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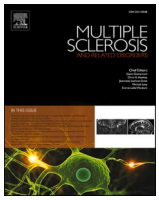

Editorial

When does multiple sclerosis start?

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The question of when multiple sclerosis (MS) starts is not a trivial one. It has implications for primary and secondary MS prevention studies (Giovannoni et al., 2025a; Zane et al., 2025). A recent matched cohort study examines patterns of healthcare utilisation in people with MS (pwMS) compared to a control group without MS (Ruiz-Algueró et al., 2025). The research focuses on the 25 years preceding clinically determined MS symptom onset, utilising linked clinical and administrative data from British Columbia, Canada. Findings indicate elevated general practice visits up to 14–15 years before MS onset, with ill-defined symptoms and signs, mental health-related issues and psychiatric consultations appearing as the earliest indicators, preceding nervous system concerns by 7–11 years (Ruiz-Algueró et al., 2025).

In this study, a hierarchy of medical problems defines the MS prodrome. Psychiatry visit showed a significant rise beginning 12 years before symptom onset and remained elevated in nearly all subsequent years (Ruiz-Algueró et al., 2025). Ophthalmology visits increased up to 9 years, and neurology visits up to 8 years before MS onset. Sensory organ–related visits were elevated from 8 years before MS onset compared to 5 years for musculoskeletal-related and 4 years for nervous system conditions (Ruiz-Algueró et al., 2025). Visits for endocrine and blood-related conditions were significantly elevated 9–10 years before MS onset (Ruiz-Algueró et al., 2025). Pregnancy and childbirth-related visits fluctuated in the years leading up to MS onset, being significant in years 2 and 5 before MS onset (Ruiz-Algueró et al., 2025). Visits for circulatory, digestive, genitourinary, infection, respiratory, skin-related conditions and neoplasms showed no patterns (Ruiz-Algueró et al., 2025).

Overall, these findings suggest a longer prodromal phase for MS than previously understood, offering potential for earlier identification of MS and intervention. How important is this study (Ruiz-Algueró et al., 2025), and how does it fit in with the Epstein-Barr virus (EBV) hypothesis of MS? There is little scientific debate about the potential for infections and vaccines to trigger autoimmune diseases such as MS. The most likely mechanism underlying this phenomenon is antigen-specific molecular mimicry (Robinson et al., 2024). However, the time from first exposure to EBV and the clinical onset of MS is approximately 7–8 years (Bjornevik et al., 2022; Vietzen et al., 2023), which is rather long and argues against molecular mimicry being the trigger of MS onset (Giovannoni et al., 2025b).

A well-documented infectious agent to trigger CNS autoimmunity is group A beta-haemolytic streptococcus (GAS) or *Streptococcus pyogenes*, which is the established cause of Sydenham's chorea and rheumatic fever (Cunningham, 2016, 2003). A characteristic of GAS-associated autoimmune diseases is the close timing between infection and the onset of disease. In subjects with acute post-streptococcal autoimmune disease, there is usually microbiological evidence of recent or current infection, i.e. there is serological evidence of recent infection or the organism can be cultured or detected from samples taken from the throat or skin (Cunningham, 2016, 2003). A similar close temporal relationship between exposure to the triggering antigen and disease onset is observed with vaccine- and enteric infection-triggered Guillain-Barré syndrome (Lasky et al., 1998; Rees et al., 1995). Similarly, the temporal association between the AS03 adjuvanted AH1N1 influenza vaccine and narcolepsy, a putative CNS autoimmune disease, is less than six months (Nohynek et al., 2012).

In comparison, the long lag time between EBV seroconversion or EBV-associated infectious mononucleosis (IM), the first exposure to EBV, and the clinical onset of MS is estimated to be approximately 7–8 years (Bjornevik et al., 2022; Vietzen et al., 2023). This long lag time would support the argument that molecular mimicry is not the mechanism by which EBV causes MS. This new study's findings provide a counterargument to this, i.e. MS has an asymptomatic or prodromal phase that could be as long as 15 years (Ruiz-Algueró et al., 2025). Hawkes suggested that people destined to get MS were risk takers, based on the increased prevalence of prior adverse health behaviours such as smoking, alcohol excess, vitamin D and EBV exposure and obesity (Hawkes, 2005). This was verified subsequently in a case-control study that confirmed smoking, alcohol and EBV as risks, as well as recreational drug use, all-night parties, gambling, more sexual partners, more pregnancies and one or more terminations of pregnancy (Hawkes and

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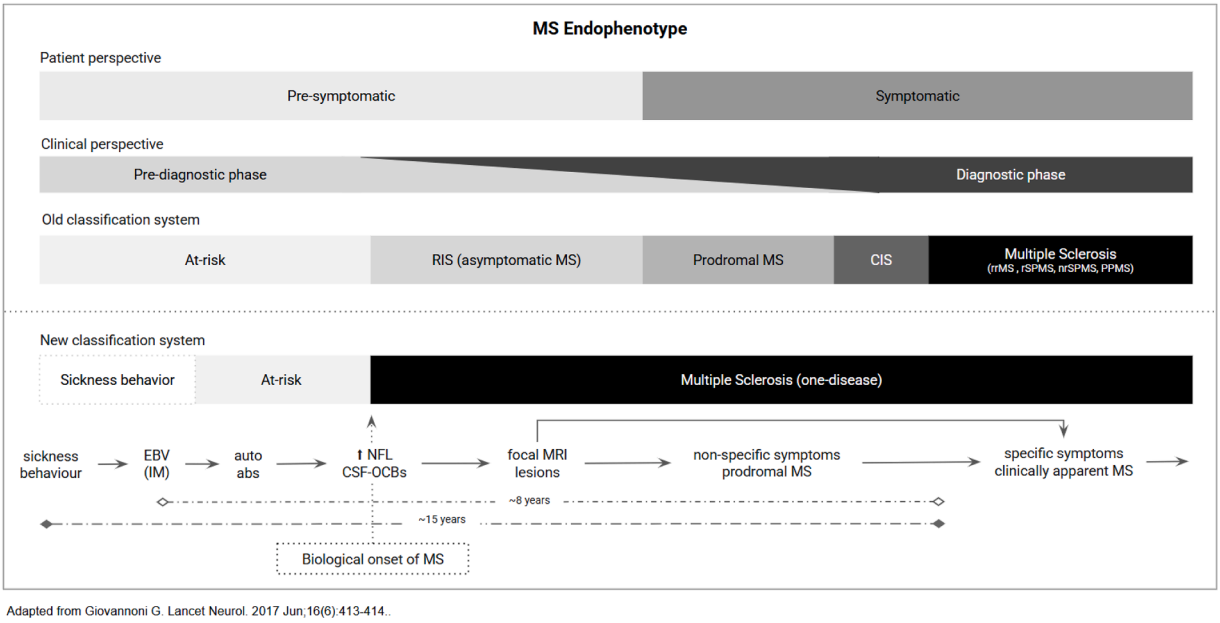

Fig. 1. The extended multiple sclerosis (MS) endophenotype depends on one's perspective. For a patient, they are either symptomatic or not. From a clinician's and healthcare system's perspective, people who have MS are either in the prediagnostic phase or have been diagnosed as having MS. The old classification system of MS is based mainly on clinical and radiological findings. People were either at risk of MS or had evidence of disease, i.e. had asymptomatic or symptomatic MS. People with symptomatic MS were further subdivided based on clinical phenotype into having prodromal MS, clinically-isolated syndrome (CIS), relapsing-remitting (rrMS), relapsing secondary progressive (rSPMS), non-relapsing secondary progressive (nrSPMS) or primary progressive (PPMS) MS. However, the new classification of MS, which is based on a biological definition of MS, now allows patients previously labelled as having radiologically-isolated syndrome (RIS) and prodromal MS to be diagnosed with MS. The latest findings appear to extend the 'MS prodrome' to a time before exposure to EBV, the likely cause of MS. This extended prodrome is characterised by sickness behaviour with increased healthcare utilisation. The question is, when does MS as a biological disease begin? Presumably, it starts after exposure to EBV and/or infectious mononucleosis (IM) and the development of putative autoantibodies (auto abs). In this cartoon, we suggest MS onset occurs when there is evidence of end-organ damage, i.e. as measured with raised blood neurofilament light chain levels (NFL), and the emergence of CNS inflammation as detected by the local synthesis of intrathecal oligoclonal IgG bands (OCB). Based on epidemiological observations the extended prodrome estimated at up to 15 years in duration is longer that the average latency, of about eight years, between exposure to EBV and specific symptoms of clinically apparent MS. This raises the hypothesis of reverse causation, i.e. it is what underlies prodromal sickness behavior which predisposes people to react abnormally when exposed to EBV that is what leads to the development of MS. This cartoon has been adapted from the figure in Giovannoni (2017) (Giovannoni, 2017).

Boniface, 2014). This could arguably be part of a behavioural prodrome, representing disinhibited behaviour from prodromal MS and not necessarily causal, by increasing the exposure to an environmental agent.

The problem is overinterpretation and reverse causation, i.e. could the MS prodrome represent a syndrome of 'sickness behaviour' and the resulting increase in healthcare utilisation, noted in this prodromal period, increase one's risk of getting MS instead of representing early MS? Sickness behaviour is a coordinated set of changes in behaviour and physiology that occur in individuals who are ill (Devlin et al., 2022). It is not the illness itself, but rather the body's adaptive response to it that causes sickness behaviour. The primary purpose of sickness behaviour is to help the body conserve energy and mount an effective immune response, to recover from illness (Devlin et al., 2022). Sickness behaviour is an evolutionary survival strategy that, while unpleasant, is ultimately beneficial. Many of the problems that define the MS prodrome could be sickness behaviour. Could chronic stress from sickness behaviour create an environment where, if one gets exposed to EBV, it makes it more likely that one gets MS? The obvious question is, do people who develop IM or symptomatic EBV infection also have a prodrome? It would be feasible using the same methodology of this study (Ruiz-Algueró et al., 2025) to answer this question.

Defining MS as a biological disease rather than using the standard clinicoradiological definition of MS will allow the diagnosis of MS to be made in the asymptomatic phase and will shorten the lag phase between the initial exposure to EBV and disease onset. This will also allow researchers to dissect the sequence of events and answer the causation-reverse-causation question. However, what constitutes a biological definition of MS is, at present, a moot point and requires further study. Some investigators support the hypothesis that immunological endophenotyping may enable the diagnosis of pre-MS relatively soon after primary EBV exposure.

A recent study has shown that after IM, raised antibody titres to an EBV epitope in EBNA-1 (EBNA-1$^{381–452}$-peptide) predict at-risk individuals who will subsequently go on to develop MS (Vietzen et al., 2025). Notably, the significantly elevated anti-EBNA-1$^{381–452}$-specific IgG titres could be identified as early as nine months after EBV-seroconversion and a median of 5.4 years before MS diagnosis. This group has also shown that these raised antibodies precede the increase of blood neurofilament light chain (NFL) levels that are thought to represent the biological onset of MS, because NFL levels are raised before symptom onset (Vietzen et al., 2025). This study's striking findings have not been reproduced by a Swedish group who have recently shown that antibody reactivities against more than one EBNA1 peptide and more than one CNS-autoantigen mimic only modestly increase the risk of developing MS (Sattarnezhad et al., 2025). However, the overall results indicate that molecular mimicry between EBNA1 and putative CNS-autoantigens - including anoctamin-2 (ANO2), alpha-B crystallin (CRYAB) and glial cellular adhesion molecule (GlialCAM) - may contribute to the pathogenesis of MS (Sattarnezhad et al., 2025). These results imply that subclinical disease processes that underlie MS onset may start quite soon after IM or first exposure to EBV.

The biological onset of MS is likely to be asymptomatic in the vast majority of people destined to develop clinically definite MS and probably occurs quite soon after primary EBV exposure. MS only manifests clinically when a subsequent lesion forms in an eloquent pathway. This explains why most people destined to develop MS have pre-existing multiple white matter lesions on their baseline brain MRI when

presenting with their first clinical attack (Miller et al., 1989). EBV differs from GAS because it establishes a latent infection that intermittently reactivates asymptomatically. It is this intermittent asymptomatic reactivation of EBV (latent-lytic cycling) that may drive MS disease activity (Giovannoni et al., 2025b). This is why we need to test EBV antivirals and EBV-targeted immunotherapies in MS (Giovannoni et al., 2025b) and, at the same time, try to prevent MS by EBV vaccination (Giovannoni et al., 2025a; Maple et al., 2022; Zane et al., 2025).

1. Conclusions

These recent findings extend the MS endophenotype (see Fig. 1). Combining the extended endophenotype with the move to define MS as a biological disease rather than a clinicoradiological entity will have implications for the diagnosis and management of MS. From a patient perspective, they are either symptomatic or not. From a clinician's and healthcare system's perspective, people who have MS are either in the prediagnostic phase or have been diagnosed as having MS. The old classification system of MS is based mainly on clinicoradiological findings, which classifies subjects as either at risk of MS or having evidence of disease, i.e. having asymptomatic or symptomatic MS. People with symptomatic MS were further subdivided based on clinical phenotyping into having prodromal MS, clinically-isolated syndrome (CIS), relapsing-remitting (rrMS), relapsing secondary progressive (rSPMS), non-relapsing secondary progressive (nrSPMS) or primary progressive (PPMS) MS. However, the new classification of MS, which is based on a biological definition of MS, now allows patients previously labelled as having radiologically-isolated syndrome (RIS) and prodromal MS to be diagnosed with MS.

The latest findings extend the 'MS prodrome' to a time before exposure to EBV, the likely cause of MS. This extended prodrome is characterised by sickness behaviour with increased healthcare utilisation. Presumably, MS begins after exposure to EBV and/or IM and the development of putative autoantibodies. MS onset likely occurs when there is evidence of end-organ damage, i.e. as measured using raised blood NFL levels and the emergence of CNS inflammation as detected by the local synthesis of intrathecal oligoclonal IgG bands (OCB). These two findings likely predate the detection of focal MRI lesions or asymptomatic MS. Based on these recent epidemiological observations the extended prodrome is estimated at up to 15 years in duration, which is longer than the average latency, of about eight years, between exposure to EBV and symptoms of clinically apparent MS. This raises the issue of reverse causation, i.e. it is the biology underlying prodromal sickness behavior, occuring very early in the causal path, that predisposes people to develop autoimmunity when exposed to EBV. This extends strategies for MS prevention to primordial prevention, i.e. targeting risk factors before exposure to EBV.

2. Disclosures

In the last two years, Gavin Giovannoni has received compensation for serving as a consultant or speaker for or has received research support from AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, Janssens/J&J, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck & Co, Merck KGaA/EMD, Moderna, Serono, Moderna, Novartis, Sandoz, Sanofi and Roche/Genentech.

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