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EARLY DETECTION OF MULTIPLE SCLEROSIS: WHEN DOES THE DISEASE REALLY BEGIN?

Valentino Rački[a,b], Vladimira Vuletić[a,b], Sten Fredrikson[c]

[a]Clinical Department of Neurology, University Hospital Center Rijeka, Rijeka, Croatia

[b]Medical Faculty, University of Rijeka, Rijeka, Croatia

[c]Division of Neurology Huddinge, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Summary

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder of the central nervous system (CNS) that is characterized by widespread demyelinating lesions in both the brain and the spinal cord. The inflammatory lesions are not the only pathophysiological process, with continuous neurodegeneration and atrophy present from the very beginning of the disease. The direct cause of the disease is not known so far but is thought to be a combination of genetic, immune and environmental factors. Significant advances in immunology and neuroscience bring us ever closer to understanding the complex pathophysiology that underly multiple sclerosis, along with enabling us to diagnose the disease earlier than before. The natural course of the disease in both relapsing and progressive phenotypes includes the radiologically isolated syndrome, in which there is evident dissemination in space without any symptoms. The majority of these patients will have radiological progression in five years, with a third experiencing their first clinical symptoms. Early diagnosis facilitates early disease-modifying therapies, which should lead to slower progression and reduced disease activity in most patients. Furthermore, the personalized approach to therapy is now a reality in MS with a comprehensive option of therapy suited for the clinical state of each patient.

Key words: multiple sclerosis; neuroinflammation; diagnosis; clinically isolated syndrome; radiologically isolated syndrome

Background

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder of the central nervous system (CNS) that is characterized by widespread demyelinating lesions in both the brain and the spinal cord [1]. Multiple sclerosis can be considered as a disease of a thousand faces, as the first symptoms vary significantly from one person to the other due to different locations where the lesions occur. The most common symptoms in the start of the disease include blurred vision, vision loss, numbness, paraesthesia and ataxia [2]. The first presentation of the disease most commonly occurs in young adults, and approximately three-quarters of patients suffering from MS are women, which follows the similar sex distribution present in autoimmune diseases [3]. The disease is present in the whole world, but the prevalence varies greatly depending on geography and regions. It is most prevalent in Europe, North America and Australasia [4]. The prevalence in Croatia has been increasing in recent times [5, 6], especially in some regions that have historically had more cases of MS than the rest of the country [7, 8].

Furthermore, MS is among the leading causes of disability in young adult and adult age groups, thus being a significant burden on society in Europe [9]. The direct cause of the disease is not known so far but is thought to be a combination of genetic, immune and environmental factors [10]. Pinpointing the start of the disease is impossible without a clear cause; however, we do know the disease is active for some time before the first clinical events are present [11]. Significant advances in immunology and neuroscience bring us ever closer to understanding the complex pathophysiology that underly multiple sclerosis, along with enabling us to diagnose the disease earlier than before. These give us the ability to focus on the early phases and treatment of the disease while bringing us within reach of finding the real beginning of the disease.

Pathophysiological evolution of multiple sclerosis

The original descriptions of multiple sclerosis by Charcot describe sclerosing plaques in the periventricular area, pons and the spinal cord, a demonstration of the dissemination in space, which is crucial in today's diagnostic criteria [12]. However, in modern times we do not depend solely on clinical features and pathology, but also on modern neuroimaging and laboratory techniques to diagnose and measure the progression of the disease. Demyelinating lesions in MS occur in both the white and gray matter, with each having specific characteristics [11]. In general, acute white matter lesions that are present in the relapsing forms of the disease are characterized by acute inflammation that can be quite

heterogenous between each person [13]. At the start, most lesions have a marked innate immune response with classical and alternative microglial activation, bloodborne macrophage infiltration and subsequent initiation of the adaptive immune response [14, 15]. Unfortunately, the intrinsic or extrinsic factors that cause the lesions to form are still unknown. Recent research reveals that microglial activation remote from established lesions could represent the earliest stage of lesion development [16]. Importantly, microglia also initiate the processes of repair during the early phase of the disease, which follows the inflammation at the same time [17]. What occurs after initial lesion activation is the recruitment of either predominantly T-cells or B-cells, which begins the complex interplay between the immune system, glial cells and neurons, and ultimately can bring the acute lesions into the chronic phase [18]. The possible outcomes of this process is a chronic inactive lesion that is characterized by a complete lack of remyelination, or a remyelinated lesion that can lead to partial restitution of function. Another possibility is a low-grade inflammation smouldering lesion, fueled by chronic microglial activation and subsequent chronic neurodegeneration, which is most common in progressive forms of multiple sclerosis [19, 20].

Gray matter lesions show a lesser inflammatory component than the white matter lesions, with significantly less disrupted blood-brain barrier [21]. They most commonly occur in the perivascular cortical space and near the leukocortical junction, which affects both white and gray matter [22]. The evolution of the lesions is less severe than in acute white matter lesions, with a more marked innate immune response, while the adaptive immune response is present in a lesser capacity. The leukocortical lesions show a more profound inflammation than the pure cortical lesions, which only encompass the gray matter [23]. Interestingly, they are more prevalent in the early stages of the disease and are rarely present in the chronic, later stages [23]. Furthermore, gray matter lesions can be present even before white matter lesions, while also predicting higher progression of disability, even in patients with a clinically isolated syndrome (CIS) [24].

The presence of lesions and focal inflammation is only one part of the pathophysiology in MS. There is clear evidence that continuous neurodegeneration, or „silent progression, is present from the very beginning of the disease and continually leads to irreversible damage of nervous tissue [25]. Regional gray matter atrophy occurs from the start and progresses through the natural course of the disease [26]. The atrophy is especially evident in the thalamus, which happens in the earliest stages of the disease and increases the risk of disease progression [27]. Deep gray matter volume loss has been shown to drive the disability progression in patients, with lacking improvement to disease-modifying therapy

[28, 29]. The progression of atrophy appears to correlate with the lesion load in MS, but it is not clear whether there is a direct connection between the two [30]. A study by Pontillo et al. confirmed the diffuse involvement of the deep gray matter (DGM) in MS, with differences between the progressive and relapsing phenotype. The atrophy in the relapsing forms was determined by the white matter lesion burden, while in progressive forms, the microstructural damage and thalamic susceptibility changes accounted for the development of DGM volume loss [31]. Therefore, the pathophysiological evolution of neurodegeneration in both forms appears to be driven by inflammation, with the atrophy in relapsing forms occurring due to structural disconnection in neuron networks, while in progressive forms as a consequence of local microstructural damage. Overall, it appears that the chronic neurodegeneration in MS is a direct consequence of chronic CNS inflammation, with production of reactive oxygen and nitrogen species, low-grade hypoxia, cytokine and glutamate release being the main drivers of damage. The homeostasis of the neurons in such a milieu is disturbed, leading to oxidative stress and mitochondrial damage that causes ion imbalances and ultimately neuroaxonal damage by apoptosis and necrosis [32]. Whether the disease beginning is driven purely by inflammation or if there is an underlying cause for neurodegeneration is not known yet as the search for the direct cause continues [33].

Clinical evolution of multiple sclerosis

Our understanding of the clinical disease evolution has improved in recent times. Multiple sclerosis is classified into two primary phenotypes based on disease progression; the relapsing forms and the progressive forms [34]. The initial evolution of the disease is similar for both phenotypes, as the disease in both cases starts before the clinical threshold is passed and observed. Early asymptomatic lesions can be detected with magnetic resonance imaging (MRI) long before first clinical events, which is called the radiologically isolated syndrome (RIS) [35]. Studies have shown that patients with RIS can progress to both the relapsing and progressive forms of multiple sclerosis [36].

On the other hand, clinically isolated syndrome (CIS) encompasses the first clinical manifestation of the relapsing form of MS and is characterized by present demyelinating lesions on MRI with neurological symptoms, but without proven dissemination in time [35]. In both cases, we should follow the patients prospectively, as the majority of cases will progress to relapsing or progressive MS within ten years [37, 38]. However, even a single clinical event can be enough to diagnose a patient with multiple sclerosis, provided it is possible to prove the

dissemination in time and space according to the latest diagnostic criteria [39]. The fast-changing diagnostic criteria have reduced the number of patients that are diagnosed with these syndromes; however, they still represent a stepping-stone in the evolution of the disease.

Radiologically isolated syndrome

Incidental MRI findings suggestive of multiple sclerosis without any neurological symptoms define the radiologically isolated syndrome (RIS) [40]. Prospective monitoring of the patients is critical as approximately two-thirds of people with RIS will show radiological progression, while one-third will develop symptoms in five years from discovery. Importantly, the patients with RIS can progress to both progressive and relapsing forms of MS [36]. The risk increases if the lesions are present in the cervical cord at first discovery, if the age of the patient is less than 37 years old, and if the gender is male [40]. Patients with RIS have evidence of brain atrophy, mild cognitive deficits, increased incidence of psychiatric diseases, axonal loss and even a subclinical inflammatory disease [41].

The current modified criteria for RIS include a demonstration of lesion dissemination in space, similar to that in MS, with the exclusion criteria being any clinical evidence of neurological dysfunction. Likewise, it is required that MRI abnormalities cannot be explained by any other disease process, especially ageing, vascular-associated damage and exposure to toxins or drugs [42]. Particular caution should be given in RIS patients who present with frequent headaches, seizures, various paroxysmal symptoms or psychiatric disturbances, as those can also be a sign of subclinical MS [43]. The likelihood is increased in there is evident dissemination in time on MRI, infratentorial or spinal cord lesions, the presence of oligoclonal bands in the cerebrospinal fluid or abnormal visual evoked potentials [43]. On the other hand, there is a debate in the field whether the term RIS is antiquated, with an overlap in both symptoms and diagnostic criteria as the McDonald criteria for MS keep evolving [44]. There is a lack of detailed epidemiological data for RIS. A population-based study conducted by Forslin et al. revealed a small incidence of RIS (0.8 cases per 100,000) in a high-incidence region for MS (10.2 cases per 100,000), although there is a need for a higher number of participants to increase the accuracy of the study [45]. Currently, there is no evidence to support treatment in patients with RIS, even if there is a suspicion of subclinical MS. However, active monitoring is advisable, provided the patients agree to it [42].

Clinically isolated syndrome

Multiple sclerosis for a vast majority of patients starts with a clinically isolated syndrome, which by definition entails the first clinical presentation that shows characteristics of inflammatory demyelination but does not meet criteria for the dissemination in time [46]. Nearly 88% of people that experience CIS with abnormal MRI will have a second episode and progress to clinically definite multiple sclerosis in within 20 years of onset [47]. The natural evolution of CIS encompasses progression to relapse-remitting multiple sclerosis after proven dissemination in time, which can be followed by continuous relapses, secondary progression or remain stationary [48]. CIS most occurs in young adults, with presenting symptoms predominately involving optic nerves, brain stem, cerebellum or spinal cord [49]. The risk rate of progression appears to be the same regardless of the presenting symptom [50]. In general, the risk for disease progression increases patients who have either abnormal MRI or positive oligoclonal bands in the cerebrospinal fluid [51].

Relapse-remitting multiple sclerosis (RRMS)

Nearly 85% of MS patients will have the relapsing form of the disease, with an established natural progression (Figure 1.). This phenotype is characterized by intermittent periods of increasing neurological disability called relapses, along with periods of clinical stability called remissions. Almost half of the relapses leave residual deficits that accumulate over time, leading to increasing disability as the disease progresses [34]. Individual states such as infections and stress appear to be associated with increased risks for relapses [52]. Pregnancy, on the other hand, has a variable effect on the risk of relapses, with significantly reduced risk of relapses during pregnancy, which increases above baseline risk during the postpartum year [53]. A significant number of patients invariably progresses into the secondary progressive multiple sclerosis (SPMS) (Figure 1.), but it is still not clear what causes this progression [48].

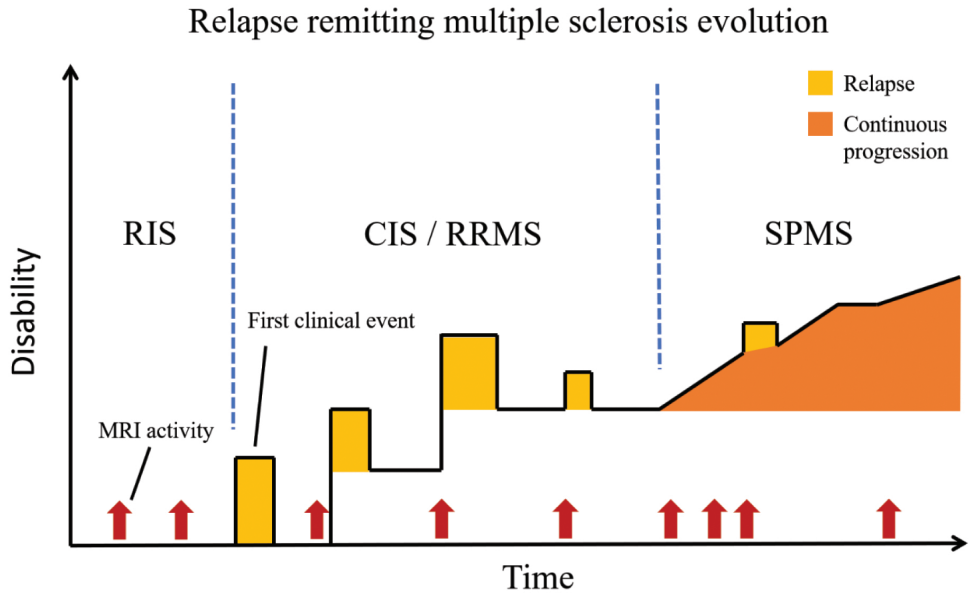

Figure 1. The evolution of the relapsing forms in multiple sclerosis. Figure style partially adapted from the National Multiple Sclerosis Society.
Abbreviations: RIS - the radiologically isolated syndrome; CIS - clinically isolated syndrome ; RRMS - Relapse-remitting multiple sclerosis ; SPMS - secondary progressive multiple sclerosis

Progressive forms of multiple sclerosis

As stated previously, the natural evolution of the relapsing form of MS leads to a progression to SPMS for most of the patients [37]. The cause for the disease progression is unknown so far, and there are no definitive clinical diagnostic criteria due to no available laboratory or imaging biomarkers [54]. The diagnosis is usually retrospective and can be delayed up to 3 years in some patients [55]. This has to be improved, as novel therapies that can be effective in SPMS create an opportunity for intervention in this stage as well. The progression of SPMS is characterised by periods of continuous progression of the disease, periods of relative stability, and possible superimposed relapse activity (Figure 1.) [50]. Much of the pathophysiological characteristics are similar in both SPMS and

primary progressive multiple sclerosis (PPMS), involving predominantly the innate immune system and a more closed off inflammation of the CNS than in the relapsing forms of MS [56].

Around 10% of MS patients have progressive phenotype

as the presenting form of the disease, which is characterized by an ongoing progression of disability [57]. The natural evolution of the disease is similar to SPMS, with possible superimposed relapses and also periods of the relative stability of disability progression [50]. Novel research shows that RIS can also precede PPMS as a first possible sign of MS (Figure 2.) [36]. Lunde et al. published a 60-year old longitudinal study that showed a two-fold increased mortality rate in PPMS compared to RRMS, with a seven-year shorter life expectancy [58]. The recent gulf in treatment options between the two only means that this difference could widen. Therefore, the progressive forms of the disease are under intense pre-clinical and clinical research in order to elucidate the pathophysiological mechanisms that could lead to novel treatment and improve patient outcomes.

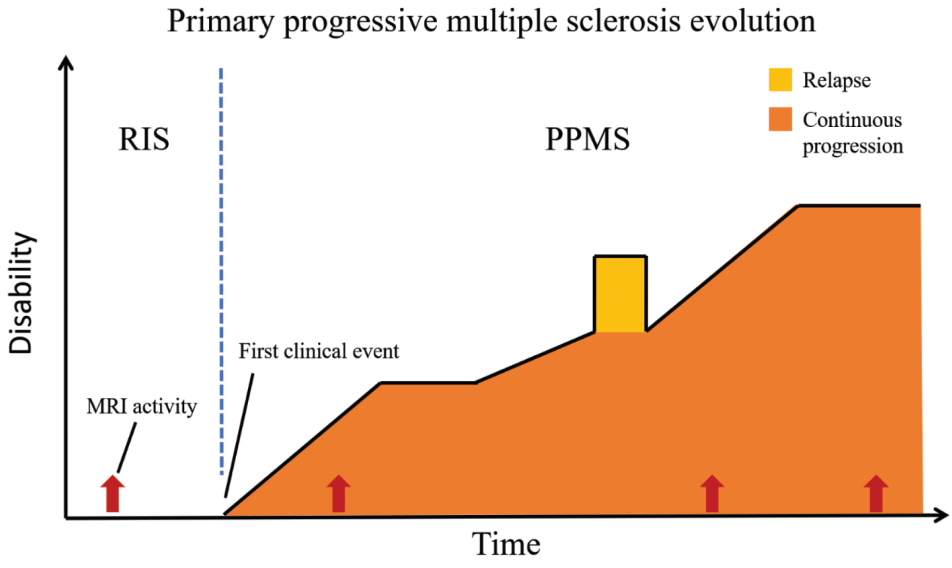

Figure 2. The evolution of primary progressive multiple sclerosis (PPMS). Figure style partially adapted from the National Multiple Sclerosis Society
Abbreviations: RIS - the radiologically isolated syndrome; PPMS – primary progressive multiple sclerosis evolution

Evolution of the diagnostic criteria

Main principles of MS diagnosis are demonstrating the dissemination in time (DIT) and space (DIS) with objective clinical and paraclinical evidence. There have been many changes to the diagnostic criteria over the last half-century. Schumacher proposed the first criteria in use at al. in the '60s of the last century, which included both dissemination in time and space using only clinical signs as there were no paraclinical markers except evoked potentials [59]. The Poser criteria included the presence of oligoclonal bands to the diagnostic criteria and expanded the possible diagnostic conclusions, although still requiring concrete clinical findings for DIT and DIS [60]. The discovery and use of MRI in clinical practice have been central to increasing speed and accuracy of the diagnosis in recent times, with the demonstration of DIS and DIT with MRI possible with criteria set by Paty (1988) [61], Barkhof (1997) [62], Tintore (Revised Barkhof, 2000) [63] and Swanton (2006) [64]. The MRI findings are central to the McDonald criteria, that is still in use today after four revisions [65]. Each iteration modified and reduced the number of lesions required for dissemination in space, while also shortening the time for a follow-up MRI's to prove the dissemination in time with gadolinium-enhancing active lesions. The 2010 revision reduced the mean time for diagnosis from the onset from 2 years (Poser criteria) to just six months [66]. Latest revision into the McDonald criteria in 2017 added the possibility of using CSF specific oligoclonal bands to demonstrate dissemination in time, drastically reducing the time required to make the diagnosis of MS [67]. The recent revisions allow us to initiate treatment earlier than ever before and have brought a significant change to the clinical management of multiple sclerosis.

Importance of early treatment

It is clear from the pathophysiological and clinical evolution of the disease that treatment must be timely to disrupt the debilitating mechanisms that lead to disability. The treatment of MS has improved significantly over the past years, with a growing number of disease-modifying therapies available for patients. All of the disease-modifying therapy (DMT) focuses on modulating the immune system. It works via three possible ways: immunosuppressive (E.g. natalizumab, siponimod, fingolimod, ocrelizumab), immunomodulatory (E.g. interferon-beta, dimethyl fumarate, glatiramer acetate, teriflunomide) or via immune reconstitution (E.g. cladribine, alemtuzumab, autologous haematopoetic stem cell transplantation) [2]. Many of these therapeutics overlap in their way of affecting the immune system and require a careful approach in consideration which is most suitable for each patient. The goal of therapy is to reduce the disease activity

as much as possible and attain no evidence of disease activity (NEDA), which in turn slows down progression. It is well known that DMTs are capable of delaying disease progression and changing the natural course of the disease that was outlined earlier in this review [68]. The general safety profile for all DMTs is favourable, with the potency being proportionately related to potential adverse events. General adverse event profiles are related to immunosuppression, with a higher incidence of infections, induction of secondary autoimmunity and possible malignancies. More studies are required as currently safety outcomes are poorly reported in most primary studies of DMTs [69].

Current guidelines for treating RRMS implemented in most European countries initially include the escalation approach in which the start of therapy is with less potent and potentially more safe DMTs such as interferon-beta or teriflunomide [70]. The therapy can then be escalated to more potent DMTs such as natalizumab or fingolimod if there is no adequate control over disease activity or progression. However; novel research by William et al. point out that starting therapy with more potent DMTs leads to lower risk of conversion to SPMS [71]. This is evident when observing the NEDA scores for various DMTs in their phase 3 trials, with the rates of patients achieving NEDA in ocrelizumab, cladribine and alemtuzumab being significantly higher than those of first-line DMTs such as interferon-beta and teriflunomide [2]. Moreover, the treatment should be initiated as soon as possible to reduce the risk of disease activity and progression [72], with current recommendations that support the use of DMTs even in CIS with abnormal MRIs [70].

The second possible strategy for treatment is the immune reconstitution therapy, which aggressively induces depletion and reconstitution of lymphocytes [73]. This method of therapy is the closest to a possible cure, as it aims to repair the aberrant immune response and induce long-term beneficial changes in the adaptive immune system [74]. Aside from the mechanism of action, the main differences between the two strategies lie in the fact that chronic immunosuppressive and immunomodulatory therapies need to be administered continuously in order to remain active. In contrast, immune reconstitution therapy is given in pulses and is effective long after the administration. The risk of such aggressive therapy is the development of secondary autoimmunity, particularly in the case of alemtuzumab [75]. Other adverse effects include the reactivation of latent infections like tuberculosis or herpes zoster [76]. The early results of this type of therapy are encouraging as nearly 60% of patients did not need additional cycles of alemtuzumab [77], while nearly 75% of patients remained relapse-free in the fourth year after cladribine treatment [78].

Unfortunately, most DMTs that are used for RRMS are not effective in preventing disease progression in the progressive forms of MS [79]. The only DMTs that have shown promise are the anti-CD20 monoclonal antibodies rituximab [80] and ocrelizumab, with the latter approved for treatment due to a favourable effect on disease progression [81]. The positive effect of these antibodies increases in younger patients who had an active inflammation on initial MRI scans. Therefore, treatment with anti-CD20 DMTs should be considered in patients with PPMS or SPMS, especially in those with shorter disease duration or signs of activity on MRI [82].

The plethora of options and the variations in their efficacy has provided us with the tools to provide highly individualized choices in treatment [83]. Starting the treatment as early as possible is the only thing clear in every patient [70]. Deciding which treatment strategy to use from the start must include a personalized analysis of prognosis in each patient. Poor prognosis is determined by demographic factors (E.g. older age, male sex, vitamin D levels), clinical factors (PPMS, high relapse rater, short interval between relapses, poor recovery, high initial Expanded Disability Status Scale score), MRI observations (high number of T2 lesions, highly active lesions, infratentorial and spinal cord lesions, significant brain atrophy) and biomarkers (oligoclonal bands in the CSF, high levels of neurofilament light chain) [83]. Patients with poor prognostic factors should be considered for early aggressive therapy to delay the progression of the disease as much as possible, although the recommendations are not equivocal in this field and further studies are required [84]. Other factors which influence the treatment decision include the patient preferences, possible pregnancy, route of administration, efficacy and cost. Therefore, two major principles in treating MS is that every diagnosed patient should be given therapy as soon as possible and that every patient deserves a personalized approach to recieve the most appropriate therapy possible as safer is not neccessearily better.

Final Thoughts

Our understanding of the beginning of MS has been challenged over recent years by discoveries in the field. The concept of the radiologically isolated syndrome (RIS) has shown that the disease mechanisms of MS can be visible on MRI scans several years before the first clinical symptoms. Nearly 2/3 of patients with RIS show radiological progression and 1/3 will develop neurological symptoms during mean follow-up times of up to five years. Therefore, it can be considered as the beginning in both MS phenotypes, until the mechanisms and cause for the disease are elucidated. RIS and CIS are getting obsolete and

rare with new criteria for MS, with the syndromes gradually being incorporated into the natural disease evolution of MS. Our understanding of the neurodegeneration and "silent progression" is increasing, and it is clear that these aspects are present from the onset of MS. In general, relapsing MS patients experience clinically significant worsening of disability that is independent of relapses or accumulation of new T2 lesions on brain MRI. Silent progression patients have similar imaging characteristics to patients with SPMS, which likely represents the same pathological process as SPMS but is not recognized

as such by either clinicians or patients. Early diagnosis will facilitate early disease-modifying therapies, which should lead to slower progression and reduced disease activity in most patients. Furthermore, the personalized approach to therapy is now a reality in MS with a comprehensive option of therapy suited for the clinical state of each patient. Ultimately, perhaps a more pertinent question, in the end, is not when the disease begins, but how fast can we detect it and initiate treatment to slow down the progression.

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Correponding author:
Sten Fredrikson
E-mail: Sten.Fredrikson@ki.se