New data in the epidemiology of multiple sclerosis in Hungary

Summary of Ph.D. Thesis

ZSANETT FRICSKA-NAGY, M.D.

Department of Neurology
Faculty of Medicine
University of Szeged

Szeged
2016
Original publications related to the Ph.D. thesis


**IF: 3.26**


**IF: 2.395**


**IF: 0.884 (2014)**

Original publications connected to the Ph.D. thesis


**IF: 0.884 (2014)**


**IF: 2.324 (2009)**


**IF: 1.681**

IV. Losonczi E, Bencsik K, **Fricska-Nagy Z**, Honti V, Szalczer E, Rajda C, Illes Z, Matyas K,

IF:2.841


IF:3.312


IF: 1.295


IF:2.472

Cumulative impact factor: 20.464
I. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. In the world, approximately 2.5 million people have MS. As regards the prevalence of MS, Hungary is a medium-risk country. In Csongrád County, the crude prevalence of MS was found to be 62/100,000 in 2001.

The etiology of MS is unknown. The role of genetic factors in MS susceptibility was confirmed by several cross-sectional studies of patients with MS and their families, as well as by twin studies. According to the data of the International Multiple Sclerosis Genetics Consortium (IMSGC), over 100 associated genes were confirmed. The principal environmental factors are the viral infections, smoking, stress and the relative deficiency of vitamin D.

MS occur in four clinical forms. These are the relapsing-remitting (RRMS), the secondary progressive (SPMS), the primary progressive (PPMS) and the progressive-relapsing (PRMS) clinical courses. The symptoms and signs of MS are very diversified. With physical examination, the patients' rate of disability can be determined by the neurologist. The generally used score to define the level of disability is the Expanded Disability Status Scale (EDSS) score. Several aspects of MS are not detectable by EDSS. These aspects are fatigue, depression, pain, sexual dysfunction and cognitive dysfunction.

Fatigue, which can be described as a lack of energy, sense of exhaustion or an abnormal feeling of trouble, fundamentally influences the patients' daily activity. Three forms of fatigue were described: physical, cognitive and social fatigue. To determine whether or not a patient has fatigue, questionnaires are used widely.

The measurement of the quality of life is used as an assessment of the well-being in a social, emotional and physical sense. The health-related quality of life expresses how these parameters change over time due to a disease or its treatment. Over the last decades, there was an expansion of studies examining health-related quality of life in the group of patients with MS. To measure this factor, questionnaires are the most adequate tools. The most frequently utilized questionnaire in MS to estimate quality of life is the Multiple Sclerosis Quality of Life Questionnaire (MSQoL-54), a combined questionnaire, which contains both general questions regarding the quality of life (Short Form-36) and 18 specific questions for patients with MS. The MSQoL-54 was validated in Hungary in 2008.
II. Aims

The aims of our studies were to:

1. determine the age- and sex-specific crude and standardized prevalence of MS according to the McDonald criteria in Csongrád County on the prevalence day (1 January 2013);
2. determine the prevalence of familial MS in Hungary;
3. determine the prevalence of fatigue and depression in glatiramer acetate-treated patients in Hungary;
4. compare the health related quality of life in fatigued and non-fatigued patients;
5. analyze the correlation of fatigue, depression, clinical disability and the disease duration with the health-related quality of life in case of patients with MS.

III. Patients and methods

III.1. Prevalence of MS in Csongrád County

At the Department of Neurology, University of Szeged, an MS outpatient unit functions for the inhabitants of Csongrád County. Since 1996 this outpatient unit has maintained an MS register containing regularly updated patient records.

We documented the female/male ratio, the proportion of each clinical form, the number of the new patients and the number of patients who moved away from the county during the study period. We also monitored the different disease-modifying treatments.

The age- and sex-adjusted prevalence of MS were calculated by the direct method of standardization using the European Standard Population as reference. The study was approved by the Human Investigation Review Board of the University of Szeged (approval number 3267) in accordance with the Helsinki Declaration.

III.2. Familial aggregation of MS in Hungary

In 2004, with the contribution of five MS centers in Hungary, we collected MS cases implying familial aggregation. At that time, altogether, 1500 patients were treated in the MS centers. The patients participating in the study were diagnosed by the McDonald criteria.
III.3. Prevalence of fatigue and its effect on HRQoL in MS

For our quality of life study, data of 428 patients with MS from 19 Hungarian multiple sclerosis centers were collected. The patients had the relapsing-remitting clinical form of MS, and they were treated with glatiramer acetate. The patients completed the Hungarian versions of the MSQoL-54, the Fatigue Impact Scale (FIS) and the Beck Depression Inventory (BDI) questionnaires for the assessment of quality of life, fatigue and depression. Statistical analysis was carried out with the Statistical Package for Social Sciences (SPSS 19.0, SPSS Inc.). All participants received appropriate information about the study both in written form and orally. They gave their written consent to the statistical evaluation of their answers. The study was approved by the Science and Research-ethics Committee of the Medical Science Council in Hungary (3462-0/2010-1018EKU (197/PI/10)) and was in full accord with the Declaration of Helsinki.

IV. Results

IV.1. Prevalence of MS in Csongrád County

According to data of the Hungarian Central Statistical Office, in 2013, 421,827 people lived in Csongrád County (199,388 males, and 222,439 females). On the day of the determination of the prevalence, January 1, 2013, 379 patients were registered in our MS register. On the basis of these data, the crude prevalence of MS was 89.8/100,000 (46.6/100,000 among males and 128.6/100,000 among females). The standardized prevalence was 83.7/100,000 for the overall MS population (42.3/100,000 for men and 122.6/100,000 for women). The female/male ratio was 3.08 in the MS population and 1.12 in the overall population of the county.

The distribution of the clinical forms was the following: clinically isolated syndrome (CIS): 11% (n=44), relapsing-remitting form: 69% (n=260), secondary progressive form: 14% (n=52) and primary progressive form: 6% (n=23). The mean EDSS score in the group of patients with clinically isolated syndrome was 0.4 ± 0.6. In the relapsing-remitting group, 91.9% of the patients (n=239) had EDSS scores in the range between 0 and 4. We confirmed, that 73.1% of the MS patients received some sort of disease-modifying therapies (DMTs).

IV.2. Familial aggregation of MS in Hungary

In 2006, with the collaboration of five Hungarian MS centers, we found 33 patients from 15
families among 1500 patients. Based on our data, which represented 25% of all MS patients in Hungary, we estimated a 2% familial rate of MS.

IV.3. Prevalence of fatigue and its effect on HRQoL in MS

Based on the data used the FIS questionnaire, the prevalence of fatigue was 62.4% (251 of 402 patients). Using the BDI, we estimated the prevalence of depression in 13.4% of the patients (51 of 381 patients). We compared the health-related quality of life of patients with fatigue to that of the patients without fatigue, and found that non-fatigued patients assessed their health-related quality of life significantly higher than patients with fatigue in all question groups of the MSQoL-54 questionnaire.

In our study, we examined the correlation of the EDSS score, depression, the three dimensions of fatigue and the disease duration with the health-related quality of life using the MSQoL-54, and subsequent correlation analysis. Depression and the three dimensions of fatigue influenced all the subscales of the MSQoL-54 questions significantly negatively. The EDSS score correlated significantly negatively with all aspects of the MSQoL-54, except for the cognitive function scale. The disease duration had a significant negative correlation with the quality of life, with the exception of the mental health, the cognitive function and the satisfaction with the sexual function.

Using regression analysis, we confirmed that the overall quality of life was significantly predicted by the EDSS score, depression and social fatigue. By examination of the patients separately on the basis of the presence of depression, we founded that in patients with depression, social fatigue was the only factor that predicted the quality of life. In case of the cognitive and the sexual quality of life, we found significant effects of depression and cognitive fatigue.

V. Discussion

In 1999, Bencsik et al. conducted an epidemiological study of MS in Csongrád County, which revealed a crude prevalence of 62/100,000. This study was based on the diagnostic criteria by Poser. The novel diagnostic criteria by McDonald and its revisions by Polman were introduced in 2001, 2005 and 2011. In our study, we examined the prevalence of MS diagnosed by these novel criteria. The crude prevalence in Csongrád County was 89.8/100,000, the standardized prevalence of MS was 83.7/100,000.

Our results are in line with the data of other prevalence studies based on the McDonald
diagnostic criteria. In these studies, data were adjusted to the European standard population.

The ratio of males to females was 1:2.75 in the MS population of Csongrád County, reported by Bencsik et al. in 2001. In our study, we found the male:female ratio in the MS population to be 1:3.08. These findings are in line with the literature data, which suggests that MS is more frequent among women, and this proportion shows an increasing tendency.

We examined the percentage of patients with different clinical forms. 68.6% of the patients with MS showed the relapsing-remitting clinical form. Disease-modifying therapies have been applied in Hungary since 1996. 73.1% of the patients with the relapsing-remitting form of MS are treated with one of these drugs. Our study revealed that 91.9% of the patients with relapsing-remitting form have either no or only mild symptoms.

We found that the percentage of the primary progressive form of MS is lower (6.1%) than it was reported previously (11%) by Bencsik et al. in 2001. This reduction may be caused by the death of the older patients with a severe state.

Hungary is a middle-risk area for MS. In high-risk regions, the relative risk of first-degree relatives in familial cases is between 5% and 10%. Our study involved 1500 patients with MS, which is almost 25% of all Hungarian patients with MS. The ratio of the familial cases was 2%, which is significantly lower than data in the literature. This difference can be explained by the lower prevalence rate in this region. In our study, we examined first-degree relatives only. Due to the low number of patients, we could not perform a subgroup analysis based on the degree of relativeness.

The researches of the last ten years pointed out the importance of the unseen symptoms of MS, such as fatigue and depression, as well as their effects on the patients' health-related quality of life. In 2012, we started a multicentre, cross-sectional study in Hungary to estimate how frequent the fatigue and the depression are among patients with the relapsing-remitting form of MS and how these factors influence the patients' health-related quality of life. We selected patients treated with glatiramer acetate, since the chance of secondary fatigue is much lower in case of this treatment than in patients treated with interferon beta. Furthermore, unlike in the case of interferon beta, the side-effects of glatiramer acetate do not include depression.

Our data on the prevalence of fatigue are in line with the literature data. Surprisingly, in our study, the prevalence of depression was significantly lower (13.4%) than that found by previous studies. The low prevalence of depression in our study may result from several factors. The majority of the respondent patients lived in family, with one or two children. In Hungary, there is a freely available phone service with the contribution of multiple sclerosis nurses. This, together with the usual medical examinations ensure a stable and well-functioning medical support for patients. Another reason for our findings may be that the participants in our study suffered from only a low
The diagnosis and effective therapy of depression are extremely important, since depression significantly worsens the patients' health-related quality of life, and can also mask the effects of the other factors, such as fatigue, the disability, as well as the duration of MS on quality of life, as demonstrated by our correlation analysis. Finally, due to the uneffective treatment of depression, the level of the patient's compliance may decrease, which may lead to the cessation of disease-modifying therapy.

In our study, we used a new approach to examine the three dimensions of fatigue separately. Our partly contradictory and surprising results which indicate that physical fatigue does not predict the health-related quality of life of patients with MS, can be explained by this new approach. However, social and cognitive fatigue have significantly negative effects on the quality of life. We believe that our results are important, since these factors cannot be measured by EDSS, and the patients do not talk willingly about their social and cognitive difficulties, as they do not find this important. However, decreasing their social or cognitive fatigue may lead to the improvement of their quality of life.

VI. Conclusions

In our studies, we investigated the prevalence of MS in Csongrád County, the familial rate of MS in Hungary and the prevalence of fatigue and depression, as well as their effects on the patients' health-related quality of life.

Our prevalence study was the first in Hungary to apply the McDonald criteria. We found that the standardized prevalence was 83.7/100,000, which means that Hungary is one of the medium-risk countries.

The ratio of the familial cases was 2% in Hungary. In a middle-risk region, our study was the first to investigate the familial risk in MS.

In our study, the prevalence of fatigue was 62.4%, which is in line with the data in the literature. The prevalence of depression was 13.4%, which is lower than it was found by earlier studies. We confirmed that the health-related quality of life of non-fatigued patients is better than that of fatigued patients. We found that depression may escalate the negative effects of the other factors on the quality of life. Our study drew attention to the importance of the social and cognitive fatigue, which can be hidden in the common medical examinations, however, besides the level of disability, these factors significantly worsen the patients' health-related quality of life in case of MS.