

**New epidemiological data of multiple sclerosis, the impact
of psychopathological symptoms on the health-related
quality of life of multiple sclerosis patients**

Ph.D. thesis booklet

Tamás István Biernacki, M.D.

Clinical and Experimental Neurosciences Program Doctoral School of Clinical
Medicine, Faculty of Medicine, University of Szeged

Supervisor: Krisztina Bencsik, M.D., Ph.D, med. habil.

Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of
Szeged

2020. 10. 13.

Introduction

Multiple sclerosis (MS), although considered as a rare disease, is the most common chronic, autoimmune, demyelinating, and neurodegenerative disease of the central nervous system. MS is characterized by continuous inflammation, demyelination, remyelination, axonal and blood-brain-barrier damage throughout its natural history, though the intensity and presence of these processes change through time, as the disease progresses. In the „early days”, when the life expectancy of the general population did not exceed the life expectancy of an MS patient by much MS was believed to only influence the patients’ quality of life, but do not affect the lifespan and mortality. This point of view was disproved in the late ’80s when it was shown that more than half of the MS patients die due to MS-related causes, a finding which was corroborated by many following studies. Subsequently, MS was shown to not only alter the patients’ cause of death but to drastically decrease their life expectancy as well. After the introduction of disease-modifying treatments (DMT) the mortality of MS patients drastically fell, they became likely to survive longer than their life expectancy at birth. As increasingly more DMTs became available and they became more effective at halting disease progression and a rise in survival followed a new, unmet medical need rose among MS patients. Not only the net amount of gained life years began to matter, but the quality of those years as well. As expected, several studies have shown MS patients’ health-related quality of life (HRQoL) to be worse compared to the general population, furthermore when compared to patients suffering from other autoimmune conditions MS patients were found to have the lowest perceived HRQoL. In recent years several studies have come to the same conclusion, that the psychological symptoms accompanying MS have a serious impact on the HRQoL of the patients, which effect is independent of their physical state. Lately, several previously under measured and neglected symptoms of MS have been identified to influence the patients’ HRQoL. However, the independent contribution and the actual level of impact of these already known, and several other, potential influencing factors on the HRQoL of PwMS, and the presence of a potential gender difference is only scarcely, if ever investigated. In addition to the significant amount of attention, the psychopathological symptoms and quality of life research has received in the past few years a new phenotype-based classification system, revisions to the McDonald criteria, and the very first international guidelines on the pharmaceutical treatment of MS were also recently published. The new revisions to the McDonald criteria make the diagnosis of MS possible faster than ever before without compromising specificity. The new therapeutic guidelines introduced in 2018 break with the

previously used escalative approach in the treatment of MS, they advise the treatment of every MS patient as soon as possible, with a DMT matching the patient's disease activity. In accordance, the novel phenotypic classification of MS breaks with the principles of prior classifications, and instead of classifying MS by disease courses, it lays much more emphasis on the presence or lack of activity and progression of the disease, both of which are heavily influenced by the DMTs used in MS.

Aims

In our first study, we aimed to give fresh epidemiological data from a previously surveyed area using the very new diagnostic and classification criteria for MS, also to provide information about the disease-, disability, and treatment status of a previously assessed cohort in light of the new therapeutic guidelines and new DMTs. In our second assessment, we aimed to explore the independent effect and level of influence of various clinical, sociodemographic, and psychological aspects on the HRQoL of MS patients. And also to explore whether there is a difference between the genders regarding these determinants and their level of effect on the HRQoL of men and women.

Patients and methods

For the epidemiological assessment, all known MS patients living in Csongrád-Csanád county (a total of 420 patients) were included. All patient data were extracted from the Multiple Sclerosis Register of the Department of Neurology of the University of Szeged, all data reflected the state of the patients on the prevalence day of the 1st of January 2019. Every patient was diagnosed according to the respective international guidelines at the time of diagnosis and re-evaluated based on the revisions of these guidelines thereafter. Imaging was consistently done in adherence to the latest MAGNIMS guidelines. After the diagnosis of MS was established every patient with clinically isolated syndrome (CIS) or relapsing-remitting (RR) disease type irrespective of treatment status, and patients with a progressive disease type who received immunomodulatory therapy were routinely examined every 3 months. Every other patient underwent a routine check-up at least annually. Patients with a diagnosis of CIS were advised to annually attend a routine check-up indefinitely, unless another disease responsible for their symptoms was diagnosed in the meantime or disease activity presented, from which point the regular visit schedule was recommended (ie. at least every 3 months). An unscheduled,

urgent appointment was always provided for the patients in the event of a relapse. If indeed a relapse was the cause of the patient's symptoms before the initiation of intravenous corticosteroids, a contrast-enhanced MRI scan was always obtained. Patients who were diagnosed with CIS underwent control brain MRI examinations 3 and 6 months after the diagnosis, and yearly thereafter if no unequivocal pathology was confirmed on the control scans. Every patient with a "classical" RR disease type underwent re-evaluation for secondary progressive disease course at the time of every visit to our clinic using the objective, 3-strata criteria proposed by Lorscheider et al. For the phenotypic classification, we used the criteria proposed by Lublin et al. The 2013 European standard population was used as reference population in the direct standardization for calculating the standardized prevalence values.

For our second study, a total of 322 CIS/RR patients with an EDSS score of less than 6.5 have been enrolled from the MS outpatient clinics of the Department of Neurology of the University of Szeged, the Jahn Ferenc Dél-Pest Hospital of Budapest, and the Markhot Ferenc Teaching Hospital of Eger. For patients from Eger and Budapest, the patient data (sociodemographic, clinical, and psychological) were obtained from the patient documentation supplied by the patient's treating physician. Data of patients from Szeged were acquired from the multiple sclerosis registry of the Department of Neurology of the University of Szeged. For the evaluation of the patients' physical status the EDSS scale was used, for the assessment of cognitive impairment, depressive symptoms, and fatigue the BICAMS, BDI, and FIS questionnaires were administered. The cohort's health-related quality of life was measured by the MSQoL-54 survey. To determine the different variables' level of influence on the HRQoL of the patients we used the model-free partial least squares regression (PLS) model. In adherence with international standards, an assessed predictive factor was considered to have a meaningful impact on a given subscale of the MSQoL-54 survey, if the given parameter's variable importance of projection (VIP) score was ≥ 1 . The VIP scores are non-binary, the greater the score, the more important a given variable is considered to be to the model. To evaluate any potential differences between the clinical and sociodemographic variables of the patients we used one-way ANOVA and Fisher's exact test. For the statistical analyses SPSS version 22.0 was used in both studies.

Results

Since the last sampling of the same area was conducted in 2011, 30 MS patients had died, 28

had moved away from the area, meanwhile, 108 new cases were discovered. Crude prevalence for the whole cohort was 105.3/100,000, 56.5/100,000 for men, and 149.3/100,000 for women, respectively. The standardized prevalence for the whole cohort was 101.8/100,000. Age- and sex-adjusted, standardized prevalence was 53.9/100,000 for men and 144.8/100,000 for women. Using the classical disease course definitions 12 patients (2.86%) were identified with CIS, 30 (7.14%) with primary progressive (PP), 102 (24.29%) with secondary progressive (SP), and 276 (65.71%) with RR disease type. Based on the novel phenotypic classification 288 patients (68.57%) were identified with a RR phenotype disease, of which 12 patients (4.16%) had only a single attack, thus were classified as CIS. Progressive disease was observed in 132 patients (31.43%). After stratification by phenotype and treatment status from the 276 RR patients 28 (9.82%) subject's disease showed activity despite being treated, 15 (5.20%) persons received no treatment despite showing disease activity. The vast majority of RR patients (202 persons, 70.13%) showed no disease activity whilst being treated. A total of 43 people (14.93%) were free of disease activity without a disease-modifying treatment (DMT), of whom 20 patients had one episode of isolated optic neuritis, but with additional diagnostic measures according to the latest McDonald criteria the diagnosis of definite MS could be made. Among patients with a progressive phenotype disease activity could be established in 31 patients; 23 persons' (17.42%) disease showed progression adjacent to activity, whilst progression wasn't seen despite disease activity in 8 patients (6.06%). A total of 53 (40.15%) patients with progressive disease showed no progression nor disease activity, while no activity, but progression was seen in 48 (36.36%) subjects. The overwhelming majority (341, 81.19%) of our patients had received some kind of immunomodulatory treatment for MS at any given time during their disease. At the time of sampling 312 patients (74.28%); 230 (79.86%) patients with an RR disease type and 72 patients (54.54%) with progressive disease type were treated. A total of 178 patients received platform therapies, and 134 were prescribed a highly active disease-modifying treatment (HADMT). As a first choice, 307 patients received platform drugs and 34 patients were started on a HADMT from the beginning of their treatment. The use of platform drugs was more common among RR patients (134 patients on platform vs. 68 on HADMT) than among patients with progressive disease (34 patients on platform vs. 48 on HADMT). The majority of our patients (134, 31.9%) were using their first choice of DMTs, treatment change was necessary once, twice, and thrice in the case of 103, 50, and 23 patients, respectively. Four and 5 treatment change was necessary only with 1-1 patient.

The cohort in our study for determining the influencing factors of MS patients' HRQoL consisted of 322 patients (102 - 31.6% men, and 220 - 68.4% women). The only difference between the sociodemographic and other attributes of the sexes was the higher presence of cognitive impairment among men ($p=0.002$). When the cohort was evaluated as a whole only depression, overall fatigue, and its composites (only physical, social, and cognitive fatigue were evaluated in our study) were observed to have a ubiquitous and profound effect on every subscale of the HRQoL composite. The rest of the evaluated factors not only did influence fewer subscales but also did it with a lower power of effect. Age and the patients' EDSS score had an impact on only 3, and 2 of the measured subscales, meanwhile disease duration, the level of education, and the presence of cognitive impairment did not have a clinically meaningful effect on any of the evaluated subscales when the cohort was assessed as a whole. When the sexes were compared differences were found between the genders on 10 domains. Of all the evaluated factors depression and total fatigue were the only variables to have a major impact on all of the 14 examined domains of HRQoL ($VIP > 1$) for both genders. In the case of men, in addition to total fatigue and depression, at least one other determinant was found to have a negative effect on the HRQoL in 9 domains, while for women such was found only in two domains.

Discussion

Our findings of the distribution of the traditional disease courses in our cohort fell in line with recent data based on large registries from both low and high prevalence countries across Europe. Comparing our recent results with data from previous examinations of the same geographical location we observed a continuous rise in the prevalence and female:male ratio of MS, which is also in accordance with both current international and national findings in the literature. Several factors have been proposed to be the cause of this tendency (most of which are valid for Hungary as well), however, no unequivocal explanation for this rise in prevalence has been born yet. Possible reasons (among others) may be the recent advancements in the diagnostics and treatment of MS, which resulted in faster diagnosis, rapid treatment, and increased overall survival of the patients, which may, at least in part, be responsible for the observed rise in both incidence and prevalence of MS. Despite this rise in prevalence and incidence, based on our current findings and previous epidemiological data from the same region Hungary is still considered a medium-risk country for MS from an international perspective. The high ratio of treated patients (83.33% for RR/CIS and 62.1% for progressive phenotype) and their disease

activity status is in line with the scarce amount of data found in the literature. Most of the RR patients were successfully treated with their current DMT, 93% of them only required 2 or less DMT change to achieve disease stability. More progressive, than RR patients have commenced their treatment with platform therapies (87.4% vs. 75.34%), but the current use of HADMTs was more common among patients with progressive disease. Decreased usage of platform therapies is expected to be seen in the near future, as several HADMTs are in the pipeline for the treatment of both RR and progressive MS.

The model-free PLS analysis indicated that in our cohort depression and fatigue had a ubiquitous, powerful effect on all subscales of the MSQoL-54, while the other examined factors had a less pronounced negative influence on a variety of subscales. Also, different factors with differing power were found to influence different aspects of the HRQoL of men and for women; when compared, differences were found between the genders on 10 domains. In the case of men, in addition to total fatigue and depression, at least one other determinant was found to have a negative effect on the HRQoL in 9 domains, while for women such was found only in two domains. Literature about the gender-specific impact of MS on the patients' HRQoL is scarce. Only a few studies have explored this question, have found that men perceive their HRQoL significantly worse than women, especially in the physical, social functioning, and vitality domains. None of these studies have explored, however, whether there is a difference in the very factors that influence the HRQoL of men and women. Information about gender's effect on the HRQoL of PwMS is scarce in the literature, ours is among the first studies to show that different factors with different power determine the HRQoL of the genders.

Conclusion

Our study is the first in the literature, that supplies epidemiological information about MS using the latest diagnostic guidelines and phenotypic classification system. Our findings of the rising prevalence and the gender ratio shifting further towards women are in line with most recent reports, additionally, the observed stable incidence rate is also consistent with data found in the literature. In addition, ours is the second to the Finnish cohort that gives information about the treatment status of the patients in addition to prevalence data and not solely the number of patients with different disease courses. Our work is, however, the first in the literature, that simultaneously gives detailed data about the physical status, treatment status, and disease course distribution of an MS cohort, does it using the most up to date classification and diagnostic criteria. Even though our sample size is relatively small in comparison to other

epidemiological studies – predominantly originating from northern countries – our findings regarding the distribution of the disease courses are similar to those seen in a most recent report from Finland. Epidemiological data from the Central European region based on the recent diagnostic and classification criteria were lacking for MS, which demand our study addressed.

Prior to our study all previous reports addressing the HRQoL of MS patients only focused on one or a very select few factors that might influence the patients' HRQoL. Ours was the first study in the literature that has examined the effect of many determinants simultaneously on several distinct aspects of one's HRQoL. Furthermore, our study is exceptional, as compared to other studies we have examined a large, young, homogenous population that was in good health despite the relatively long average disease duration, also other than the prevalence of cognitive impairment there was no difference between women and men in any attributes. Our findings thus cannot be attributed to the patients' bad physical state, cognitive decline, or the distorting effect of the psychopathological symptoms. Our results regarding fatigue and depression corroborate other recent studies' findings; we too have found these two factors to be the main determining factors of MS patients HRQoL many years into their disease, not only in the short period of time following disease onset and diagnosis, as it was previously thought. However, we have shown that several other factors in play have a significant influence on a number of different aspects of the patients' HRQoL. Furthermore, we have demonstrated that different factors with different power influence the HRQoL of men and women.

Our findings further underline and emphasize the fact that in contrast to traditional belief not one's physical state, but the much less evaluated psychological burdens (especially fatigue and depression) are the main determinants of the HRQoL of MS patients. The involvement of psychological and psychiatric specialists and teamwork for the proper management of patients burdened by MS is called for, as many of the shown factors that play a major role in determining the patients' HRQoL have been shown to be able to be ameliorated and managed by not only a psychopharmacological but by a psychotherapeutic approach as well.