1 Mortality in Hungarian patients with multiple sclerosis between 1993-2013

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Abstract

Objective: We aimed to assess the causes of death, the mortality and survival time of MS patients in Hungary.

Patients and methods: Between 1993-2013, 740 patients (10303 person-years) were treated at our Outpatients' Clinic, of which 121 died. The causes of death were established from the pathological records or the medical certificates of the cause of death. The standardized mortality ratios (SMR) were calculated. Survival time was assessed with Gehan-Breslow test.

Results: Sixty-four percent of our patients died of MS-related causes. The SMR was 2.52. Primary progressive (PPMS) patients' SMR was higher (4.10) than initially relapsing patients' (RR/SPMS) was. There was no difference between the genders (2.46 for men vs 2.57 for women). The median survival time of woman was 3 years longer ($p<0.001$). RR/SPMS patients' median survival (35 years) was more than twice as long as PPMS patients' (14 years).

Discussion: The frequency of the MS-related cause of death, SMR and the median survival times were mostly similar to previous results from Scandinavia and North-America, despite the very different socio-economic backgrounds of these areas which shows that the survival risk can solely be attributed to MS itself. These are the first data on the topic from Central-Eastern-Europe.

Key words: multiple sclerosis, mortality, cause of death, survival time, Hungary

2 Introduction

Multiple Sclerosis (MS) is an autoimmune demyelinating, neurodegenerative disease of the central nervous system (CNS) that mainly affects young adults. The prevalence of MS shows a North-South gradient, rates are higher in the North (166.3/100000 in Norway) [1] and lower in the South (32/100000 in Spain) [2]. In Hungary the prevalence was estimated 83/100000 [3]. The disease is more common among women, the female/male (F/M) ratio is approximately 3:1 [3-5].

MS was long considered to be a disease only affecting the patients' quality of life, yet studies in the past decade showed that MS patients have an almost threefold increased risk of dying than the general population (SMR:2.8) [6]. This risk increases as the disease progresses [6] and becomes over fourfold (greater than Type II. diabetes mellitus [7]) if the disease onsets before the age of twenty[6].

The data on MS patients' mortality are sparse and studies report variable results, mainly due to the different methodologies, sample-sizes and choices of endpoints throughout these evaluations. Yet, they conclude that the majority of the patients (47-75%) die of MS-related causes[8-11]. As MS leads to severe disability and the patients become bedridden at the end of their lives these causes are decubitus, sepsis and pneumonia [8]. The deaths unrelated to MS are the causes of death in the general population such as cancer, cerebral- and cardiovascular diseases (CVD), respiratory and infectious diseases, suicide and accidents [8, 9, 12].

The objective of our study was to determine: (I) the causes of death, (II) the standardized mortality ratios (SMR), the (III) survival times from disease onset among the Hungarian MS patients with any possible difference between the genders or the different clinical courses of the disease from January 1st 1993 to January 1st 2013.

3 Patients and methods

The MS outpatient's clinic of the Department of Neurology of the University of Szeged is responsible for the health care of all MS patients from Csongrád-county (population: 419.366 [13]) and parts of Bács-Kiskun- (population: 522.312 [13]) and Békés- (population: 357.740 [13]) counties (total number of the population is approximately 900000 people) in the southern region of Hungary. All MS patients were included into the multiple sclerosis register of the Department of Neurology of the University of Szeged since 1993. We have obtained the socio-demographic data such as the gender, the date of birth, the date of MS onset, the course of the disease and the date of death of the patients from the register. The patient's diagnosis was based on the Poser diagnostic criteria [14] between 1993 and 2001 and after 2001, the McDonald diagnostic criteria [15]. The different courses of MS were determined based on the Lublin-criteria [16].

The cause of death was determined from the pathological records (in case of 53 patients) or the medical certificates of the cause of death provided by the families (in case of 68 of the patients). Data on the number of deaths and the causes of death in the Hungarian general population distributed by gender, age and calendar year were derived from the Hungarian Central Statistical Office. Standardized Mortality Ratios (SMRs) were estimated. The SMR is calculated as the ratio of the observed to the expected numbers of deaths thus it can be used for comparing mortality rates of MS patients with those of the general population [17]. The expected numbers of deaths were calculated by multiplying the age-, gender- and time-specific person-years of observation by the respective age-, gender- and time-specific population death rate. SMRs and 95% confidence intervals

(CIs) were established assuming that the numbers of deaths followed a Poisson distribution. For the analysis of survival time from MS onset of the genders and patients with different clinical courses, we utilized Gehan-Breslow test.

The study was approved by the Human Investigation Review Board of the University of Szeged (approval number 3267) in accordance with the Helsinki Declaration.

In the assessed 20 years, 740 MS patients were treated for MS at our Outpatients' Clinic of the Department of Neurology of the University of Szeged, with a total follow-up person years of 10303 years. Two-hundred and four were men (27.5%, 2806 person years), 536 were women (72.5%, 7497 person years), and the F/M ratio was 2.63:1. Six-hundred and eighty-eight patients suffered from either the relapsing-remitting (RR) or the secondary progressive (SP) form of the disease (93%, 9733 person years) and 52 patients from the primary progressive (PP) course (7%, 570 person years). During the examined period 121 patients (16%) died, 46 men and 75 women, 23 suffered from PPMS, 98 from RR/SPMS. Fourty patients (33%) received disease modifying therapy (DMT; interferon-β, glatiramer-acetate or mitoxantrone), the mean duration of treatment was 6.2 (95% CI: 5.1-7.3) years, their EDSS score at the beginning of the treatment was 3.3 (95% CI: 2.5-4.0).

4 Results

4.1 Causes of death

Seventy seven of the 121 patients died due to MS-related causes, which corresponds to 63.6% of all deaths. These causes were the effects of long-term disability such as bronchopneumonia, sepsis, uro-infection. The other 44 deaths (36.4%) occurred due to non-MS-related causes and were categorized as CVD (stroke, acute myocardial infarct and aortic rupture), malignant tumors, suicide and other causes (hepatic failure, pulmonary emboli). CVD caused the death of 16 patients (13.2%), malignant tumors were responsible in 14 cases (11.6%), 4 people committed suicide (3.3%) and 10 patients (8.3%) died of the other causes described above (Table 1).

Table 1: Causes of death of Hungarian multiple sclerosis (MS) patients between 1993-2013 and in the general Hungarian population

Cause of death	MS patients treated at Szeged	General population in Hungary
MS-related (ICD10: G35, A00-B99, J00-J99)	63.6%	6.0%
Cerebro- and cardiovascular diseases (ICD10: I20-I25, I60-I69, I71)	13.2%	35.6%
Malignant tumors (ICD10: C00-D09)	11.6%	28.0%
Suicide (ICD10: X71-83)	3.3%	1.5%
Other (Hepatic failure, pulmonary emboly) (ICD10: K70-77, I26-I41)	8.3%	8.1%

4.2 Survival risk

Table 2 – Expected and observed numbers of deaths and standardized mortality ratios (SMR) with 95% confidence intervals (CI) for the different causes of death during follow-up 1993-2013, all patients and sorted by genders.

	All patients				Men				Women			
Causes of death	**Expected number of death**	**Observed number of death**	**SMR**	**95%CI**	**Expected number of death**	**Observed number of death**	**SMR**	**95%CI**	**Expected number of death**	**Observed number of death**	**SMR**	**95%CI**
All causes	47.93	121.00	2.52	2.10-3.01	18.71	46.00	2.46	1.82-3.25	29.22	75.00	2.57	2.03-3.20
MS-related	0.73	77.00	105.34	83.13-131.60	0.29	25.00	86.23	57.03-125.40	0.44	52.00	117.91	88.97-153.40
CVD	18.98	16.00	0.84	0.50-1.34	6.70	6.00	0.90	0.36-1.86	12.28	10.00	0.81	0.41-1.45
Malignant tumor	17.78	14.00	0.79	0.45-1.29	6.71	7.00	1.04	0.46-2.06	11.07	7.00	0.63	0.28-1.25
Suicide	3.89	4.00	1.03	0.33-2.48	2.02	2.00	0.99	0.17-3.27	1.87	2.00	1.07	0.18-3.54
Other	6.55	10.00	1.53	0.78-2.72	2.98	7.00	2.01	0.82-4.19	3.57	4.00	1.12	0.36-2.71

MS, multiple sclerosis; CVD, cardio- and cerebral vascular diseases

During the 20 years of observed period, 121 patients died, while the expected number of deaths in this period based on the data from the general population was 47.93. Thus the SMR was 2.52 (95%CI: 2.10-3.01) (Table 2). The SMR for MS-related causes of death was 105.34 (95%CI: 83.13-131.60), while SMRs for other causes were all below 1.00 or around it (Table 2). The median survival time from disease onset was 35 years.

There was virtually no difference between the genders as the SMR for men was 2.46 (95%CI: 1.82-

3.25) and the SMR for women was 2.57 (95%CI: 2.03-3.20). The SMR for MS-related causes were the highest in both genders, but it was markedly higher in women than men (Table 2). The survival risk was virtually the same regarding CVDs, malignant tumors and suicide, yet men had a double risk of dying caused by hepatic failure or pulmonary emboli than women did (Table 2). The median survival time from disease onset for men was 32 years, while it was 35 years for women, which difference is statistically significant ($p<0.001$), but clinically not relevant (Figure 1).

Table 3 – Expected and observed numbers of deaths and standardized mortality ratios (SMR) with 95% confidence intervals (CI) for the different causes of death during follow-up 1993-2013, sorted by different clinical courses (PPMS, primary progressive course, RR/SPMS, relapsing-remitting and secondary progressive disease course) of multiple sclerosis (MS).

	RR/SPMS				PPMS			
Causes of death	**Expected number of death**	**Observed number of death**	**SMR**	**95%CI**	**Expected number of death**	**Observed number of death**	**SMR**	**95%CI**
All causes	41.90	98.00	2.34	1.91-2.84	5.62	23.00	4.10	2.66-6.05
MS-related	0.64	62.00	96.42	74.56-122.80	0.09	15.00	170.50	99.05-274.80
CVD	16.24	12.00	0.74	0.40-1.26	2.65	4.00	1.51	0.48-3.67
Malignant tumor	15.73	12.00	0.76	0.41-1.30	2.09	2.00	0.96	0.16-3.16
Suicide	3.49	4.00	1.15	0.36-2.75	0.44	0.00	0.00	-
Other	5.80	8.00	1.38	0.64-2.62	0.35	2.00	5.78	0.97-19.10

MS, multiple sclerosis; CVD, cardio- and cerebral vascular diseases

Regarding the different clinical courses of MS, the SMR for RR/SPMS patients was 2.34 (95%CI: 1.91-2.84), while for PPMS patients SMR was much higher: 4.10 (95%CI: 2.66-6.05). The SMR for MS-related causes of death was almost double in PPMS patients than in RR/SPMS patients (Table 3). PPMS patients' survival risk associated with CVDs was higher than in RR/SPMS patients (Table 3). No PPMS patient committed suicide, while the survival risk associated with hepatic failure and pulmonary emboli was almost six-fold (SMR: 5.78) than in the RR/SPMS group (Table 3).
The median survival times significantly ($p<0.001$) differed: PPMS patients' median survival time from disease onset was 14 years, while it was 35 years for RR/SPMS patients ($p<0.001$) (Figure 2).

Figure 1: Kaplan- Meier survival curves representing survival from onset of the Hungarian multiple sclerosis patients by gender, with median survival times and 95% CIs.

Figure 2: Kaplan- Meier survival curves representing survival from onset of the Hungarian multiple sclerosis patients by clinical courses (RR/SPMS, relapsing-remitting/secondary progressive multiple sclerosis, PPMS, primary progressive multiple sclerosis) with median survival times and 95% CIs.

5 Discussion

The data on mortality in MS is relatively scattered and somewhat controversial. The first evaluation dedicated to the subject was carried out in Scotland in 1987 that found that 62% of the patients died because of MS and indicated that CVD and malignancies are the second and third leading cause of death in this population [8]. The forthcoming studies found a wider range of MS-related causes of death between 47-75% [10, 11] but most of them put it between 55-62% [6, 9, 12, 18-21]. In our evaluation, 64% of the patients died of MS-related causes, which is in accordance to most of the previous data in the literature.

The non-MS-related causes of death can predominantly be attributed to CVD and malignancies (13% and 11% respectively). Previously some studies indicated both lower and higher ratios regarding both disease-types, but their range is generally between 10-20% similarly to ours, CVD being the more common cause[8, 9]. It is important to note, that our patients were relatively young (mean age at death was 54.2 years) just like the patients in the 21-year follow-up IFN-β study (51.7 years) and that evaluation yielded very similar results considering the cause of death[22].

The SMR for all causes of death was 2.52, which is very well similar to findings of the last decade[23]. In our assessment this excess overall mortality risk can solely be attributed to the excess deaths caused by MS (SMR: 105.34), as none other disease caused excess mortality. CVD and malignant tumors posed a slightly lower mortality risk than in the general population (SMR: 0.84 and 0.79 respectively). Earlier studies indicated both higher and lower SMRs for both disease groups[9, 12, 24], yet the incidence of these diseases is getting higher with the patients' age. We can conclude that as CVD and malignancies tend to be the leading cause of death among the elderly rather than the younger population, the majority of our patients most likely died before these diseases can manifest or progress to late phases. Interestingly, the rate of suicide was the same as in the general population (SMR: 1.03), yet the majority of previous studies found that it is more frequent among MS patients[25, 26]. Two factors can possibly explain this finding: the relatively low number of our patients as compared to the mentioned previous studies and the fact that Hungary - sadly - is one of the leading countries in rate of suicide. Furthermore, in Finland, where suicide rates are also considered to be very high, the mortality risk was also similar to the general population[6].

The difference between the genders regarding the overall SMRs was negligible in our assessment. Previous results on this difference are controversial at best: some studies reported similarly no differences[11, 27], yet there were cohorts which showed higher SMRs for women[6, 9, 28] . Yet, similarly to assessments finding higher mortality risks in women, SMR for MS-related causes of death were markedly higher in women than in men[6]. Also we found that deaths due to malignancies, hepatic failure and pulmonary emboli are rarer in women than in either men or the general population. This maybe partially explained by the higher rate of chronic alcohol abuse among men, but this is needed to be evaluated further.

We found that PPMS patients' SMR is far higher (4.10) than RR/SPMS patients' (2.34). Kingwell et al. reported a significantly higher relative mortality risk for PPMS patients in British Columbia, and in Western-Norway, Grytten-Torkildsen et al. found that PPMS patients' SMR rates were higher than

SMR of RRMS patients[12, 28]. Yet in our cohort, the difference between the clinical courses was far more pronounced than in Norway or Canada. We found that PPMS patients' mortality risk is almost twice as high as patients' with RR/SPMS (SMR: 170.50 and 97.62 respectively). Also the SMR for CVDs was double, and the mortality risk due to hepatic failure and pulmonary emboli was fivefold in the PPMS group than in the RR/SPMS. These differences can partially be explained with the differences between the clinical courses: PPMS is more aggressive, patients become bedridden far earlier thus causing the death of the patient faster than initially relapsing MS. Also it starts in older age, so CVDs' prevalence might be higher among these patients. Also it is noteworthy, that in our cohort there was a lower rate of PPMS patients than in the Norwegian and the Canadian population (7%, which corresponds to only 52 patients vs 10%[28] and 12%[12]), which could bias the results.
The median survival time from MS onset was 35 years, 32 years for men and 35 years for women. These results are similar to data from Canadian and Danish cohorts and those studies also describe a longer median survival time for women over men [9, 28, 29]. PPMS patients' median survival time from MS onset (14 years) is less than half as long as the RR/SPMS patients' (35 years), which is in accordance to previous results [12, 28].

As conclusion we can state that many of our results are similar to those in the literature, but those data are predominantly from North-America, Northern- and Western-Europe. To our best knowledge, we are the first to give data on MS patients' mortality risk from Central-Eastern-Europe. Hungary has a very different socio-economic background than Western countries. For illustration, the gross domestic product (GDP) per capita in Hungary was 13 464 USD in 2013 as compared to 59 950 USD in Denmark and 52 393 USD in Canada [30]. In 2013, the life expectancy at birth in Hungary was 75 years, while it was 80 years in Denmark and 81 years in Canada [31]. Yet, the very similar Hungarian results to the North-American and North-European findings and the fact, that the SMRs of the other causes of death were not increased suggests that the higher mortality rate does not depend on any outside factors, it can solely be attributed to the disease itself.

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7 Conflict of Interests:

The authors declare that they have no conflicts of interest.

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