Author/s:
Sharmin, S;Malpas, C;Roos, I;Diouf, I;Alroughani, R;Ozakbas, S;Izquierdo, G;Eichau, S;Horakova, D;Havrdova, EK;Patti, F;Terzi, M;Boz, C;Yamout, B;Khoury, SJ;Onofrj, M;Lugaresi, A;Altintas, A;Prat, A;Girard, M;Duquette, P;Sa, MJ;Spitaleri, D;Sidhom, Y;Gouider, R;Soysal, A;Turkoglu, R;Amato, MP;Fragoso, Y;Kalincik, T

Title:
Early Predictors of Disability in Paediatric Multiple Sclerosis: Evidence from a Multi -National Registry

Date:
2022-09-30

Citation:
Sharmin, S., Malpas, C., Roos, I., Diouf, I., Alroughani, R., Ozakbas, S., Izquierdo, G., Eichau, S., Horakova, D., Havrdova, E. K., Patti, F., Terzi, M., Boz, C., Yamout, B., Khoury, S. J., Onofrj, M., Lugaresi, A., Altintas, A., Prat, A. ,... Kalincik, T. (2022). Early Predictors of Disability in Paediatric Multiple Sclerosis: Evidence from a Multi -National Registry. Journal of Neurology, Neurosurgery and Psychiatry, 93 (12), pp.1322-1329. https://doi.org/10.1136/jnnp-2022-329713.

Title: Early predictors of disability in paediatric multiple sclerosis: evidence from a multi-national registry

Authors:

Sifat Sharmin, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

Charles B Malpas, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Izanne Roos, MD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Ibrahima Diouf, PhD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

Raed Alroughani, MD; Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait

Serkan Ozakbas, MD; Dokuz Eylul University, Izmir, Turkey

Guillermo Izquierdo, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Sara Eichau, MD; Hospital Universitario Virgen Macarena, Sevilla, Spain

Dana Horakova, MD; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Eva Kubala Havrdova, MD; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Francesco Patti, MD; Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania, Italy; Multiple Sclerosis Center, University of Catania

Murat Terzi, MD; Medical Faculty, 19 Mayis University, Samsun, Turkey

Cavit Boz, MD; KTU Medical Faculty Farabi Hospital, Trabzon, Turkey

Bassem Yamout, MD; Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon

Samia J. Khoury, MD; Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon

Marco Onofrj, MD; Department of Neuroscience, Imaging, and Clinical Sciences, University G. d'Annunzio, Chieti, Italy

Alessandra Lugaresi, PhD; IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italia

Ayse Altintas, MD; Department of Neurology, School of Medicine, Koc University, Istanbul, Turkey

Alexandre Prat, MD; CHUM MS Center and Department of neuroscience, Faculty of Medicine, Université de Montréal, Montréal, Canada

Marc Girard, MD; CHUM MS Center and Department of neuroscience, Faculty of Medicine, Université de Montréal, Montréal, Canada

Pierre Duquette, MD; CHUM MS Center and Department of neuroscience, Faculty of Medicine, Université de Montréal, Montréal, Canada

Maria Jose Sa, MD; Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal

Daniele Spitaleri, MD; Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy

Youssef Sidhom, MD; Department of Neurology, Razi Hospital, Manouba, Tunisia

Riadh Gouider, MD; Department of Neurology, Razi Hospital, Manouba, Tunisia

Saloua Mrabet, MD; Department of Neurology, Razi Hospital, LR 18SP03; Clinical Investigation Center Neurosciences and Mental Health, Faculty of Medicine, University Tunis El Manar, Tunis, Tunisia

Aysun Soysal, MD; Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey

Recai Turkoglu, MD; Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

Maria Pia Amato, MD; Department NEUROFARBA, University of Florence, Florence, Italy

Yara Fragoso, MD; Universidade Metropolitana de Santos, Santos, Brazil

Tomas Kalincik, MD; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia on behalf of the MSBase Study Group

Corresponding authors

Professor Tomas Kalincik

Clinical Outcomes Research (CORe) Unit, University of Melbourne, Royal Melbourne Hospital

L4 East, 300 Grattan St, Melbourne, VIC 3050, Australia

Telephone: +61 3 93424404, Fax: +61 3 93495997

Email: tomas.kalincik@unimelb.edu.au

Sifat Sharmin

Clinical Outcomes Research (CORe) Unit, University of Melbourne

L4 East, 300 Grattan St, Melbourne, VIC 3050, Australia

Telephone: +61 3 93424404, Fax: +61 3 93495997

Email: sifat.sharmin@unimelb.edu.au

Word count, manuscript: 2774

Word count, abstract: 249

References: 28

Figures: 5

Tables: 2

Key words: paediatric multiple sclerosis; disease-modifying therapies; disability markers; Bayesian

Abstract

Background Early recognition of markers of faster disability worsening in paediatric-onset multiple sclerosis (MS) is a key requisite of personalised therapy for children with MS at the earliest possible time.

Objective To identify early predictors of rapid disability accrual in patients with paediatric-onset MS.

Methods Using the global MSBase registry, we identified patients who were <18 years at the onset of MS symptoms. The clinico-demographic characteristics examined as predictors of future MS Severity Score (MSSS) included: sex, age at symptoms onset, absence of disability at the initial assessment, and maximum Expanded Disability Status Scale (EDSS) score, relapse frequency, and presence of brainstem, pyramidal, visual, or cerebellar symptoms in the first year. A Bayesian log-normal generalised linear mixed model adjusted for cumulative proportion of time on higher-efficacy disease-modifying therapies (DMTs) was used to analyse the data.

Results 672 patients (70% female) contributing 9357 visits were included. The median age at symptoms onset was 16(quartiles 15-17) years. Older age at symptoms onset (exp(β)=1.10[95% Credible Interval:1.04,1.17]), higher EDSS score (1.22[1.12,1.34]), and pyramidal (1.31[1.11,1.55]), visual (1.25[1.10,1.44]), or cerebellar (1.18[1.01, 1.38]) symptoms in the first year were associated with higher MSSS. MSSS was reduced by 4% for every 24% increase in the proportion of time on higher-efficacy DMTs (0.96[0.93,0.99]).

Conclusions A relatively later onset of MS in childhood, higher disability, and pyramidal, visual, or cerebellar symptoms during the first year predicted significant worsening in disability

in patients with paediatric-onset MS. Persistent treatment with higher-efficacy DMTs was associated with a reduced rate of disability worsening.

Key messages

- Clinical prognostic markers in the first year from symptoms onset could help predicting the risk of faster disability worsening in children with multiple sclerosis (MS).
- Apart from more substantial disability during the first year, these markers also include presence of pyramidal, visual, or cerebellar symptoms.
- Persistent treatment with higher-efficacy disease-modifying therapies has the potential to modify the risk of faster disability accrual in children with MS.

Data availability statement

MSBase is a data processor, and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Each principal investigator will need to be approached individually for permission to access the datasets.

Introduction

Multiple sclerosis (MS) is relatively rare among children, with incidence ranging from 0.13 to 0.66 per 100000 children per year[1], compared to an average of 8 cases per 100000 adults[2]. In children, its clinical course is highly inflammatory with frequent exacerbations (relapses), especially during the initial years following symptoms onset.[3,4] The long-term prognosis of paediatric-onset MS is often poor, with significant limitations in physical capacity reported as early as the third decade of life.[5] With advent of higher-efficacy disease-modifying therapies (DMTs), the past decade has seen substantial advances in clinical management of adult-onset MS. These therapies are most effective in preventing long-term disability when started during the early, typically highly active years after clinical MS onset.[6,7] Two observational studies[8,9] and a randomised clinical trial[10] have recently provided novel insights that will help guide treatment of paediatric-onset MS, paving the way for a more liberal use of higher-efficacy DMTs. Early identification of children at risk of faster disability worsening is a requisite of targeted early use of these therapies, with the aim of optimising long-term outcomes in paediatric-onset MS. Prior studies have identified several potential imaging and clinical prognostic markers available in paediatric-onset MS.[5,8,11-13] In this study, we used a large multi-national cohort to identify predictors of disability as early as first year after the clinical onset of paediatric MS, considering their potential for guiding the use of higher-efficacy DMTs. Of particular interest was the information conveyed by the phenotype of early relapses.

Methods

Participants

We used the international MS registry, MSBase (WHO International Clinical Trials Registry Platform [ACTRN12605000455662]), which prospectively collects observational data as part of routine clinical care from 129 centres in 34 countries, as per the MSBase study protocol.[14,15] Demographic and longitudinal clinical and radiological data from MSBase cohort was extracted in April 2021.

We retrospectively identified patients who were younger than 18 years of age at symptoms onset, with diagnosis of relapsing-remitting MS, clinically isolated syndrome, or radiologically isolated syndrome,[16,17] and had been followed up annually in one of the MSBase centres. Children with onset MS course classified as 'progressive' were excluded. Patients had to have 2 visits at least 12 months apart with disability score recorded and their first neurological assessment completed within one year from symptoms onset. Patients who participated in randomised clinical trials were excluded (due to lack of exact information about treatment exposure).

Outcomes

The study years were split into two non-overlapping periods: data from first 12 months after symptoms onset were used to define the early prognostic factors and disability outcomes were assessed after the first 12 months of disease.

The primary outcome was the Multiple Sclerosis Severity Score (MSSS)[18], a rank of disability normalised for disease duration. EDSS scores recorded within 30 days of a relapse were excluded from the analyses. Heterogeneity in the assessment of EDSS scores was minimised through Neurostatus certification.[19] We analysed multiple eligible MSSS scores per patient.

Secondary outcome was 6-month confirmed EDSS score≥3. The time of reaching this outcome was the time when an EDSS score≥3 was reached for the first time, with confirmation requiring

that a score of ≥3 was sustained over ≥6 months and remainder of the recorded follow-up. Only scores recorded >30 days after a prior relapse were considered for confirmation.

Potential prognostic markers

Potential predictors investigated included sex, age at symptoms onset, absence/presence of disability at the initial assessment (EDSS 0), and maximum EDSS score, relapse frequency, and presence of brainstem, pyramidal, visual, or cerebellar symptoms (either a relapse with the recorded corresponding symptom or worsening in EDSS with the relevant functional system score>0) during the first 12 months. Early activity on MRI of the brain was categorised as absence of a new lesion/ presence of at least one new hyperintense T_2 lesion or gadolinium-enhancing T_1 lesion/ no record from the first 12 months of the disease. The MSBase study protocol recommends that cerebral MRI is performed annually. The used scanning protocols reflect local clinical practices, and represent a broad range – varying from 2D (non-gapped or gapped) or 3D protocols, including a T2/FLAIR/proton density and T1/MPRAGE sequences. A proportion of centres uses gadolinium contrast for routine scans, and an small number of centres uses lesion detection softwares to aid radiology reporting.

Statistical analysis

The primary analysis used log-normal generalised linear mixed effect model to identify predictors of MSSS disability rank among the clinical characteristics recorded in the first year following presentation of MS.

We conducted a secondary analysis with time to reach 6-month confirmed EDSS score 3 as the outcome of interest. A Bayesian proportional hazards model with parametric baseline hazard

modelled using cubic M-splines was designed to identify predictors of reaching the EDSS milestone.

The models were developed within a Bayesian framework and were estimated with Markov chain Monte Carlo sampling. We specified either non-informative flat priors or weakly informative normal priors because we have little prior information for all the parameters to be estimated and we wanted our data to dominate over the prior distribution. Convergence of the simulated chains were accelerated by standardising the continuous covariates to mean 0 and standard deviation 1. A total of 80000 iterations were performed simulating 2 chains of 40000 iterations. 60000 samples were used for inference because the first 10000 of each chain were used as burn-in. The chain convergence was assessed by trace plots and Rhat values with values ≤1.1 indicating convergence. Posterior predictive check was performed to evaluate model fit by comparing the observed outcome with the simulated dataset from the posterior predictive distribution. Generalised linear mixed effect modelling was performed using the R package *brms*[20] and proportional hazards model was implemented using the R package *rstanarm*[21].

Two sensitivity analyses of the primary outcome in relation to relapse in first year were performed: one in which we investigated whether relapse phenotypes (classified as brainstem, pyramidal, visual, and cerebellar) are predictive of MSSS disability rank, and one in which relapse frequency was separated into frequency of relapses with complete and incomplete recovery. We also assessed sensitivity of the primary analysis to only partially available radiological findings by including available brain MRI data recorded in the first year from MS onset.

All models were adjusted for cumulative proportion of time on higher-efficacy DMTs (alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, or

rituximab) during the follow-up, age at the onset of MS symptoms and age at each visit (for the secondary analysis of time to EDSS score 3, age at the EDSS milestone or last recorded visit). In combination, these adjustments also account for disease duration. The secondary analysis was also adjusted for the number of EDSS scores recorded during each year of the follow-up, as this is a known modifier of the risk of capturing confirmed EDSS worsening.[22] We included a random effect term for country to account for potential inter-country variability of prognostics and assessment.

Results

We included 672 patients from 30 countries (Figure 1). Demographic and clinical characteristics of the included patients are reported in Table 1. The median age at MS onset was 16 (quartiles 15-17) years (97% of the cohort represents adolescents<18 years) and majority were female (70%). At the time of entry to the MSBase registry, median EDSS score was 1.5 (quartiles 1.0-2.5) with a mild median improvement to 1.0 (0.0-2.0) at the end of the median follow-up period of 3.3 (quartiles 1.2-7.3) years. Of the 672 patients, 671 had clinically isolated syndrome and 1 patient had radiologically isolated syndrome at inclusion. The majority (88%) of patients converted to relapsing-remitting MS during the recorded follow-up, including the patient with radiologically isolated syndrome (median time to MS …). 91% of the patients fulfilled the 2017 McDonald diagnostic criteria.

Table 2 lists the details of treatment with different DMTs during the available study follow-up. 510 (76%) of 672 patients were treated with DMTs. Of them, 396 started a DMT before the age of 18 years; 108 started a higher-efficacy and 288 a lower-efficacy (interferon beta, glatiramer acetate, dimethyl fumarate, or teriflunomide) DMT. Median disease duration at the time of initiation of their first DMT was shorter in children compared to patients who commenced DMT

after age 18 years (23 vs. 53 weeks). Of the children with MRI data recorded during the first year of their disease, 39% vs. 31% had at least one new MRI lesion reported if they started a DMT before vs. after age 18, respectively. The variability in the use of DMTs in children across countries is represented in Figure 2.

Of the included patients … (…%) first presented with symptoms of MS before age 11.

In the primary analysis (Figure 3), older age at MS onset (exp(β)=1.10 [95% credible interval: 1.04, 1.17]) and a higher EDSS score (1.22 [1.12, 1.34]) in the first year of the disease were associated with higher MSSS disability rank accounting for disease duration. Each 1 step (one standard deviation) increase in EDSS score was associated with increase in MSSS by 22%. Male sex was not found to be predictive of future MSSS (0.96 [0.83, 1.11]). The presence of pyramidal (1.31 [1.11, 1.55]), visual (1.25 [1.10, 1.44]), or cerebellar (1.18 [1.01, 1.38]) symptoms in year 1 were also predictive of higher MSSS. EDSS 0 at the initial assessment was weakly indicative of a favourable prognosis (0.87 [0.71, 1.07]). The trace plots and posterior predictive fit of the primary model are available in the supplemental materials (Supplemental Figures 1 and 2).

We identified 30 patients (out of 672) who reached EDSS score ≥3 after year 1. The secondary analysis (Figure 4) showed that children who were relatively older at symptoms onset (Hazard Ratio, HR=6.95 [95% credible interval: 3.67, 13.46]) or experienced pyramidal symptom (3.61 [1.22, 12.18]) in the first year were at a substantially higher risk of reaching EDSS score 3. The hazard of reaching EDSS score 3 in male children appeared to be 2-fold higher than in female children (2.09 [0.90, 4.48]), although the association did not reach the level of statistically supported evidence.

The sensitivity analysis (Figure 5) modelling phenotypes of relapses recorded during year 1 showed that the presence of brainstem relapse in the first year was a favourable prognostic sign ($\exp(\beta)=0.81$ [95% credible interval: 0.69, 0.94]). Second sensitivity analysis, which separated the information about relapses during year 1 into the frequency of relapses with complete and incomplete recovery, showed that a higher MSSS disability rank was seen among patients with greater number of relapses with incomplete recovery (1.15 [1.01, 1.31]). In comparison, the association between relapses with complete recovery and MSSS was 1.06 [0.95, 1.18]. Third sensitivity analysis included available MRI data from the first year of disease among 279 patients. It suggested that the presence of a new hyperintense T2 lesion or gadolinium-enhancing T1 lesion tended to predict a marginally lower future MSSS (0.81 [0.66, 0.99]). Of note, 91% of the patients with at least one new MRI lesion in year 1 were treated with DMTs and 64% of them were treated with higher-efficacy therapies. On the other hand, 77% of the patients with no new MRI lesion in the first year were treated with DMTs of whom only 38% were treated with higher-efficacy therapies.

Across all the models, we have explored an adjusted association between the time treated with higher-efficacy DMTs and the probability of less severe disability. Importantly, a longer time spent on higher-efficacy DMTs was associated with improved disease prognosis. A 4% lower MSSS (0.96 [0.93, 0.99]) was estimated for a 24% (one standard deviation) increase in the proportion of time patients spent on higher-efficacy DMTs. A 41% reduction in the hazard of reaching EDSS score 3 was estimated for a 28% increase in the proportion of time spent on higher-efficacy DMTs.

Discussion

Using the largest multi-national MS registry, we have studied predictors of disability available within one year from the onset of multiple sclerosis symptoms in children. This approach enables clinicians to prognosticate as early as during clinically or radiologically isolated syndrome. The study showed that more severe disability in children and adolescents<18 years with paediatric-onset MS is predicted by several clinical characteristics observed during the first year of the disease. These include older age at MS onset, more severe disability during the first year of the disease, and presence of pyramidal, visual, or cerebellar symptoms or signs, which are all predictive of higher disability rank (quantified with MSSS and accounting for time from MS onset).

Interestingly, visual symptoms, presenting either as a relapse or abnormal findings on a neurological assessment, were also predictive of disability worsening. This is in contrast to findings from some of the other cohort studies, which suggested favourable prognosis of initial visual symptoms in adults and children diagnosed with MS[23,24]. On the other hand, a recent study in an Italian cohort of 123 patients with paediatric-onset MS identified optic nerve lesions on brain MRI at disease onset as predictors of 9-year disability[8].

There is a consensus that older age at MS onset, higher EDSS, and presence of pyramidal symptoms are associated with more severe disability in the future.[12,25] Newly, we have identified early cerebellar symptoms as being predictive of higher MSSS disability rank in paediatric-onset MS. This observation complements the negative prognostic value of early cerebellar signs in adults with MS.[26] Our previous study in adult MS identified lower rate of complete recovery from pyramidal and cerebellar relapses.[27] In our present study, an association between the frequency of relapses early after MS onset with disability outcomes was only weak. This suggests that regenerative capacity within the CNS among children shortly after the onset of MS

is probably substantial, thus mitigating the short- to medium-term impact of the early inflammatory episodes on long-term deterioration of neurological function.[28]

In contrast with a study from a cohort of 127 children in Kuwait, which reported an increased risk of secondary progression in paediatric MS patients with brainstem involvement at MS onset, our sensitivity analysis identified brainstem relapse in the first year as a favourable prognostic marker of slower disability accrual.[23,25] We have previously shown a similar association among 10513 adults with MS[26] and a higher likelihood of complete recovery from relapses that present with brainstem symptoms[27]. Interestingly, recovery of brainstem functional system score within 30 days after onset of a relapse is greater in paediatric MS compared to adults.[28]

A recent study documented higher chance of disability accumulation over the long-term in patients with paediatric-onset MS with more radiological activity (≥2 new T2 lesions) in the first 2 years of the disease.[8] We investigated MRI activity in the first year and found that the presence of a new hyperintense T_2 lesion or gadolinium-enhancing T_1 lesion was a positive prognostic marker, predictive of lower MSSS disability rank. This could be at least partly attributed to the personalisation of treatment choice in children with radiologically more active MS, where higher-efficacy therapies have now become available. In fact, a considerable number of patients included in the present study commenced natalizumab, fingolimod, or dimethyl fumarate before age 18. Importantly, the proportion of time that patients were treated with higher-efficacy DMTs was consistently associated with less severe disability across all our analyses.

Evidence that supports the use of higher-efficacy therapies in paediatric MS is emerging. So far the only phase 3 clinical trial reported an effect of fingolimod on reducing disability in paediatric MS.[10] Two recent observational studies suggested better disease activity control with higher-efficacy therapies[8,9], but did not examine its cumulative effect. Our study is the first to show a

significant slowing of disability accumulation associated with a longer time spent on higher-efficacy therapies among patients with paediatric-onset MS.

This study is limited by the size of the eligible study cohort – mainly determined by the low prevalence of paediatric-onset MS and the requirement to capture and monitor the disease within one year from its first clinical presentation. However, in the context of the data that are presently available globally, this cohort is considered large. The cohort from the large international registry represents patients from 30 countries from all populated continents. Detailed clinical follow-up, including disability quantified with EDSS score, from the earliest stages after first clinical presentation of paediatric-onset MS from different geographical regions allowed us to capture the heterogeneity in approaches to treatment, due to differences in drug licensing and availability. The use of multi-national registry data creates potential for further heterogeneity in patient selection and inclusion; this heterogeneity was modelled through inclusion of a random effect in the analyses. The Bayesian approach serves to provide more accurate estimates than conventional frequentist approach by accounting for a greater degree of uncertainty in parameter estimation. Unlike the frequentist approach, Bayesian modelling is not reliant upon the large sample theory and thereby further offsets the limited availability of data from paediatric-onset MS to enable unbiased estimation of the value of prognostic markers. The international multicentric nature of the registry limited our ability to utilise harmonised, detailed, volumetric MRI information to further enhance prognostics. However, we were able to incorporate a simplified analysis of the prognostic value of early radiological activity among patients in whom brain MRI data were recorded. Information about spinal cord involvement early in MS carries a valuable prognostic value. However, the data on spinal cord lesions was unavailable in most of the patients and was not included in the analysis. Body mass index represents another recently

confirmed prognostic marker in MS. As MSBase does not systematically capture patients' weights, evaluation of this information is better suited for inception cohorts.

In summary, this study identified readily accessible clinical characteristics that will help clinicians prognosticate disability trajectories in patients with paediatric-onset MS as early as within a year from the first symptom of MS. These include age at the onset of paediatric MS and overall disability as well as presence of pyramidal, visual, or cerebellar symptoms/signs during the first year of the disease. The accrual of disability is reduced among patients who persist with treatment with higher-efficacy DMTs. The improved prognostic information and initial insights into the effect of persistent potent immunotherapy are key steps towards personalisation of therapy for children with MS.

Ethics approval

MSBase was approved by the Melbourne Health Human Research Ethics Committee and by the site institutional review boards, or exemptions were granted according to the local regulations. Written informed consent was obtained from all enrolled patients or their guardians.

Role of the funding source

This study was conducted separately and apart from the guidance of the funding source. The corresponding authors confirm that they had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

We thank the children and parents who contributed to the MSBase registry, the participating neurologists, and the principal investigators for supporting this study.

The list of MSBase Study Group contributors is provided in supplemental materials. This study was funded by the NHMRC Australia [grant 1129189 and fellowship 1140766]. The MSBase Foundation is a not-for-profit organisation that receives support from Merck, Biogen, Novartis, Roche, Bayer Schering, Sanofi Genzyme, and Teva Pharmaceutical Industries.

Declaration of interests

Sifat Sharmin has nothing to disclose.

Charles Malpas has nothing to disclose.

Izanne Roos served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen.

Ibrahima Diouf has nothing to disclose.

Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.

Serkan Ozakbas has nothing to disclose.

Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.

Sara Eichau received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva.

Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme, and Novartis, as well as support for research activities from Biogen and Czech Ministry of Education [project Progres Q27/LF1].

Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has been a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; has been supported by the Czech Ministry of Education research project PROGRES Q27/LF1.

Francesco Patti received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association and University of Catania.

Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Bassem Yamout has nothing to disclose.

Samia J. Khoury received personal compensation for participation in the Roche MaeStro Exchange Program and in Merck-Serono medical advisory board.

Marco Onofrj has nothing to disclose.

Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Bristol Myers Squibb, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva. Her institutions have received research grants from Novartis [last 4 years].

Ayse Altintas received personal fees and speaker honoraria from Teva, Merck, Biogen - Gen Pharma, Roche, Novartis, Bayer, Sanofi-Genzyme; received travel and registration grants from Merck, Biogen - Gen Pharma, Roche, Sanofi-Genzyme and Bayer.

Alexandre Prat has nothing to disclose.

Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD. He has also received a research grant from Canadian Institutes of Health Research.

Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

Maria Jose Sa has nothing to disclose.

Daniele Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck.

Youssef Sidhom has nothing to disclose.

Riadh Gouider has nothing to disclose.

Aysun Soysal has nothing to disclose.

Recai Turkoglu has nothing to disclose.

Maria Pia Amato received honoraria as a consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck, Teva and Sanofi-Aventis; has received research grants by Biogen, Bayer-Schering, Merck, Teva and Novartis.

Yara Fragoso has nothing to disclose.

Tomas Kalincik served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

Author contributions

Sifat Sharmin conceptualised and designed the study, carried out statistical analyses, interpreted the results, have drafted, and edited the manuscript. Tomas Kalincik conceptualised and designed the study, contributed data, interpreted the results, and have edited the manuscript.

Charles Malpas and Ibrahima Diouf contributed to the concept of the study, interpreted the results, and have edited the manuscript. Izanne Roos contributed to the concept of the study, contributed data, interpreted the results, and have edited the manuscript.

Raed Alroughani, Serkan Ozakbas, Guillermo Izquierdo, Sara Eichau, Dana Horakova, Eva Kubala Havrdova, Francesco Patti, Murat Terzi, Cavit Boz, Bassem Yamout, Samia J. Khoury, Marco Onofrj, Alessandra Lugaresi, Ayse Altintas, Alexandre Prat, Marc Girard, Pierre Duquette, Maria Jose Sa, Daniele Spitaleri, Youssef Sidhom, Riadh Gouider, Aysun Soysal, Recai Turkoglu, Maria Pia Amato, and Yara Fragoso recruited patients, contributed data, interpreted the results, and have edited the manuscript.

References

1. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. The Lancet Neurology. 2014;13(9):936-948.
2. Koch-Henriksen N, Magyari M. Apparent changes in the epidemiology and severity of multiple sclerosis. Nature Reviews Neurology. 2021:1-13.
3. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Archives of neurology. 2009;66(1):54-59.
4. Benson L, Healy B, Gorman M, Baruch N, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Multiple sclerosis and related disorders. 2014;3(2):186-193.
5. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. The Lancet Neurology. 2007;6(10):887-902.
6. He A, Merkel B, Brown JWL, Ryerson LZ, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. The Lancet Neurology. 2020;19(4):307-316.
7. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. The Lancet Neurology. 2019;18(10):973-980.
8. De Meo E, Bonacchi R, Moiola L, Colombo B, et al. Early Predictors of 9-Year Disability in Pediatric Multiple Sclerosis. Annals of Neurology. 2021.

9. Krysko KM, Graves JS, Rensel M, Weinstock-Guttman B, et al. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. Annals of neurology. 2020;88(1):42-55.

10. Chitnis T, Arnold DL, Banwell B, Brück W, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. New England Journal of Medicine. 2018;379(11):1017-1027.

11. McKay KA, Hillert J, Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. Neurology. 2019;92(24):e2764-e2773.

12. Santoro JD, Waltz M, Aaen G, Belman A, et al. Pediatric Multiple Sclerosis Severity Score in a large US cohort. Neurology. 2020;95(13):e1844-e1853.

13. De Meo E, Filippi M, Trojano M, Comi G, et al. Comparing natural history of early and late onset pediatric multiple sclerosis. Annals of Neurology. 2022;91(4):483-495.

14. Butzkueven H, Chapman J, Cristiano E, Grand'Maison F, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Multiple Sclerosis Journal. 2006;12(6):769-774.

15. Registry MN-I. *MSBASE REGISTRY OBSERVATIONAL STUDY PROTOCOL*. 2020.

16. Polman CH, Reingold SC, Banwell B, Clanet M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of neurology. 2011;69(2):292-302.

17. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018;17(2):162-173.

18. Roxburgh R, Seaman S, Masterman T, Hensiek A, et al. Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. Neurology. 2005;64(7):1144-1151.

19. D'Souza M, Yaldizli Ö, John R, Vogt DR, et al. Neurostatus e-Scoring improves consistency of Expanded Disability Status Scale assessments: a proof of concept study. Multiple Sclerosis Journal. 2017;23(4):597-603.

20. Bürkner P-C. Advanced Bayesian multilevel modeling with the R package brms. arXiv preprint arXiv:170511123. 2017.

21. Brilleman SL, Elci EM, Novik JB, Wolfe R. Bayesian survival analysis using the rstanarm R package. arXiv preprint arXiv:200209633. 2020.

22. Kalincik T, Cutter G, Spelman T, Jokubaitis V, et al. Defining reliable disability outcomes in multiple sclerosis. Brain. 2015;138(11):3287-3298.

23. Alroughani R, Ahmed SF, Al-Hashel J. Pediatric-onset multiple sclerosis disease progression in Kuwait: a retrospective analysis. Pediatric neurology. 2015;53(6):508-512.

24. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain. 2003;126(4):770-782.

25. Akhtar S, Alroughani R, Ahmed SF, Al-Hashel JY. Prognostic indicators of secondary progression in a paediatric-onset multiple sclerosis cohort in Kuwait. Multiple Sclerosis Journal. 2016;22(8):1086-1093.

26. Le M, Malpas C, Sharmin S, Horáková D, et al. Disability outcomes of early cerebellar and brainstem symptoms in multiple sclerosis. Multiple Sclerosis Journal. 2021;27(5):755-766.

27. Kalincik T, Buzzard K, Jokubaitis V, Trojano M, et al. Risk of relapse phenotype recurrence in multiple sclerosis. Multiple Sclerosis Journal. 2014;20(11):1511-1522.

28. Chitnis T, Aaen G, Belman A, Benson L, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. Brain. 2020;143(9):2733-2741.

Table 1: Demographic and clinical characteristics of patients included in the study

Characteristic	**Median (quartiles)[a]**
Patients, n (% female)	672 (70)
Age at symptom onset, year, n (%)	
<10	19 (3)
10-12	31 (5)
13-15	178 (26)
16-17	444 (66)
Age at symptom onset, year	16 (15-17)
Age at inclusion, year	17 (15-18)
Disease duration from symptom onset to inclusion, days	71 (26-181)
Follow-up duration, days	1204 (446-2651)
Disease course, n (%)	
At inclusion	
Clinically isolated syndrome	671 (99.85)
Radiologically isolated syndrome	1 (0.15)
At censoring	
Clinically isolated syndrome	73 (11)
Relapsing-remitting	593 (88)
Secondary progressive	6 (1)
EDSS score	
At inclusion	1.5 (1.0-2.5)
At censoring	1.0 (0.0-2.0)
Annualised visit density	9 (4-19)

[a]unless otherwise indicated

Table 2: Treatment with disease-modifying therapies during study period

Disease-modifying therapy	Number (%[a]) of patients treated	Recorded time on therapy in years; Median (quartiles)	Number (%[a]) of patients treated before age 18
Alemtuzumab	2 (0.30)	2.6 (2.3, 2.8)	0 (0)
Cladribine	8 (1.19)	1.2 (0.5, 1.7)	1 (0.15)
Daclizumab	2 (30)	2.4 (1.6, 3.3)	0 (0)
Fingolimod	143 (21.28)	2.7 (1.0, 4.5)	43 (6.40)
Mitoxantrone	7 (1.04)	1.4 (0.6, 1.6)	2 (0.30)
Natalizumab	117 (17.41)	2.6 (1.7, 4.3)	57 (8.48)
Ocrelizumab	25 (3.72)	1.5 (0.8, 2.1)	4 (0.59)
Rituximab	13 (1.93)	0.5 (0.5, 1.1)	7 (1.04)
Interferon beta	361 (53.72)	2.5 (1.1, 4.9)	273 (40.63)
Glatiramer acetate	88 (13.09)	1.4 (0.6, 3.1)	55 (8.18)
Dimethyl fumarate	59 (8.78)	1.3 (0.5, 2.6)	23 (3.42)
Teriflunomide	25 (3.72)	1.1 (0.8, 2.2)	8 (1.19)

[a] Denominator is total number of patients (672) included in the study

Figure Legends

Figure 1: CONSORT chart of patient disposition

Figure 2: Variability in the use of higher-efficacy disease-modifying therapies in children with MS across MSBase centres in the (A) World and (B) Europe and Middle East

Figure 3: Primary analysis: early predictors of MSSS disability rank

The plot shows parameter estimates, exp(β), and 95% credible intervals from the Bayesian log-normal generalised linear mixed effect model with random effects for patient and country, adjusted for age at each MSSS score. Brainstem, pyramidal, visual, and cerebellar symptoms refer to either a relapse with the recorded corresponding symptom or worsening in EDSS with the relevant functional system score >0.

Figure 4: Secondary analysis: early predictors of 6-month confirmed and sustained EDSS 3

The plot shows hazard ratio and 95% credible intervals from the Bayesian mixed effect survival model of time to EDSS score 3, with a random effect for country, adjusted for number of EDSS scores recorded during each year of the follow-up and age at EDSS milestone or last visit. Brainstem, pyramidal, visual, and cerebellar symptoms refer to either a relapse with the recorded corresponding symptom or worsening in EDSS with the relevant functional system score >0.

Figure 5: Sensitivity analyses: MRI activity and phenotypes of early relapses as predictors of MSSS disability rank

The plots show parameter estimates, exp(β), and 95% credible intervals from the Bayesian log-normal generalised linear mixed effect models with random effects for patient and country, adjusted for age at each MSSS score. MRI activity (left) and phenotypes of the relapses (right) recorded during the first year were analysed as dummy variables.

Supplemental Figure S1: Trace plot of the Bayesian log-normal generalised linear mixed effect model of the primary analysis

Supplemental Figure S2: Posterior predictive fit of the Bayesian log-normal generalised linear mixed effect model of the primary analysis

Supplemental Table: List of MSBase contributors