilled the MRI criteria for dissemination in space using the 2010 MS diagnostic criteria without meeting the 2009 Okuda definition of RIS (four of whom were in the high-risk group) and two (3%) fulfilled formal criteria for RIS (one in each of the high-risk and low-risk groups). Similarly, other studies of asymptomatic relatives of individuals with either sporadic or familial MS have shown that ~3–10% have RIS[55,56]. Together, the occurrence of RIS and subtle neurological signs in high-risk relatives of patients supports the hypothesis that these characteristics precede clinical symptoms of MS and could therefore be markers of prodromal MS.

Insight from other diseases

Several neurodegenerative and immune-mediated diseases seem to have identifiable prodromal phases. The approaches to classification of the phases vary between diseases, but knowledge from these diseases can be used in the development of a frame work for MS

(BOX 1). Ultimately, such a framework could lead to the development of interventional studies in prodromal MS with the aim of secondary prevention.

Other neurodegenerative diseases.

According to the International Parkinson and Movement Disorder Society, early Parkinson disease (PD) can be divided into three phases: preclinical PD, in which neurodegeneration has commenced but no outward signs or symptoms are apparent; prodromal PD, in which signs and symptoms are present but are insufficient to fulfil the diagnostic criteria for PD; and clinical PD, when a diagnosis of PD can be made on the basis of characteristic motor signs and symptoms[57,58]. The concept of a prodromal phase of PD is therefore widely accepted and defining features of this prodrome have been identified, although a precise definition continues to evolve[58,59]. Factors that are included in the research criteria for prodromal PD include current age, risk factors for PD (including sex, caffeine use, smoking status, genetic markers and echogenicity of the substantia nigra on ultrasound), clinical non-motor markers (including REM sleep behaviour disorder, olfactory dysfunction and constipation), clinical motor markers (including possible subthreshold parkinsonism on expert examination or abnormal quantitative motor tests), and neuroimaging markers on PET or single-photon emission tomography[58]. These factors enable the calculation of the probability of prodromal PD and are intended to help with identifying individuals for enrolment in clinical trials of neuroprotective agents[57,58].

As in PD, the pathology of Alzheimer disease (AD) is thought to begin years before the onset of typical symptoms, and the disease is thought to progress through a continuum of normal, age-expected changes to mild cognitive impairment and, finally, clinical AD. A conceptual framework and operational criteria have been proposed for preclinical AD for research purposes[60]. These criteria span three stages: biomarker (amyloid-β) detection in stage one, amyloid-β accumulation and markers of neuronal injury in stage two, and subtle cognitive changes in stage three[60].

The concept that PD and AD progress through a continuum of disease from the initial pathological processes that do not cause typical symptoms to a prodromal phase and then to the development of characteristic signs and symptoms is well established. MS shares some of the neurodegenerative features of these diseases and, although its initial course is more commonly relapsing–remitting than primary progressive, MS is also likely to evolve through preclinical to clinical phases. We can therefore learn from our understanding and definitions of the early stages of PD and AD and apply this knowledge to defining the MS prodrome. In particular, the development of research criteria for preclinical and prodromal MS, including imaging and other biomarkers, could greatly aid the design of studies for the primary and secondary prevention of MS.

Other inflammatory diseases.

Besides neurodegenerative diseases, prodromal phases have been characterized in other relapsing inflammatory conditions, including rheumatoid arthritis, systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD). For rheumatoid arthritis, six phases of disease have been proposed: (1) the presence of genetic risk factors; (2) the

presence of environmental risk factors; (3) systemic autoimmunity (for example, anti-citrullinated protein antibodies and rheumatoid factor); (4) symptoms without arthritis; (5) undifferentiated arthritis; and (6) rheumatoid arthritis[61]. People with imaging abnormalities in the absence of arthritis are thought to fit between phases 3 and 4. In a study of samples stored as part of a blood donation programme, at least one autoantibody (rheumatoid factor and/or anti-cyclic citrullinated peptide) was present in nearly half of the 79 individuals who later developed rheumatoid arthritis at a median of 4.5 years before symptom onset[62]. Detection of these autoantibodies in combination with prodromal features and other characteristics (such as family history) has been harnessed to identify individuals who are at high-risk of developing clinical rheumatoid arthritis and offer them enrolment into clinical trials[63–65].

In SLE, autoantibodies, including antibodies to nuclear antigens, have also been detected before the onset of characteristic symptoms, at ~3–8 years before diagnosis[66,67]. As in rheumatoid arthritis, there is great interest in whether individuals who are at high risk of SLE might benefit from interventions to delay clinical onset. Similarly, for IBD (Crohn disease and/or ulcerative colitis), several characteristics of the prodromal phase have been suggested. For example, a study of 240,984 young men aged 18–19 years who underwent assessment for military conscription in Sweden showed that an elevated erythrocyte sedimentation rate (≥15 mm/h versus 1 mm/h) was associated with an increased risk of subsequent diagnosis of Crohn disease or ulcerative colitis after a median follow-up time of 33 years[68]. In another study of 1,420 asymptomatic first-degree relatives of individuals with Crohn disease, increased intestinal permeability was associated with an increased risk of a subsequent diagnosis of Crohn disease over a mean follow-up period of 7 years[69]. Taken together, these studies in other relapsing inflammatory diseases suggest that a combination of clinical features and other biomarkers are likely to characterize the MS prodrome and could aid its categorization into distinct phases[23,70].

Shared prodromal features of inflammatory diseases.

Inflammatory, immune-mediated diseases might be expected to share prodromal features, with some evidence suggesting this is the case. In one study conducted in Canada, population-based administrative data from the province of Manitoba on 12,141 individuals with immune-mediated inflammatory disease (IBD, MS or rheumatoid arthritis) and 65,424 controls matched for birth year, sex, region and disease were analysed[23]. The incidence of psychiatric disorders was higher among patients with inflammatory immune-mediated diseases as early as 5–10 years before diagnosis. The findings were consistent when the three diseases were considered separately. This study focused on the time period before diagnosis rather than at symptom onset so the findings could be influenced by the variable application of diagnostic criteria or diagnostic delays; however, the 10-year findings are nonetheless likely to reflect features of the prodromal phase[23].

Research and clinical implications

Risk factors versus prodromal features.

As knowledge of the MS prodrome develops, the literature surrounding the causes of MS needs to be re-evaluated as presumed risk factors for MS onset could actually be prodromal features. One salient example is pregnancy and oral contraceptive use. Previously, fewer pregnancies and greater use of oral contraceptives were thought to increase a woman's risk of developing MS[71–73]. However, knowledge of the prodrome suggests reverse causation as a plausible explanation — women in the prodromal phase of MS might instead be changing their behaviour in reaction to their escalating (prodromal) health concerns[9].

The differentiation of true risk factors or triggers of MS from prodromal features will require further investigation. This process is also complicated by the fact that the length of the MS prodromal phase is unknown but a pragmatic approach can be taken to minimize the risk of reverse causation when studying risk factors. For example, the date of MS symptom onset or of the first clinical demyelinating event can be used to demarcate the outcome rather than the date of diagnosis and a clear gap can be left between this outcome and the period during which a person is considered at risk[74–77]. These approaches can increase the confidence that a true risk factor is being examined rather than a prodromal feature.

In addition, some aspects are highly likely to be a feature of the MS prodrome as well as a risk factor or trigger of MS. For example, low sunlight exposure and/or low serum levels of vitamin D could be a true risk factor for MS in some populations but could also be a feature of the MS prodrome. As individuals enter the prodromal phase, the deterioration of health and increased physician and hospital visits could reduce time spent outside, thus reducing sunlight exposure and lowering serum levels of vitamin D[78]. More work is therefore needed to determine which factors might be risk factors and which are prodromal features and to understand when and in whom these factors are most clinically relevant.

Refining identification of the prodrome.

The process of identifying the clinical features of the MS prodrome is likely to be iterative — identification of possible clinical features of the prodrome will inform the better characterization of the early manifestations of clinical MS. Currently, we could be classifying true early manifestations of clinical MS as prodromal features, in which case we could be missing opportunities for prompt recognition of clinical demyelinating syndromes and MS. This could be particularly true when individuals are assessed in primary care or by non-specialists who are less familiar with the clinical features of MS. Conversely, care is needed to avoid over diagnoses and over treatment of atypical clinical syndromes[65,79], which could cause unnecessary harm. Given that the putative prodromal features of MS identified thus far are relatively common and often non-specific, the identification of MRI and/or laboratory biomarkers is needed to increase specificity for prodromal MS and develop a reliable definition of the prodromal phase.

Earlier recognition and management of MS.

Knowledge of the MS prodrome could facilitate the earlier recognition and management of the disease. The development of research criteria for prodromal MS that include a combination of clinical features and biomarkers with high sensitivity and specificity could enable reliable identification of individuals in the prodromal phase. This ability has clear implications for individuals who could benefit from enrolment in trials of interventions designed to prevent clinical MS and/or offer neuroprotection to mitigate future disability (BOX 1).

Conclusions

Several lines of evidence strongly indicate the existence of a prodromal phase in MS. While the field remains nascent, knowledge of the MS prodrome is likely to change our understanding of what causes MS and could directly affect clinical practice in the coming years. Further work is therefore needed to increase our understanding of the MS prodrome and its implications.

The pathophysiological mechanisms that underpin the MS prodrome remain speculative. For example, the high mental health burden observed in the prodromal phase of MS and other immune-mediated conditions, such as rheumatoid arthritis and IBD, could reflect a threshold of inflammation being reached that increases the risk of depression[23], but direct evidence for this mechanism is lacking. In addition, different mechanisms are highly likely to drive the various prodromal symptoms observed as is thought to be the case for the prodromal phases of other diseases such as PD[80]. Therefore, a better understanding of the underlying biological mechanisms is needed.

Many other questions remain. The duration of the prodrome is uncertain and we need a clearer understanding of the myriad of signs and symptoms that can occur in the years leading up to MS onset. Many of the apparent clinical features of the MS prodrome are common among the general population, suggesting that a combination of factors, including imaging and other biomarkers, is needed to reliably identify individuals with prodromal MS. Ultimately, validated research criteria to identify individuals with prodromal MS will help to advance the goals of early recognition and treatment of MS.

Competing interests

N.M. is funded by NIH/NINDS (grant number K23NS101099) and the Charles H. Hood Foundation. H.T. is the Canada Research Chair for Neuroepidemiology and Multiple Sclerosis. Current research support has been received from the National Multiple Sclerosis Society, the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada and the Multiple Sclerosis Scientific Research Foundation. In the past 5 years, she has received research support from the UK MS Trust and travel expenses to present at CME conferences from the Consortium of MS Centres (2018), the National MS Society (2016, 2018), ECTRIMS and ACTRIMS (2015, 2016, 2017, 2018, 2019, 2020), and the American Academy of Neurology (2015, 2016, 2019). Speaker honoraria are either declined or donated to an MS charity or to an unrestricted grant for use by H.T.’s research group.

References

1. Thompson AJ et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17, 162–173 (2018). [PubMed: 29275977]

2. Wolfson C & Wolfson DB The latent period of multiple sclerosis: a critical review. Epidemiology 4, 464–470 (1993). [PubMed: 8399696]
3. Giovannoni G The neurodegenerative prodrome in multiple sclerosis. Lancet Neurol. 16, 413–414 (2017). [PubMed: 28504102]
4. Hogg T et al. Mining healthcare data for markers of the multiple sclerosis prodrome. Mult. Scler. Relat. Disord 25, 232–240 (2018). [PubMed: 30121490]
5. Tremlett H & Marrie RA The multiple sclerosis prodrome: emerging evidence, challenges, and opportunities. Mult. Scler 27, 6–12 (2020). [PubMed: 32228281]
6. Wijnands JMA et al. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. Lancet Neurol. 16, 445–451 (2017). [PubMed: 28434855]
7. Marrie RA Mounting evidence for a multiple sclerosis prodrome. Nat. Rev. Neurol 15, 689–690 (2019). [PubMed: 31654040]
8. The Multiple Sclerosis International Federation. Atlas of MS 3rd Edition https://www.msif.org/wp-content/uploads/2020/10/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf (2020).
9. Wijnands JM et al. Five years before multiple sclerosis onset: phenotyping the prodrome. Mult. Scler 25, 1092–1101 (2019). [PubMed: 29979093]
10. Wijnands JMA et al. Prodrome in relapsing-remitting and primary progressive multiple sclerosis. Eur. J. Neurol 26, 1032–1036 (2019). [PubMed: 30714270]
11. Yusuf F et al. Fatigue, sleep disorders, anaemia and pain in the multiple sclerosis prodrome. Mult. Scler 27, 290–302 (2020). [PubMed: 32250183]
12. Zhao Y et al. Interrogation of the multiple sclerosis prodrome using high-dimensional health data. Neuroepidemiology 54, 140–147 (2020). [PubMed: 31940638]
13. Yusuf FLA et al. A systematic review of morbidities suggestive of the multiple sclerosis prodrome. Expert Rev. Neurother 20, 799–819 (2020). [PubMed: 32202173]
14. Poser CM et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann. Neurol 13, 227–231 (1983). [PubMed: 6847134]
15. Matthews WB McAlpine's Multiple Sclerosis 2nd edn (Churchill Livingstone, 1991).
16. Byatt N, Rothschild AJ, Riskind P, Ionete C & Hunt AT Relationships between multiple sclerosis and depression. J. Neuropsychiatry Clin. Neurosci 23, 198–200 (2011). [PubMed: 21677250]
17. Gout O et al. Prior suggestive symptoms in one-third of patients consulting for a "first" demyelinating event. J. Neurol. Neurosurg. Psychiatry 82, 323–325 (2011). [PubMed: 21097550]
18. Sinay V, Perez Akly M, Zanga G, Ciardi C & Racosta JM School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis. Mult. Scler 21, 945–952 (2015). [PubMed: 25344372]
19. Disanto G et al. Prodromal symptoms of multiple sclerosis in primary care. Ann. Neurol 83, 1162–1173 (2018). [PubMed: 29740872]
20. Cortese M et al. Preclinical disease activity in multiple sclerosis: a prospective study of cognitive performance prior to first symptom. Ann. Neurol 80, 616–624 (2016). [PubMed: 27554176]
21. Marrie RA et al. Increased mental health care use by mothers of children with multiple sclerosis. Neurology 94, e1040–e1050 (2020). [PubMed: 31919112]
22. Marrie RA et al. High rates of health care utilization in pediatric multiple sclerosis: a Canadian population-based study. PLoS ONE 14, e0218215 (2019). [PubMed: 31185042]
23. Marrie RA et al. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. Epidemiol. Psychiatr. Sci 28, 333–342 (2019). [PubMed: 29098977]
24. Ponsonby AL et al. Offspring number, pregnancy, and risk of a first clinical demyelinating event: the AusImmune Study. Neurology 78, 867–874 (2012). [PubMed: 22402857]
25. Okuda DT et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 72, 800–805 (2009). [PubMed: 19073949]
26. Makhani N et al. Radiologically isolated syndrome in children: clinical and radiologic outcomes. Neurol. Neuroimmunol. Neuroinflamm 4, e395 (2017). [PubMed: 28959703]

27. Granberg T, Martola J, Kristoffersen-Wiberg M, Aspelin P & Fredrikson S Radiologically isolated syndrome — incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. Mult. Scler 19, 271–280 (2013). [PubMed: 22760099]
28. Morris Z et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 339, b3016 (2009). [PubMed: 19687093]
29. Kuhle J et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. Mult. Scler 21, 1013–1024 (2015). [PubMed: 25680984]
30. Filippi M et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. Lancet Neurol. 17, 133–142 (2018). [PubMed: 29275979]
31. Tintore M et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138, 1863–1874 (2015). [PubMed: 25902415]
32. Tintore M et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology 87, 1368–1374 (2016). [PubMed: 27566747]
33. Lebrun-Frenay C et al. Radiologically isolated syndrome: 10-year risk estimate of a clinical event. Ann. Neurol 88, 407–417 (2020). [PubMed: 32500558]
34. Kantarci OH et al. Primary progressive multiple sclerosis evolving from radiologically isolated syndrome. Ann. Neurol 79, 288–294 (2016). [PubMed: 26599831]
35. Okuda DT et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS ONE 9, e90509 (2014). [PubMed: 24598783]
36. Lebrun C, Blanc F, Brassat D, Zephir H & de Seze J Cognitive function in radiologically isolated syndrome. Mult. Scler 16, 919–925 (2010). [PubMed: 20610492]
37. Amato MP et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology 78, 309–314 (2012). [PubMed: 22262744]
38. Menascu S et al. Assessing cognitive performance in radiologically isolated syndrome. Mult. Scler. Relat. Disord 32, 70–73 (2019). [PubMed: 31054500]
39. Azevedo CJ et al. Early CNS neurodegeneration in radiologically isolated syndrome. Neurol. Neuroimmunol. Neuroinflamm 2, e102 (2015). [PubMed: 25884012]
40. George IC et al. Cerebellar volume loss in radiologically isolated syndrome. Mult. Scler 27, 130–133 (2019). [PubMed: 31680617]
41. Alcaide-Leon P et al. Quantitative spinal cord MRI in radiologically isolated syndrome. Neurol. Neuroimmunol. Neuroinflamm 5, e436 (2018). [PubMed: 29359174]
42. Giorgio A et al. Cortical lesions in radiologically isolated syndrome. Neurology 77, 1896–1899 (2011). [PubMed: 22076541]
43. Giorgio A et al. Appraisal of brain connectivity in radiologically isolated syndrome by modeling imaging measures. J. Neurosci 35, 550–558 (2015). [PubMed: 25589750]
44. Stromillo ML et al. Brain metabolic changes suggestive of axonal damage in radiologically isolated syndrome. Neurology 80, 2090–2094 (2013). [PubMed: 23635962]
45. Bjornevik K et al. Serum neurofilament light chain levels in patients with presymptomatic multiple sclerosis. JAMA Neurol 77, 58–64 (2020). [PubMed: 31515562]
46. Matute-Blanch C et al. Neurofilament light chain and oligoclonal bands are prognostic biomarkers in radiologically isolated syndrome. Brain 141, 1085–1093 (2018). [PubMed: 29452342]
47. Makhani N et al. Oligoclonal bands increase the specificity of MRI criteria to predict multiple sclerosis in children with radiologically isolated syndrome. Mult. Scler. J. Exp. Transl Clin 5, 2055217319836664 (2019).
48. Schafflick D et al. Integrated single cell analysis of blood and cerebrospinal fluid leukocytes in multiple sclerosis. Nat. Commun 11, 247 (2020). [PubMed: 31937773]
49. Beltrán E et al. Early adaptive immune activation detected in monozygotic twins with prodromal multiple sclerosis. J. Clin. Invest 129, 4758–4768 (2019). [PubMed: 31566584]
50. Simone IL et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology 59, 1922–1928 (2002). [PubMed: 12499484]

51. Chitnis T, Glanz B, Jaffin S & Healy B Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult. Scler 15, 627–631 (2009). [PubMed: 19299440]
52. Jansen PR et al. Incidental findings on brain imaging in the general pediatric population. N. Engl. J. Med 377, 1593–1595 (2017). [PubMed: 29045203]
53. Polman CH et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol 69, 292–302 (2011). [PubMed: 21387374]
54. Xia Z et al. Assessment of early evidence of multiple sclerosis in a prospective study of asymptomatic high-risk family members. JAMA Neurol. 74, 293–300 (2017). [PubMed: 28114441]
55. De Stefano N et al. Imaging brain damage in first-degree relatives of sporadic and familial multiple sclerosis. Ann. Neurol 59, 634–639 (2006). [PubMed: 16498621]
56. Gabelic T et al. Prevalence of radiologically isolated syndrome and white matter signal abnormalities in healthy relatives of patients with multiple sclerosis. AJNR Am. J. Neuroradiol 35, 106–112 (2014). [PubMed: 23886745]
57. Berg D et al. MDS research criteria for prodromal Parkinson's disease. Mov. Disord 30, 1600–1611 (2015). [PubMed: 26474317]
58. Heinzel S et al. Update of the MDS research criteria for prodromal Parkinson's disease. Mov. Disord 34, 1464–1470 (2019). [PubMed: 31412427]
59. Postuma RB Prodromal Parkinson disease: do we miss the signs? Nat. Rev. Neurol 15, 437–438 (2019). [PubMed: 31152151]
60. Sperling RA et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 280–292 (2011). [PubMed: 21514248]
61. Mankia K & Emery P Preclinical rheumatoid arthritis: progress toward prevention. Arthritis Rheumatol. 68, 779–788 (2016). [PubMed: 26814677]
62. Nielen MM et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 50, 380–386 (2004). [PubMed: 14872479]
63. van de Stadt LA, Witte BI, Bos WH & van Schaardenburg D A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann. Rheum. Dis 72, 1920–1926 (2013). [PubMed: 23178208]
64. Greenblatt HK, Kim HA, Bettner LF & Deane KD Preclinical rheumatoid arthritis and rheumatoid arthritis prevention. Curr. Opin. Rheumatol 32, 289–296 (2020). [PubMed: 32205569]
65. van der Helm-van Mil A & Landewé RBM The earlier, the better or the worse? Towards accurate management of patients with arthralgia at risk for RA. Ann. Rheum. Dis 79, 312–315 (2020). [PubMed: 31915123]
66. Arbuckle MR et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N. Engl. J. Med 349, 1526–1533 (2003). [PubMed: 14561795]
67. Eriksson C et al. Autoantibodies predate the onset of systemic lupus erythematosus in northern Sweden. Arthritis Res. Ther 13, R30 (2011). [PubMed: 21342502]
68. Melinder C et al. Physical fitness in adolescence and subsequent inflammatory bowel disease risk. Clin. Transl. Gastroenterol 6, e121 (2015). [PubMed: 26540026]
69. Turpin W et al. Increased intestinal permeability is associated with later development of Crohn's disease. Gastroenterology 159, 2092–2100 (2020). [PubMed: 32791132]
70. Porter CK, Cash BD, Pimentel M, Akinseye A & Riddle MS Risk of inflammatory bowel disease following a diagnosis of irritable bowel syndrome. BMC Gastroenterol. 12, 55 (2012). [PubMed: 22639930]
71. Runmarker B & Andersen O Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain 118, 253–261 (1995). [PubMed: 7895009]
72. McKay KA, Jahanfar S, Duggan T, Tkachuk S & Tremlett H Factors associated with onset, relapses or progression in multiple sclerosis: a systematic review. Neurotoxicology 61, 189–212 (2017). [PubMed: 27045883]

73. Yong HY, McKay KA, Daley CGJ & Tremlett H Drug exposure and the risk of multiple sclerosis: a systematic review. Pharmacoepidemiol. Drug Saf 27, 133–139 (2018). [PubMed: 29210147]
74. Wijnands JMA & Tremlett H Concussion may not cause multiple sclerosis. Ann. Neurol 82, 651–652 (2017).
75. Montgomery S et al. Reply to “concussion may not cause multiple sclerosis”. Ann. Neurol 82, 652–653 (2017). [PubMed: 28976595]
76. Montgomery S et al. Concussion in adolescence and risk of multiple sclerosis. Ann. Neurol 82, 554–561 (2017). [PubMed: 28869671]
77. Smith KA et al. Hospital diagnosed pneumonia before age 20 years and multiple sclerosis risk. BMJ Neurol. Open 2, e000044 (2020).
78. Lucas A & Wolf M Vitamin D and health outcomes: then came the randomized clinical trials. JAMA 322, 1866–1868 (2019). [PubMed: 31703117]
79. Yung AR & Nelson B The ultra-high risk concept-a review. Can. J. Psychiatry 58, 5–12 (2013). [PubMed: 23327750]
80. Liu S-Y, Chan P & Stoessl AJ The underlying mechanism of prodromal PD: insights from the parasympathetic nervous system and the olfactory system. Transl Neurodegener. 6, 4 (2017). [PubMed: 28239455]

Box 1 |

Development of criteria for prodromal MS

We propose the following steps for the development of criteria for prodromal multiple sclerosis (MS) and interventional studies. All steps will require involvement of multiple stakeholders, including people and families affected by MS. Strong leadership is required to obtain international consensus, ideally led by a coalition of national and international MS bodies with a common set of goals.

- Develop consensus terminology for the phases of MS from the risk factor phase through the prodromal phase to clinical MS
- Improve understanding of the clinical signs and symptoms, neuroimaging findings, and other biomarkers associated with the prodromal phase
- Develop accurate prediction models, which could include clinical prodromal symptoms, neuroimaging findings and other biomarkers combined with risk markers of MS (for example, female sex, family history, polygenetic risk score, environmental exposures)
- Create validated criteria for prodromal MS that are suitable for research purposes and commit to their regular refinement and updating
- Consider results from ongoing intervention trials in high-risk populations (for example, in patients with radiologically isolated syndrome)
- Identify appropriate interventions and clearly defined, clinically relevant outcomes
- Develop large-scale, multicentre networks with supporting infrastructure for intervention trials in prodromal MS