Preventing disease progression in multiple sclerosis—insights from large real-world cohorts

Sinah Engel* and Frauke Zipp

Abstract
Multiple sclerosis is a chronic neuroinflammatory disease with a highly heterogeneous disease course. Preventing lasting disability requires early identification of persons at risk and novel approaches towards patient stratification for personalized treatment decisions. In this comment, we discuss the importance of large datasets of real-world cohorts in order to address this unmet need.

Keywords: Biomarkers, Multi-omics, Patient stratification, Personalized treatment

Background
Multiple sclerosis (MS) is a chronic autoimmune-mediated disease affecting the central nervous system (CNS) through inflammatory and neurodegenerative processes. Although thousands of patients have benefitted from the recent introduction of highly efficient immunotherapies, including monoclonal antibodies against integrins (natalizumab), CD52 (alemtuzumab), and CD20 (ocrelizumab, ofatumumab), there is also a considerable proportion of patients who experience ongoing disease activity and progression of disability. Within 20 years of diagnosis, 30–60% of patients with initial episodic clinical attacks followed by complete or partial recovery (so-called relapsing-remitting MS (RRMS)) convert to a secondary progressive disease course (SPMS) with relapse-independent disability progression resulting in severe limitations of the quality of life, whereas others are spared from persisting neurological deficits despite long disease duration and old age [1]. This apparent heterogeneity between individual patients highlights the importance of more personalized treatment approaches, especially in order to prevent disease progression. Real-world cohorts are a key element to address this unmet need, since datasets from large observational studies, registries, and multi-omics approaches allow pharmaceutically independent testing of hypotheses in the presence of high heterogeneity in disease pathology, course, therapy response, and occurrence of side effects. Of similar importance are novel methodologies for prognostication and patient stratification, in particular, in deeply phenotyped (i.e., patients with available data on multiple molecular levels) real-world cohorts.

Prevention and early diagnosis of MS
Insights gained from large international real-world cohorts demonstrate that early efficacious treatment is crucial for the long-term outcome of MS patients. However, there is increasing evidence of substantial neuronal damage already occurring in presymptomatic patients (e.g., in patients with abnormalities in magnetic resonance imaging (MRI) without clinical symptoms, the so-called radiologically isolated syndrome) and even in a prodromal phase that precedes the detection of first abnormalities in MRI. For example, increased neurofilament light chain (NFL) levels, a biomarker of neuronal damage, have been detected in blood samples obtained from seemingly healthy US military personnel up to 6 years before they presented with the first clinical episode of MS [2]. Moreover, large-scale cognitive testing...
of more than 20,000 individuals revealed that men later receiving a diagnosis of MS had lower cognitive scores than healthy controls up to 2 years before their first clinical event [3]. These observations highlight that delaying treatment initiation until clinical disease onset might be too late for preventing long-term progression of physical and cognitive impairment. Thus, strategies that enable the identification of individuals at risk and of patients with presymptomatic MS along with the initiation of preventive measures (e.g., modification of known risk factors like smoking and obesity, disease-specific education, and early detection examinations) might be a key to overcoming MS progression.

To date, studies by the International Multiple Sclerosis Genetics Consortium (IMSGC), an international research collaboration aiming to identify the genetic basis of MS and its disease course, have identified 233 independent genome-wide significant associations with MS susceptibility by leveraging genotype data from more than 48,000 MS patients and almost 70,000 controls [4]. Of note, many of these associations would not have been detected in smaller-scope studies due to minor contributions of individual variants to the overall genetic risk. There have already been attempts, for example, through the development of polygenic risk scores, to leverage the knowledge of these genetic risk variants in order to identify persons at risk to develop MS. In addition, the clinical implementation of new biomarkers such as serum NfL [5] may be feasible in the near future. With regard to enabling an earlier diagnosis, two recent studies conducted in large national registries provide interesting insights into how the population-wide screening of electronic health records could be used to identify MS patients before they perceive signs of neurological deficits. The first is a matched cohort study that used data linked from health administrative and clinical databases from four Canadian provinces and included 14,428 MS patients and 72,059 matched controls. The authors observed a steadily increasing annual healthcare use between 5 years and 1 year before the first demyelinating event [6]. In a second population-based observational study, the occurrence of a variety of clinical disturbances with particular attention to autonomic symptoms, psychiatric conditions, cognitive impairment, fatigue, and pain was compared between 10,204 patients who would later receive a diagnosis of MS or clinically isolated syndrome (i.e., a clinical episode suggestive of MS but not fulfilling the diagnostic criteria of dissemination in time and space) and 39,448 controls. Remarkably, MS patients had a significantly higher risk of presenting with symptoms like gastrointestinal disturbances, anxiety and mood disorders, fatigue, and pain up to 10 years prior to the first mention of an MS diagnosis in their healthcare records. The authors suggested that the integration of these symptoms into the diagnostic procedure might aid in earlier diagnosis [7].

Findings from these real-world cohort studies have considerably contributed to our understanding of MS disease course as they have led to the identification of a presymptomatic phase (the MS prodrome) and have highlighted the importance of timely preventive measures. Moreover, they indicate potential strategies for the early identification of persons at risk.

**Prognostication for personalized treatment**

Large datasets and intelligent computational approaches have laid the foundation for current evidence on demographic, clinical, MRI, and cerebrospinal fluid- and blood-based biomarkers with prognostic potential in MS that may aid patient stratification and consultation. For example, in a recent international collaborative work including almost 3,000 MS patients, higher age at disease onset, reaching moderate disability levels due to persisting neurological deficits reflected by an Expanded Disability Status Scale (EDSS) score of at least 3 points within the first year after disease onset, and impairment of motor functions were associated with aggressive MS [8]. On the other hand, younger age at disease onset, lower number of relapses within the first years after onset, and full recovery from the first relapse were associated with a favorable disease course, as was being female [9]. An additional recent study aimed to define MS subtypes based on a data-driven assessment of MRI alterations [10]. By applying a novel unsupervised machine learning algorithm with the ability to model heterogeneity of phenotypes along with distinct temporal progression patterns in almost 10,000 MRI scans of patients with MS and healthy controls, the authors identified three MRI-based subtypes: cortex-led, normal-appearing white matter-led, and lesion-led. Remarkably, these subtypes differed with regard to disability progression, disease activity, and treatment response, which suggests that they reflect different pathobiological mechanisms relevant to disease manifestation and could be used for patient stratification and personalized treatment decisions [10].

Importantly, a recent genome-wide association study of MS disease progression conducted by the IMSGC was able to demonstrate for the first time that there is a genetic basis for MS severity that is clearly distinguishable from the genetic architecture of MS susceptibility [11]. This highlights the link between the molecular background of MS and its phenotypic presentation. However, genetic variation alone will not be able to unravel a condition as complex as MS, since it is most probable that
hundreds of weak genetic factors interact with each other and the environment to elicit disease phenotypes. Therefore, it is necessary to also investigate data types that reflect biological processes more dynamically, e.g., in an integrative multi-omics approach. For example, quantitative gene expression data obtained from transcriptomic or proteomic studies could be combined with knowledge of genetic risk factors (after solving interface problems with existing databases and data harmonization), as is done in quantitative trait locus analyses that investigate the associations between risk loci and gene expression levels, in order to better understand the mechanisms involved in MS pathogenesis and for the stratification of patients into disease endotypes. To this aim, deeply phenotyped cohorts are needed.

Conclusions
The current major challenges in the management of MS patients include the identification of persons at risk to enable preventive strategies and early diagnosis along with patient stratification for prognostication and targeted treatment decisions. Large real-world cohorts have already contributed to our understanding of pathology and disease entities as well as of treatment responses and associated adverse events. However, in order to further increase our knowledge of risk factors and to avoid persisting and progressing disability, it is necessary to foster methodological innovations that will allow us to acquire more detailed insights into the pathomechanisms, especially of the difficult-to-target local processes within the CNS. A key future task for advancing the goal of eventual translation to the clinic is the generation of large well-characterized and deeply phenotyped longitudinal data-sets of patients of diverse ethnic backgrounds and diverse conditions (e.g., response to nutrition, environment, therapy) to enable sufficiently powered study designs that may yield generalizable results. In our opinion, this can only be achieved through the integration of existing real-world cohorts including biosample collections, in an international and multi-disciplinary collaboration of researchers, clinicians, and patients alike.

Abbreviations
CIS: Clinically isolated syndrome; CNS: Central nervous system; EDSS: Expanded Disability Status Scale; IMMSGC: International Multiple Sclerosis Genetics Consortium; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; NfL: Neurofilament light chain; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis.

Acknowledgements
The authors thank Dr. Cheryl Ernest for proofreading and editing the manuscript.

Authors’ contributions
SE and FZ: conceptualization and writing of the manuscript. The authors read and approved the final manuscript.

Funding
This study was supported by the Deutsche Forschungsgemeinschaft (DFG, SFB CRC-TR-128 to F.Z.).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 30 March 2022   Accepted: 4 April 2022
Published online: 20 April 2022

References
1. Larochelle C, Uphaus T, Prat A, Zipp F. Secondary progression in multiple sclerosis: neuronal exhaustion or distinct pathology? Trends Neurosci. 2016;39(5):325–39.
2. Bjornevik K, Munger KL, Cortese M, Baro C, Healy BC, Niebuhr DW, et al. Serum neurofilament light chain levels in patients with presymptomatic multiple sclerosis. JAMA Neurol. 2020;77(1):58–64.
3. Cortese M, Riise T, Bjornevik K, Bhan A, Farbu E, Grytten N, et al. Preclinical disease activity in multiple sclerosis: a prospective study of cognitive performance prior to first symptom. Ann Neurol. 2016;80(4):66–24.
4. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science. 2019;365(6460).
5. Bittner S, Oh J, Havrdová EK, Tintoré M, Zipp F. The potential of serum neurofilament as biomarker for multiple sclerosis. Brain. 2021;144(10):2954–63.
6. Wijnands JMA, Kingwell E, Zhu F, Zhao Y, Hogg T, Stadnyk K, et al. Early clinical markers of aggressive multiple sclerosis. Brain. 2017;140(5):1400–13.
7. Disanto G, Zecca C, MacLachlan S, Sacco R, Handunnetthi L, Meier UC, et al. Prodromal symptoms of multiple sclerosis in primary care. Ann Neurol. 2018;83(6):1162–73.
8. Malpas CB, Manouchehrinia A, Shamin S, Roos I, Horakova D, Havrdova EK, et al. Early clinical markers of aggressive multiple sclerosis. Brain. 2020;143(5):1400–13.
9. Crielaid L, Kavaliunas A, Ramanujam R, Olsson T, Hillert J, Stridh P, et al. Factors associated with and long-term outcome of benign multiple sclerosis: a nationwide cohort study. J Neurol Neurosurg Psychiatry. 2019;90(7):761–7.
10. Eshagh A, Young AL, Wijeratne PA, Prados F, Arnold DL, Narayanvan S, et al. Identifying multiple sclerosis subtypes using unsupervised machine learning and MRI data. Nat Commun. 2021;12(1):2078.
11. Harroud A, Multiple MS, International Multiple Sclerosis Genetics Consortium. The genetic basis of multiple sclerosis severity suggests central nervous system involvement (ECTRIMS 2021 -P927). Mult Scler J. 2021;27:756.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.