Emerging trends and challenges in multiple sclerosis in Europe: rethinking classification and addressing COVID-19 impact

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Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. It is one of the most common causes of neurological disability in the young adult population. Worldwide about 2.8 million people are affected, with an increasing incidence and prevalence over the last decades.[1]

Progress in MS care has occurred on multiple levels, but particularly includes earlier diagnosis and higher efficacy of therapies, improving the likelihood of disease control and also long-term prognosis.[2] Furthermore, although the COVID-19 pandemic challenged MS care, the lessons and advances made at that time are now being used to improve patient care.

Two papers published in *The Lancet regional Health–Europe* for the Series on Multiple Sclerosis 2024 outline the emerging epidemiological trends in Europe while stressing the limits of traditional classification of MS course[3] and highlight the impact of COVID-19 pandemic on MS care in Europe.[4]

Portaccio et al.[3] discuss current trends in incidence and prevalence in Europe. In this article they identify certain factors that have contributed to shifting the peak prevalence to the sixth decade of life – modifying the risk of comorbidities and side effects – such as improved prognosis and reduced disease-related mortality, different diagnostic criteria and demographic changes. In Europe, there is a latitudinal gradient of MS with a high-risk region in the northern part, which probably underlines the predominant role of distinct environmental factors. Besides differences in incidence, differences in the availability of disease-modifying therapies (DMTs) and rehabilitation in Europe remain a challenge in a chronic disease with a high socioeconomic burden.

Furthermore, this article challenges the traditional view of the clinical course of MS, as a separation between relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP) disease course. This concept did not always reflect the clinical reality with indistinct boundaries, especially between RR and SPMS (see Fig. 1). Thus, there is a clear need for a more uniform and data driven view that considers more than two dimensions (relapses and progression) in MS.[5]

The advent of highly effective therapies in MS has revealed a phenomenon known as evidence of disease progression independent of relapse activity (PIRA), contributing significantly to disability[6] accumulation. PIRA,[7] also referred to as silent progression, smouldering disease and compartmentalized neuroinflammation, can lead to disability even in the absence of relapses, impacting long-term prognosis more than relapse associated worsening (RAW).[6] However, the concept of PIRA is still evolving without a universally accepted definition. Relying solely on traditional disability assessment scales may overlook hidden symptoms and delay progression detection. To address this, a more comprehensive assessment approach is needed to identify patients at high risk of PIRA, utilizing digital markers, biomarkers, and clinical symptom awareness. While PIRA plays a substantial role in disability accrual, challenges remain in early detection and implementation in routine clinical settings. The integration of biomarkers and digital tools may aid in early identification and understanding of underlying disease mechanisms. This concept calls for a reevaluation of clinical practices, improved monitoring granularity, and a focus on enhancing patient care and treatment outcomes in MS.

Prosperini et al.[4] highlight the impact of the COVID-19 pandemic and lessons learned. While general risk factors were rapidly detected in patients with MS, the fear of triggering MS activation, the impact of vaccination on MS course, as well as questions of safety and efficacy of vaccination in patients with MS were challenging. Although data on risk of patients with MS in general were inconclusive, data especially from Europe and North America indicated that, besides risk factors like higher disability and progressive disease, CD20+ depleting agents increased the risk of severe disease course. However, no overall increase in disease activity or MS progression was reported after COVID-19 infections, although relapses or new symptoms could occur partly due to increased body temperature.

As discussed in the article, vaccine hesitancy is common in patients with MS[8] and was a challenge during the pandemic. Most specialists recommended continuous therapy during the pandemic, however, delayed interval therapies occurred frequently and were found to be safe.

Vaccination against COVID-19 was safe in patients with MS independent of DMTs[9] but efficacy was significantly reduced in patients on CD20 depleting therapy and unselective S1P-R modulators. Repetitive
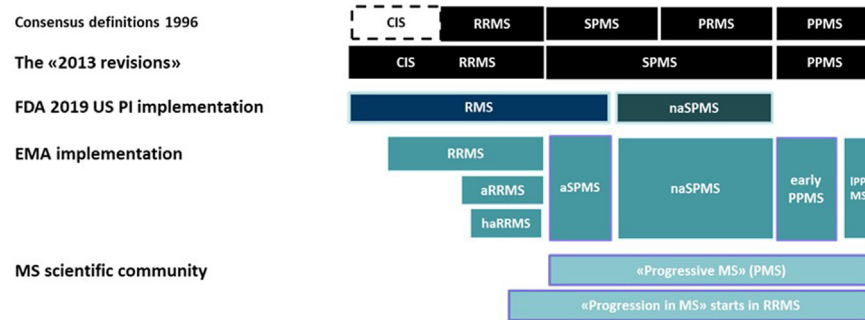
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Fig. 1: Clinical course of multiple sclerosis-traditional and emerging classification. CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS; RMS, relapsing MS; naSPMS, non active SPMS; aRRMS, active RRMS; naRRMS, non-active RRMS; PMS, progressive MS.[5]

vaccination and delaying vaccination to the last treatment cycle can increase vaccination efficacy. With CD20+ depleting agents, cellular response was mostly sufficient, while with unselective S1P-R modulator, both humoral and cellular response were diminished.

Insights from the pandemic have shaped vaccination recommendations in Europe[10] for MS patients, emphasizing early vaccination and continuous monitoring, especially for those on MS therapy. The pandemic has also boosted the use of telemedicine and digital tools in MS care, showcasing their potential for detailed assessment and effective tele-rehabilitation. The future is likely to see digital technology playing a key role in detecting cognitive impairment during clinical assessments.

In conclusion, novel treatments, especially high efficacy therapy approaches, have changed and will continue to change the natural history of MS. Therefore, here is a need for better (individual) stratification and prognostication of early MS, for early identification, understanding and tackling of relapse independent "progression". Lower dimensionality (clinical) assessments in big cohorts/registries together with higher dimensionality approaches integrating imaging/biological data will increase knowledge and enable a more accurate, uniform characterization of MS (based on a data driven approach). There is a need for integration of biological/immunological data as well as digital medicine into diagnosis, prognosis, treatment stratification, disease monitoring to improve **disease understanding** and MS care. Last but not least: there is an unmet need for prevention strategies, repair strategies, and tolerance induction strategies.

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