EPIDEMIOLOGIC FEATURES OF MULTIPLE SCLEROSIS, BASED ON ADMINISTRATIVE HEALTHCARE DATA

PhD thesis

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1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system with supposed autoimmune origin. Tipically it is diagnosed in adults aged 20-40 years, meaning that patients have to live with this condition for decades and struggle with its challenges for example in employment, and family planning. Even using modern, effective disease-modifying drugs (DMDs), primary or secondary axonal degeneration may lead to irreversible physical, psychical and cognitive disability with a negative impact on mobility, independence, quality of life and productivity of patients.

According to the estimations, MS affects almost 1.2 million people in Europe and 2.8 million worldwide. Numerous recent studies agree that the prevalence of MS increases in every world region due to various plausible factors, but significant differences are found among regional rates of prevalence, incidence and sex-ratio of MS. The better knowledge about regional epidemiologic features and trends also can help to understand the still ambiguous role of various environmental and genetic factors in the pathomechanism of the disease.

Long-term treatment and complex management of MS is a burden for the health care system, social services and caregivers as well. Given the rapidly evolving scene of costly immunomodulatory drugs, optimal allocation of resources and planning of health services require accurate data on the number and age-distribution of patients affected by the disease.

2. Objectives

Given the absence of nationwide MS-registry, in Hungary only regional studies were conducted on the epidemiology of MS until 2020. Therefore, we aimed to describe prevalence, incidence, age-distribution, and DMD-use of patients living with MS in the whole country.

We have analyzed anonymized health claim data supplied by the National Health Insurance Fund (NHIF). Since the methodology for case ascertainment mostly depends on the type, content and extent of available datasets, we have first developed and validated a

case definition of „administrative MS-patient". Applying this administrative case definition on the NEUROHUN database and an independent database of pharmacy dispension, we could estimate the number of incident and prevalent MS-patients, as well as ratio of patients treated with immunomodulatory drugs and trends of their changes between 2010-2015. Finally, it made possible the analysis of sex- and age-distribution of people living with MS in Hungary, and its changes through a decade.

3. Methods

We have studied the NEUROHUN database that captures data submitted to the NHIF by healthcare providers with contract – including all public and contracted private hospitals and outpatient specialist services –, from 2004 to 2016. It contains each individual and their healthcare history, who had received a neurological diagnostic code (based on International Classification of Diseases 10th Edition) at least once during this 13 years of observation, meaning 4.29 million subjects. The anonymized database contains basic patient features (year of birth, gender, postal code of residence) and data on all hospitalizations, all outpatient specialist care or diagnostic services: the date of care, the specialty and institution of provider and at least one diagnosis. We have identified all subjects who were given at least once the diagnostic code assigned for MS (G35) as primary or secondary diagnosis. It resulted an "MS-database" of nearly 34,400 subjects.

Of them, we considered an individual as a person living with MS if he or she had fulfilled all of the following 3 criteria between 2004 and 2016: receiving the diagnostic code of G35 at least 3 times at 3 separate medical contacts; at least one of these ≥3 claims for MS was submitted by a neurologist (ie. during hospitalization on a neurology ward or at neurological outpatient care); receiving G35 codes in at least 2 different calendar years that can be consecutive or not. Altogether 14,437 persons fulfilled all the three administrative criteria and are therefore considered as MS-patients.

Then, we performed the validation of the administrative case definition: we compared the concordance between administrative MS-cases and clinical diagnosis in medical documentation held by our department.

After showing a high concordance between administrative and clinical classification of non-MS and MS-patients, as well as excellent specificity and sensitivity,

this case definition was applied on the nationwide database and thus we could determine the number of MS-patients yearly, and calculate prevalence and incidence of MS in Hungary each year during the observational period. We have also analyzed the changes in age-distribution of prevalent and incident patients.

An independent database of drug refills between 2010-2016 was merged with the healthcare utilization database, with a linkage of subjects by their unique pseudonymized number. It made possible to study the medicine-utilization of MS-patients together with the number and ratio of DMD-treated subjects.

The date of the first medical inpatient or outpatient contact when ICD-10 code G35 was assigned as primary or secondary diagnosis was considered to be the date of establishing diagnosis of MS. Patients were counted as incident cases for that year and prevalence was calculated as incident cases added to prevalent cases from the previous year, after subtracting patients who died during the year. We estimated the annual crude incidence and prevalence per 100,000 inhabitants (for women, men and both sexes), with the help of corresponding data of the latest nationwide census in 2011 as denominators. Using the direct standardization method, these results were also age-adjusted to the European Standard Population of 2013.

As a consequence of the setting of our database, those patients who had been diagnosed with MS before 2004 would also – wrongly – appear as incident cases at the time of their first medical encounter for MS between 2004-2016. In order to reduce this bias, we allowed a 6-year „run-in" period when incidence data (and prevalence data derived from it) were not taken into account for final analysis. It also has to be noticed, that our 3rd administrative criteria of MS requires claims in 2 separate calendar years. Therefore, those patients who first received G35 code in the last year of observation (2016) administratively would not appear as MS patients, even if they turn to be „real" MS patients in subsequent years. Thus, incidence rate is not applicable for 2016 and might be underestimated in the last 2-3 years of the observational period, so for statistical analysis of incidence and prevalence, we have used only data between 2010-2015. When studying trends of age-distribution, we were more permissive and ignored only the first 3 years' incidence data, so calculations concerning incident patients were made on data between 2007-2015, and concerning prevalent patients the whole observational period was analyzed.

Gamma distribution was used when calculating confidence intervals for the prevalence and incidence rates. The significance of the trends of changes of incidence, prevalence, DMD-utilisation rates and ratio of elderly patients was tested with linear regression. When analyzing changes of average age of prevalent and incident MS-patients, we used multiple linear regression modell to test what impact have the passing years and male/female gender in interaction on these values. In each modell, *p*-value was considered significant if ≤ 0.05. The goodness of fit of all linear regression models was tested with the Shapiro-Wilks test of normality. The calculations were conducted with the R programming language.

4. Results

Validation of administrative case definition

We have randomly chosen two 2-months-long periods and identified altogether 309 individuals who had received the diagnostic code of G35 during that period at Neurology Department of Semmelweis University. After scrutinizing their medical documentation and applying the administrative case definition, the concordance between these two were as follows: 275 MS-patients – correctly – fulfilled administrative definition, 15 non-MS patients – correctly – did not fulfilled administrative definition, together representing 94% of subjects. Further 1 MS-patient fulfilled only 2 criteria of administrative case definition, so he can be considered as "false negative". Eighteen individuals, of whom MS diagnosis was excluded or remained undetermined – wrongly – fulfilled the administrative case definition, they are "false positive" cases. Consequently, the sensitivity of the definition is 99% and its positive predictive value is 94%.

For calculation of specificity, we have created an administrative „true negative reference cohort". The number of individuals in NEUROHUN database, who have never undergone cranial nor spinal MRI and have never had prescription of any drugs for MS between 2004-2016 turned out to be 3,223,001. This cohort was then linked to the cohort of administrative MS-patients: of 14437 subjects 1023 (7%) were overlapping and thus regarded as false positive. Thus, the specificity of the case definition is >99%.

Prevalence of MS in Hungary between 2010 and 2015

For methodological reasons discussed above, trends observed between 2010 and 2015 were analyzed and discussed. The annual crude prevalence of MS has increased continuously from 109.3/100,000 to 130.7/100,000, mirroring a rise from 150.8/100,000 to 179.5/100,000 among women and from 63.3/100,000 to 76.8/100,000 among men (see yearly data in **Table 1**.) These growing trends were significant (*p*-value of linear regression model was <0.05 for all the three datasets). Similarly, age adjusted standardized prevalence of MS has also significantly and continuously increased among women, men and in whole population. The ratio between number of women and men living with MS remained invariably 2.6 during these years.

Table 1. Number of MS-patients, incidence and prevalence rates of MS in Hungary between 2010 and 2015

	number of incident cases / number of prevalent cases	**total crude incidence[1]**	**total incidence[1] women / men**	**total crude preva-lence[1]**	**crude prevalence[1] women / men**
2010	703 / 10859	7.1	9.6 / 4.3	109.3	150.8 / 63.3
2011	616 / 11338	6.2	8.2 / 4.0	114.1	157.2 / 66.4
2012	653 / 11809	6.6	8.6 / 4.4	118.8	163.7 / 69.2
2013	625 / 12234	6.3	8.3 / 4.0	123.1	169.7 / 71.6
2014	592 / 12634	6.0	7.5 / 4.3	127.1	174.6 / 74.6
2015	538 / 12993	5.4	7.2 / 3.5	130.8	179.5 / 76.8
***p*-value**	not applicable	0.018276*	0.011609* / 0.258283	0.000003*	0.000006* / 0.000002*

1: incidence and prevalence are expressed as number of living patients/100,000 inhabitants.

*p-value: p-value of trend significance test using linear regression. The p-value ≤0.05 was considered significant and is marked with asterisks**

Incidence of MS in Hungary between 2010 and 2015

On the other hand, the number of incident cases decreased and crude total incidence has significantly declined: the latter was 7.1/100,000 in 2010 and 5.4/100,000 in 2015. The crude incidence for women has also diminished from 9.6/100,000 to 7.2/100,000, showing a negative significant trend, in line with crude total incidence. The incidence among men has changed from 4.3/100,000 to 3.5/100,000, but the trend was not significant. Yearly data are shown in **Table 1**. Age-adjusted standardized incidence ratios follow the same trends as crude ratios.

Age distribution of MS patients between 2004 and 2016

We have examined the average age and age-distribution of prevalent and incident patients in each calendar year. We used multiple linear regression model to analyze the effect of calendar years and gender in interaction on the age of prevalent patients, shown in **Table 2**. We found that each year, female prevalent subjects are older compared to male patients, by 6 months on average (this difference is significant). Also, between 2004-2016 the average age of male prevalent subjects increased by 0.22 year (ie. by 2.5 months) by calendar year (significant change), and the average age of female prevalent patients grew even more rapidly, by 0.32 year per calendar year (the difference between the two genders is significant).

Concerning the average age of incident patients, between 2007 and 2015 we have observed a significant decrease of 4 months/year (p-value <0.001) without difference between genders (see **Table 2**.).

The proportion of elderly subjects grow: while in 2010 we could identify 945 persons living with MS above age of 65 years (8.7% of prevalent cases), in 2015 their number was 1537, accounting for 11.8% of prevalent patients in Hungary. This rise of proportion is significant (p-value of linear regression model is <0.001).

Besides these linear trends, other changes of age-distribution can also be observed: when divided into five-year age groups, age-specific prevalence rates are higher in 2015 compared to 2005, except for childhood intervals, see **Figure 1**. Prevalence rate used to be the highest among persons aged 50-54 in 2005, while peak prevalence is reached in the group of 45-49 aged subjects in 2015. Our data also suggest that at the same time the most populous age groups shift towards the younger intervals: after 2010, those below 44 years

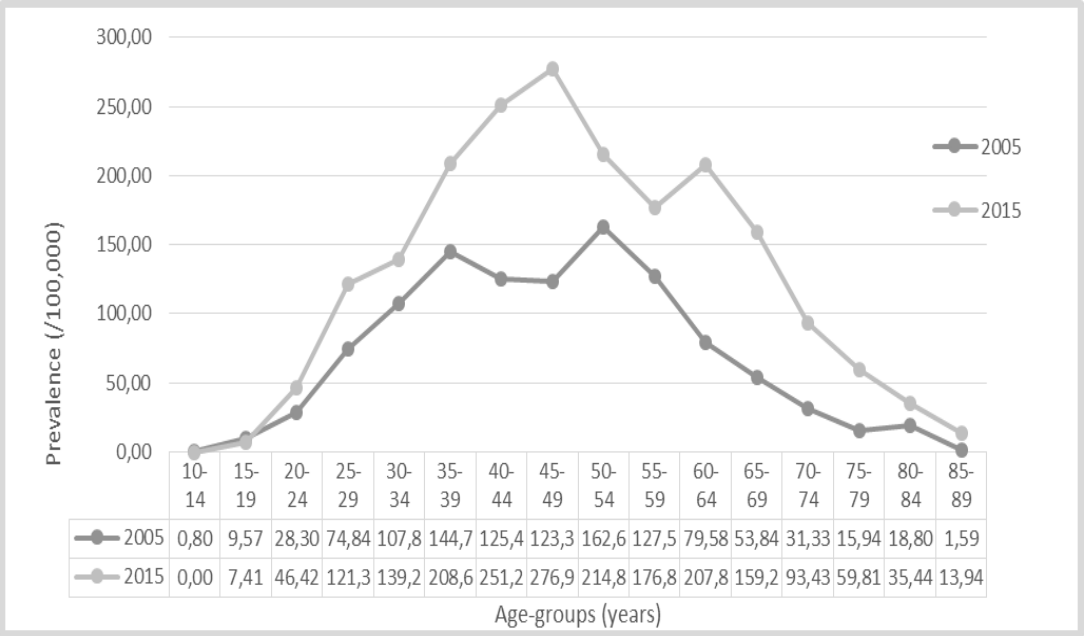
have the most subjects, instead of 50-54 year-old prevalent patients seen between 2004-2009 (data not illustrated separately).

Table 2. Average age of prevalent and incident MS-patients between 2004 and 2016

Year	Average age of prevalent cases (year)			Average age of incident cases (year)		
	men	women	total	men	women	total
2004	44,29	45,05	44,84	*44,29*	*45,05*	*44,84*
2005	44,65	45,41	45,20	*42,10*	*42,75*	*42,56*
2006	45,00	45,69	45,50	*41,98*	*41,13*	*41,37*
2007	45,18	45,97	45,75	39,90	40,56	40,37
2008	45,51	46,24	46,04	40,15	39,31	39,54
2009	45,54	46,56	46,28	37,38	39,26	38,68
2010	45,66	46,78	46,47	36,68	37,63	37,35
2011	46,07	47,13	46,83	40,04	38,51	38,98
2012	46,08	47,46	47,05	36,24	38,02	37,46
2013	46,24	47,74	47,33	36,92	38,20	37,80
2014	46,45	48,06	47,61	37,44	37,68	37,60
2015	46,80	48,40	47,95	37,21	37,54	37,44
2016	47,39	49,17	48,68	na	na	na
p-value	Difference between genders: 0,002*		Increase: Men: <0,001* Women compared to men: <0,001* Together: <0.001*	Difference between genders: 0,118		Decrease: Together: <0,001* (no difference between genders)

*na: not applicable. The p-value ≤0.05 was considered significant and is marked with asterisks**

For trend calculations, incidence data of 2004-2006 (marked in ithalic) were not taken into account for methodological reasons detailed in Methods.



	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
2005	0,80	9,57	28,30	74,84	107,8	144,7	125,4	123,3	162,6	127,5	79,58	53,84	31,33	15,94	18,80	1,59
2015	0,00	7,41	46,42	121,3	139,2	208,6	251,2	276,9	214,8	176,8	207,8	159,2	93,43	59,81	35,44	13,94

Figure 1. Prevalence rates in different age-groups in 2005 and in 2015

Drug dispension data between 2010 and 2015

Independent data of NEUROHUN and pharmacy refills could be linked with the help of the pseudonymized number and analyzed between 2010-2015, see **Table 3**. During these 6 years, the number of patients who refilled any medication with an indication for MS – i.e. with a diagnosis code of G35 on the prescription – has increased. Of them, the number of those individuals who do not fulfil our case definition of MS stays quite stable (around 800). If healthcare data on family doctors' visits – that NEUROHUN doesnot contain – would have been available, it could have helped to explain this phenomenon.

We investigated for each year the number of those subjects who have at least once refilled any of the 11 DMDs available that time (column number 2. of **Table 3.**). As these drugs are specifically used for MS and their prescription is reserved for neurologists, these individuals were therefore considered as MS patients by the prescribing neurologist. The number of DMD-treated patients has nearly doubled from 2010 until 2015 (from 2089 to 3808). We also considered the number of previously treatment-naive, newly DMD-treated patients: those who first refilled any DMD in the observed year (column number 3 in **Table 3.**). For methodological reasons, in 2010 all treated subject will appear as new so this number is not valid. In further years, after a high number in 2011 we observe a drop in 2012 and 2013, followed by a rise in 2014. These changes are paralell with the launch date

of some DMDs on Hungarian market. The proportion of those subjects, who refill DMD and do not fulfil our administrative MS-definition, stays below 2% in each query, that is considered as an indirect argument for its validity.

The proportion of DMD-treated MS-patients can be assessed each year by dividing the number of subjects refilling DMD with that of prevalent MS-cases. This ratio significantly increased between 2010 and 2015 from 0.19 to 0.29 (column number 4 in **Table 3.**).

Table 3. Yearly drug dispension data (titles of columns see below Table)

	1*.	**2*.**	**3.**	**4.**
2010	6162 (*5358 / 804*)	2089 / 23	2089[a] / 23[a]	19%
2011	6326 (*5535 / 791*)	2746 / 34	828 / 33	24%
2012	6539 (*5758 / 781*)	2969 / 42	392 / 38	25%
2013	6671 (*5920 / 751*)	3108 / 52	357 / 48	25%
2014	7130 (*6314 / 816*)	3482 / 60	500 / 56	28%
2015	7399 (*6573 / 826*)	3808 / 70	466 / 63	29%

1: Number of patients refilling ANY drug with G35 diagnosis in that year (*those who fulfil our MS case definition / those who do not*)

2: Number of patients refilling any of the 11 DMD in that year and fulfilling our case definition of MS / Number of patients refilling any of the 11 DMD and NOT fulfilling our case definition of MS

3. Number of patients refilling any DMD for the first time and fulfilling our case definition of MS / Number of patients refilling any DMD for the first time and NOT fulfilling our case definition of MS

4. Ratio of MS patients who received DMD that year

**One patient can appear in more than one year.*

[a]*Drug dispension data are available only from 2010 therefore all patients will appear as "first time refill" this year.*

5. Conclusions

In this thesis I presented our work on the epidemiology of MS in Hungary based on analysis of healthcare administrative data covering 13 years. Before, nationwide data were lacking in our country about prevalence, incidence and age-distribution of MS, or proportion of DMD-treated subjects, as only regional studies had been conducted and national MS-registry is lacking. We first have *established and validated an administrative case-definition of MS, that is proved to have a specificity and sensitivity both above 99%*. After applying it on the anonymized database of healthcare claims, we could identify almost 14,400 MS-patients and analyze the annual number and age of new and prevalent cases.

My findings highlight that *MS prevalence shows a significant increase between 2010-2015 and is notably higher than previously reported in Hungary*: total crude prevalence being 130.8/100,000 in 2015, corresponding to 179.5 and 76.8/100,000 in women and men, respectively. Female to male ratio of prevalent patients is stable (2.6) and similar to international values. On the other hand, *crude incidence is relatively low (5.4/100.000 in 2015) and shows a decreasing tendency among women and in the total population (but not in men) between 2010-2015*, that need further investigation.

While the *average age of incident subjects gradually lowers* (ie. newly diagnosed patients are younger, reaching 37.5 years in 2015), *the average age of prevalent individuals significantly rises, especially in women*: in 2015 it was 46.8 years for men and 48.4 years for women. This growth can be attributable to increased longevity of people living with MS, which has an important consequence: the *significantly growing number and proportion of elderly patients*, that is yet a rather neglected phenomenon. Indeed, in 2015 more than 10% of prevalent cases were older than 65 years. Once MS used to be regarded as a disease of young exclusively, but in the era of various effective disease-modifying treatments and rising life-expectancy of the general population as well, neurologists will have to face the challenge of the diagnosis and complex management of elder MS-patients. Not only the neurologic and non-neurologic comorbidities are more frequent among them (raising sometimes difficulties of differential diagnosis and also of contraindications for DMDs), but the accumulation of physical and cognitive disability as well.

Concerning drug dispension analysis, the *number of DMD-treated patients increases* each year. This feature is partly explained by the introduction of new DMDs in the Hungarian market and the growing number of prevalent MS patients. *The proportion of DMD-treated MS-patients also shows a significant growth, but still turned out to be rather low (29% in 2015),* that may partly be due to special restrictions of their prescription in Hungary.

Our above discussed results fit well in the epidemiologic changes of MS described in international and Hungarian scientific literature. These results and their comparison with data of other regions may help to clarify environmental and genetic factors possibly having role in patomechanism of MS. These data also have importance in understanding and estimating the burden of the disease on patients, families, healthcare providers, and society in order to plan future allocation of human and financial resources for complex management of multiple sclerosis.

6. Bibliography of the candidate's publications

The thesis is founded on the following publications:

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