Epidemiological studies in dementia

PhD thesis

Nóra Balázs MD

János Szentágothai Doctoral School of Neurosciences
Semmelweis University

Supervisor: Tibor Kovács MD PhD

Official reviewers: Péter Vajer MD PhD
Eszter Hidasi MD PhD

Head of Examination Committee: György Purebl MD PhD

Members of Examination Committee: Zoltán Hidasi MD PhD
Gábor Fazekas MD PhD

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1. Introduction

Dementia is a clinical syndrome characterized by progressive cognitive decline interfering with the ability to function independently, while the diagnosis of mild cognitive impairment (MCI) is used to describe symptoms that are measurable by cognitive testing but do not interfere with functional abilities. Several pathomechanism can lead to synaptic dysfunction, neuronal and glial cell death: in addition to toxic, infectious, metabolic, traumatic or vascular damage, the accumulation of intra- and extracellular pathological proteins is characteristic of dementias of degenerative origin. Mixed degenerative and non-degenerative processes make biomarker-based differential diagnosis difficult, currently, neuropathology (autopsy) is still the definitive diagnosis of degenerative nervous system diseases. The combined use of clinical course, neuropsychological tests, imaging procedures, cerebrospinal fluid biomarkers and genetic testing represent a significant advance in the most accurate *in vivo* diagnostics. Alzheimer's disease (AD) is the most common form of dementias, accounting for roughly 60% of all cases. Vascular dementia (VaD) and Lewy body dementia follow in the over-65 age group, while frontotemporal dementia is the second most common in the younger population after AD. With advancing age, the prevalence of dementia continues to increase, 90% affect the population over 65 years of age. In some countries (e.g. England, Scotland) dementias are among the leading causes of death, thereby placing an increasing social, health and economic burden on aging societies worldwide. It is estimated that in 2015, 45 to 50 million people had some form of dementia, generating a total cost of $ 818 billion that year, while that number is expected to nearly triple by 2050. In Europe and in the countries of the Western European region, the prevalence of any type of dementia in the population over 60 years of age has been estimated at around 7% and according to some estimates, this may also apply to the population of Central and Eastern Europe.

Therapeutic options for dementia are limited despite decades of research. Non-pharmacologic therapy primarily includes cognitive stimulation and rehabilitation, risk factor modification, social support, assistance with activities of daily living, long-term health care financial planning as well as providing support to caregivers. Currently the available pharmacologic treatment is only symptomatic, targeting neurotransmitter

disturbances in the brain. Disease-modifying medication is only beginning to emerge in clinical practice nowadays.

More than half of the people over the age of 65 should take five or more medications regularly for chronic diseases and more than half of these patients had complication to follow the recommendation of their physicians. Different types of dementias also mainly affect this age group and use precise use of different drugs is even more complicated because of the behavioral and psychological symptoms of dementia. It has been shown that antidementia medications are associated with longer survival, nonetheless the prevalence of their use and the compliance with them are quite different worldwide.

2. Objectives

2.1 Study of prevalence of MCI and dementia in Hungary

Recognizing and caring for people with dementia as early as possible during the course of the disease is essential for better life expectancy, both for patients and their caregivers. Previously, the number of affected people with dementia in Hungary was estimated by projecting the results of small population examinations of the residents of family medicine practices and nursing homes to the total population. However, these surveys considerably overestimated the number of demented patients, as compared to the international data. Our aim was to estimate the incidence and prevalence of dementia and its various forms (AD, VaD, miscellaneous dementia) using a multiple validated method covering the entire population and to define the age and sex distribution of patients, together with survival from the diagnosis in different forms of dementia.

2.2 Pharmacoepidemiological study of antidementia drugs

Causal therapy for dementia is currently unknown, but cholinesterase inhibitors (ChEi) and the NMDA receptor inhibitor memantine are available to alleviate symptoms (primarily in AD). Patients taking antidementia drugs are expected to improve both in their quality of life and their life expectancy after diagnosis. Our study aimed to explore the use of antidementia therapy and medication adherence in patients diagnosed with dementia.

3. Methods

Hungary has a single-payer health insurance system, while inpatient and outpatient care and medication prescription reports are documented in a unified system at a nationwide level enabling comprehensive data collection. The NEUROHUN database was created from these data, contained complete, professional care data, with the exception of general practitioner (GP) reports. The original patient identifier codes were anonymized and encrypted identifiers were used.

3.1 Definition of dementia

Based on the 10th edition of the International Classification of Diseases (ICD-10), all diagnoses with cognitive impairment were selected and then grouped into four categories (**Table 1)**.

Table 1. The ICD-10 codes of dementia subtypes and the definition of them

ICD-10 code	ICD definition	Definition in our study
F00	Dementia in Alzheimer disease	Alzheimer's dementia (AD)
G30	Alzheimer's disease	
F01	Vascular dementia	Vascular dementia (VaD)
F02	Dementia in other diseases classified elsewhere	miscellaneous dementia (mD)
F03	Unspecified dementia	
G31.0	Circumscribed brain atrophy	
G31.8	Other specified degenerative diseases of nervous system	
F06.7	Mild cognitive disorder	Mild cognitive impairment (MCI)

Only those ICD codes were selected which were given by medical specialty services; diagnostic and non-medical services were excluded.

The diagnosis of dementia or MCI was accepted only when the patient had at least two visits to a health institution with a defined diagnosis and received the diagnosis at least once from a neurological or psychiatric specialty service, thus enhancing the specificity of the diagnosis.

3.2 Selection of drugs

Prescription antidementia products available during the study period are summarized in **Table 2**. The date of prescription redeeming was analyzed, according to that patients were grouped into two classes: ChEi-fillers and ChEi-non-fillers. The ChEi-non-filler definition has not provided information that the ChEi has not been redeemed or has not been prescribed after prescription, so it does not indicate a lack of patient cooperation.

Table 2. Summary of antidementia drugs in Hungary Drugs are categorized according to their Anatomical Therapeutic Chemical (ATC) codes allowing them to be clearly identified

ATC code	Drug	Form	Dose (mg)	Min. effective dose (mg)	Recomm. daily dose (mg)
N06DA02	donepezil	tablet	5/10	5	10
N06DA03	rivastigmine	capsule	1,5/3/4,5/6	2x3	2x6
		oral solution	2mg/ml		
		transdermal patch	4,6/9,5 mg/24h	-	9,5mg/24h
N06DX01	memantine	tablet	5/10/20	-	20
		oral solution	5		
N06BX03	piracetam	tablet	800/1200	2400	2400-4800
		solution (infusion)	200mg/ml		
N06BX18	vinpocetin	tablet	5/10	15	15-30
		solution (infusion)	5mg/ml	20	20-50
C04AE02	nicergolin	tablet	30	30	30-60

3.3 Selection of the patients

Epidemiological studies were performed with data from patients diagnosed with dementia or MCI between 2011 and 2016. For the pharmacoepidemiological study, the analysis started in 2013; the period of 2011-2013 was used to exclude patients with ChEi or memantine fills in this period. Data till 2017 were available in the NEUROHUN at the time of the study, so patients were included till the end of 2016 in order to provide at least one year follow-up. (**Figure 1**).

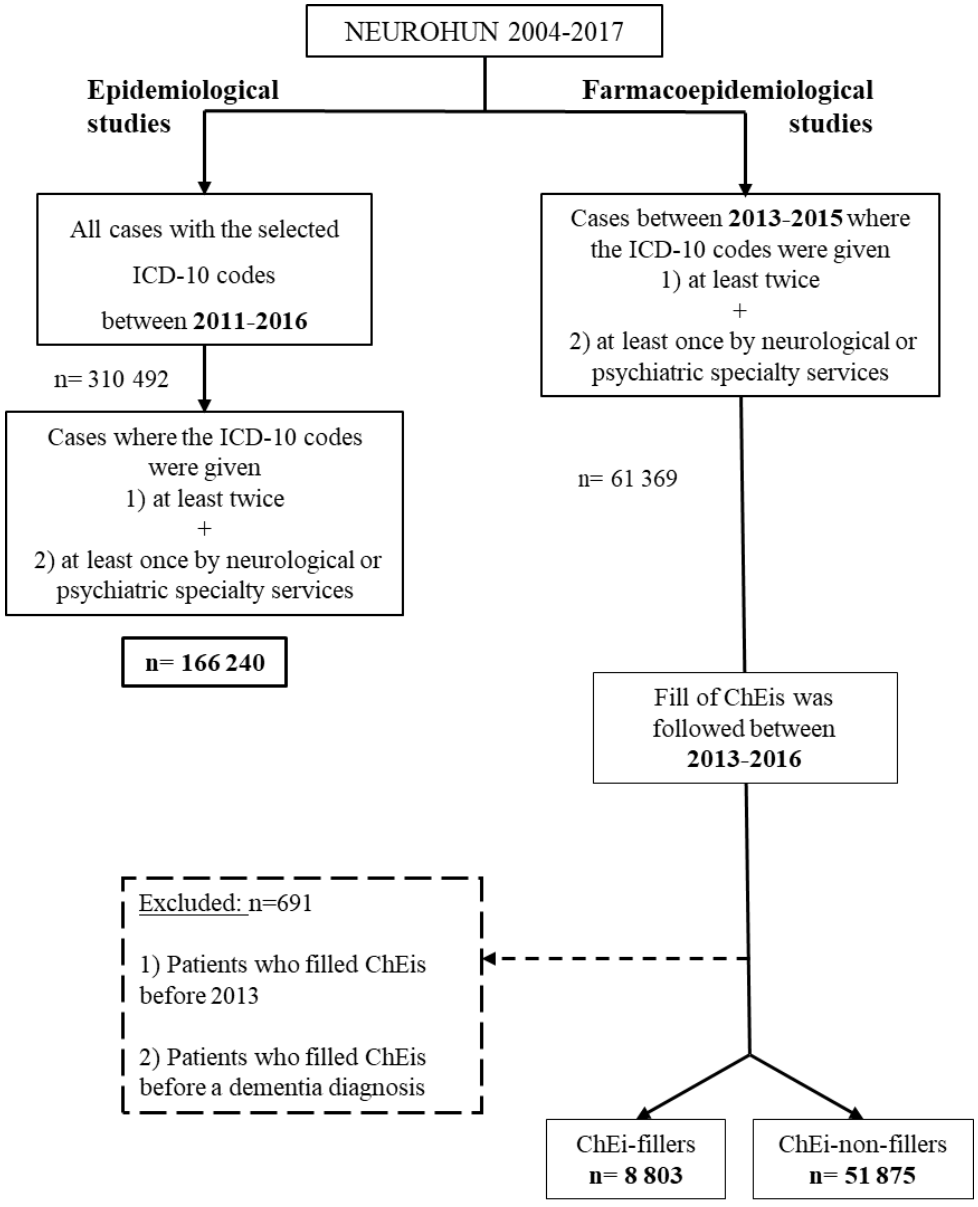

Figure 1 Flowchart of patient selection

3.4 Database validation

Validation of the clinical diagnosis criteria of dementias on a smaller subsample was performed. We checked patients who had records with the defined ICD-10 codes in the local integrated hospital healthcare information technology system (MedSol) of Semmelweis University, Budapest, in a selected period (October 2013) and we compared them to the records in the NEUROHUN database. For further clarification, we reviewed the medical records of these patients to ensure that the clinical findings support the diagnosis of dementia.

3.5 Analysis of adherence and persistence

Adherence was used to define the degree of redeemed prescriptions in a given interval by the application of the proportion of days covered (PDC) formula. Patients were divided into 3 groups: adherents were those with a PDC of at least 80%, partially adherents with a PDC between 20 and 79% and patients with a PDC less than 20% were categorized as non-adherent.

Persistence was applied to represent the duration of time over which a patient continued to fill ChEi prescriptions. In our analysis, the permissible gap (i.e. the threshold to the period of time with absence of treatment) was determined in 30 days. If a patient had gap(s) in its therapy longer than 30 days, the persistence was calculated as the mean of the periods.

3.6 Statistical analysis

Incidence and prevalence were calculated, data were analyzed by sex, age group and specialty services (neurology, psychiatry and both). Descriptive and survival analyzes were performed by type of dementia and for ChEi-filler and ChEI-non-filler populations.

4. Results

In the 2011-2016 period more than 1,956,000 (689,000 neurological, 1,087,000 psychiatric) appearances of 144,407 patients in the health care system were associated with any type of dementia diagnosis and 467,063 (148,773 neurological and 318,290 psychiatric) appearances of 21,833 patients with MCI alone, data from GP practices were not included. The incidence and prevalence of all dementias, AD alone (+/- MCI) and MCI alone were estimated from the mean of the annual values (**Table 3**).

Table 3 Summary of prevalence and incidence data of dementia types between 2011-2016

Incidence: new patients per 100,000 inhabitants/year, prevalence: number of patients per 100,000 inhabitants. Age standardization was performed using the 2013 European standard population

		All dementias	AD	MCI
Incidence	Crude	242	15	59
	Standardized	287	18	70
Prevalence	Crude	570	39	203
	Standardized	649	45	238

In the analysis by age, men are predominant in the 35-65 age group, while the ratio of women are higher under the age of 35 and over the age of 65. For the entire sample, more women were diagnosed with AD than men. With advancing age, the proportion of AD increased in both sexes, reaching the peak in the 80-84 age group, followed by a decline in male dominance. The mean age ranged from 70 to 80 years for all types of dementia (**Figure 2**). The mean age of the men was lower for all dementia types. The case fatality was the highest in VaD and the mortality rate for men was higher for all types.

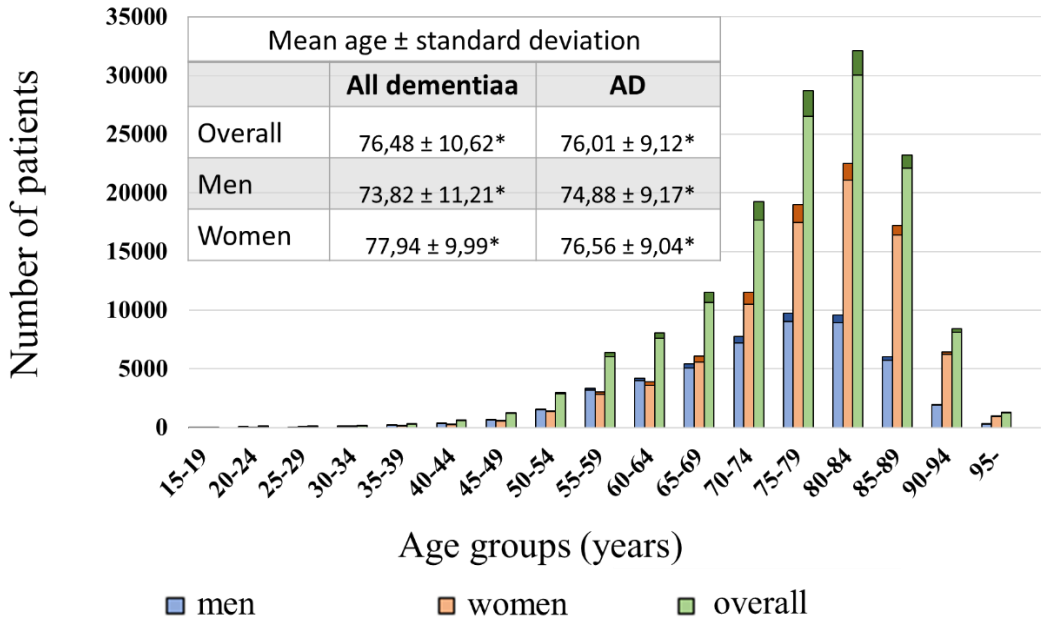

Figure 2 Cases of dementias and AD between 2011 and 2016 by age groups
The bars indicate the total dementia, of which AD is highlighted with darker colors

Dementia diagnoses were given by psychiatric specialty alone in 45.1% of the cases, while in 20.6% and in 34.3% by neurological and both specialties, respectively. There was a significant difference between the three groups in the mean age (one-way ANOVA, $p<0.00002$) and median survival after the diagnosis : the highest mean age and the shortest survival was observed in patients with diagnoses given by psychiatric specialties only. The survival was the longest in patients with neurological diagnosis.

The VaD:AD ratio was the highest in patients with psychiatric diagnoses only (4.85:1) and was the lowest in patients with only neurological diagnoses (1.32:1). Two-thirds of patients diagnosed without a head imaging visited psychiatric specialty services only (**Table 4**).

Table 4. Comparison of the neurological and psychiatric diagnoses
Patients were categorized according to which specialty gave the dementia diagnosis. The three groups are patient who were diagnosed only by neurological or psychiatric specialty or got diagnosis from both specialties. AD and VaD categories include the mixed pathologies as well. Differences between the mean age were significant (one-way ANOVA, *p<0.00002), the same was observed between the survival after the dementia diagnosis (logrank test, *p<0.0001).

ICD-10 code given by	**Neurologist**	**Psychiatrist**	**Both**
Nr. of patients	29,720	65,118	49,569
Nr. of AD diagnoses	8980	8873	15,731
Nr. of VaD diagnoses	11,869	43,024	30,465
VaD:AD ratio	1.32:1	4.85:1	1.93:1
Age (mean ± standard deviation)	74.39 ± 11.61*	77.61 ± 10.61*	76.27 ± 9.65*
Median (95% Confidence interval) years of survival after diagnosis	5.23 (5.11-5.41)*	2.25 (2.21-2.29)*	3.14 (3.08-3.19)*
Nr. of patients with head imaging	23 780 (80.0%)	39 725 (61.0%)	43 064 (86.9%)

The median survival after the first diagnosis in all dementia cases was 3.01 years. There was a significant difference between the types: survival was the longest with AD and the shortest with VaD (**Figure 3**).

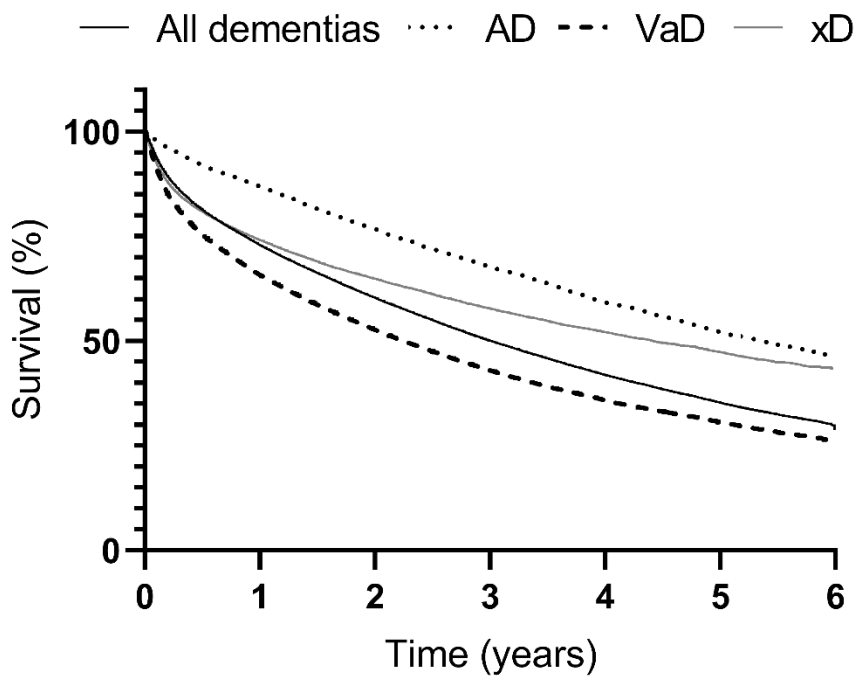

Figure 3 Survival from the diagnosis of dementia subtypes
plotted on a Kaplan-Meier curve, logrank test p<0.0001

The median survival in the ChEi-non-filler group was 2.50 years, while in case of ChEi-fillers, the median could not be determined during the analyzed period, as it was more than 4 years. The median survival was more than 4 years in all groups of ChEi-fillers and the mean survivals based on Kaplan-Meier analyses were significantly different, being 3.25 (CI95: 3.22-3.27), 3.1 (CI95: 3.00-3.22) and 3.4 (CI95: 3.29-3.51) years for donepezil, rivastigmine and switcher, respectively. Case fatality and survival were the worst in the ChEi-non-fillers, while the best in switchers (**Figure 4**). ChEi use had the strongest positive effect on survival (odds ratio (OR) 2.98, CI95: 2.82-3.14). Female gender was also protective (OR 1.80, CI95: 1.73-1.87), while older patients had the worst case fatality (OR 0.920, CI95: 0.917-0.921) (multiple logistic regression, p<0.00001).

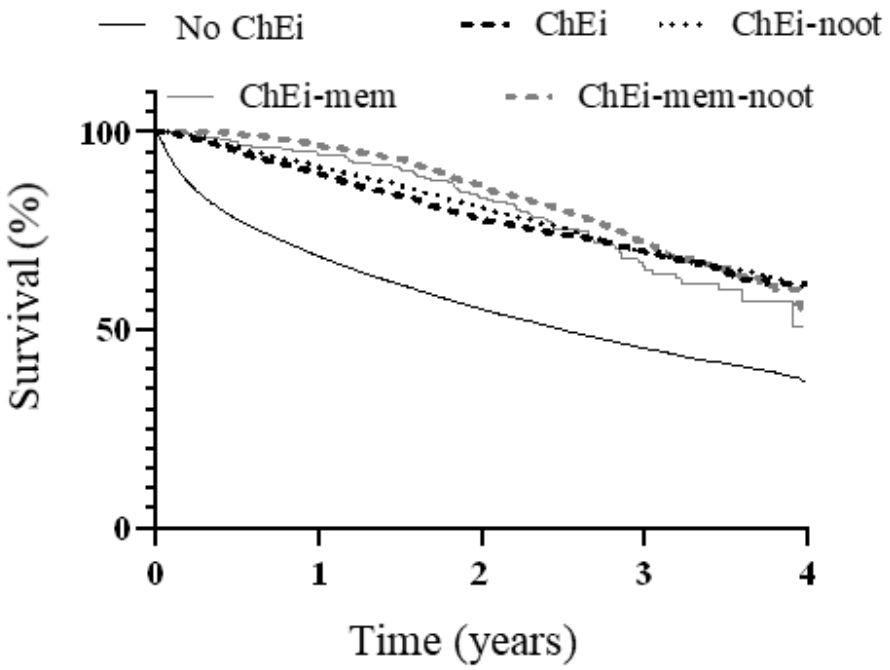

Figure 4 Survival of patients with or without taking ChEis
The median survival of ChEi-non-fillers was 2.50 years. In all groups of the ChEi-fillers the median survival was more than 4 years ($p<0.0001$). Among the ChEi-fillers, significant difference was found between ChEi vs ChEi-mem-noot (combination of ChEi, memantine and nootropics) ($p<0.0004$) and ChEi-noot vs ChEi-mem-noot ($p<0.0027$). (Combined used means that patients were filled with the drugs at least once during the study period, but not necessarily used the drugs simultaneously.) Kaplan-Meier curves, log rank test. Abbreviations: mem – memantine, noot – nootropics

19.7% of donepezil and 17.0% of rivastigmine fillers used ChEis for a maximum of 30 days. Among switchers, there were 14 patients (3.8%) taking ChEis for a maximum of 60 days. The median persistence for ChEis was significantly different in the 3 groups. Non-adherent patients also had a short persistence, while adherent patients had longer prescription-filling durations. The adherence to donepezil and rivastigmine was similar, while in the switcher group, the proportion of partially adherent patients was higher (**Figure 5**).

Figure 5 Adherence and persistence of all ChEi filler patients

The adherence was categorized in 3 groups on the X axis, while persistence was visualized as a continuous time line in days on the Y axis. Each dot represents a patient, donepezil was marked with grey, rivastigmine with blue and switcher with purple

5. Conclusions

In Europe and in the countries of the Western European region, the prevalence of any type of dementia in the population over 60 years of age was estimated at around 7%, and it is supposed that this also applies to the population of Central and Eastern Europe. Based on our results, the prevalence of any type of dementia in Hungary over the age of 65 is only 2.5%, suggesting that it is considerably underdiagnosed. It is possible that patients with MCI and in early stages of dementia were managed in the GP practices and they were referred in later stages for specialty services. In addition to the late detection, a significant problem could be that according to the strict national regulations in Hungary, prescriptions of antidementia medication must be made by a neurologist or a psychiatrist, the specialist's recommendation for the products cannot be issued to the GP, so there is no way to temporarily relieve cognitive symptoms in patients who are out of sight of neurological and psychiatric specialty services.

The ratio of VaD to AD is approximately 1:3 in Europe and in the United States, while in the developing countries it is 1:2. In our study, the ratio of the VaD and AD diagnoses was reversed, 2.54 times more VaD diagnoses were assigned than AD (this ratio includes mixed diagnoses also). When accounting pure VaD and AD diagnoses, VaD:AD ratio increases to 3.95:1. The VaD:AD ratio was the lowest among those receiving neurological care alone, although it was still the opposite compared to international data (1.32: 1). It could be hypothesized that neurologists might more often notice the focal signs of cerebral circulatory problems during physical examination and indicate head imaging, as well as in the absence of symptomatic vascular lesions on imaging studies they less frequently diagnose VaD. Accurate differentiation between types of dementias is important not only for the choice of the ideal treatment, but also because of the quality of life of patients and their caregivers, which could be significantly different. There is a significant difference in the course of different types of dementia: survival is worse in VaD followed by all dementias and AD. In our study, the median survival of patients with all dementias (3.01 years) was shorter than the published ones (3.2-6.6 years), being the shortest in VaD (2.25 years).

Antidementia medications are associated with longer survival, nonetheless the prevalence of their use and the compliance with them are quite different worldwide. During the 4-year period, only 14.5% of patients with a dementia diagnosis filled at least one ChEi

prescription. The strict national regulation of ChEi-prescription could also influence the availability of antidementia drugs: the diagnosis of dementia and prescriptions of ChEis must be made by a neurologist or a psychiatrist and continued prescription depends on the progression rate of the disease measured on the Mini Mental State Examination (MMSE) test. This may play a role in interrupting the continuity or in leaving therapy, as referrals to specialty services, waiting lists, and approach of the outpatient department may all make it difficult for a patient to access medication.

Among the ChEi-non-fillers, the proportion of nootropics users was outstandingly high, two-thirds of the them took at least one of these drugs. Nootropics may have a beneficial effect on cognitive function, but their use is not or just partially included in current therapeutic recommendations. In our study, the survival of ChEi-filler patients was significantly longer than in ChEi-non-fillers. The survival was also significantly longer in patients taking only nootropic drugs than in patients with no medication (data not shown). Multivariate analysis confirmed that ChEi-filling was an independent significant predictor, even after data were adjusted to age and gender as well. It could be hypothesized that ChEi-fillers had a more consistent medical attention, which is also supported by the more common use of neuroimaging among them. In addition to the hardly but significantly lower mean age of ChEi-fillers, these patients might be in earlier stages of dementia, suggested by the fewer inpatient appearances.

Classifying dementias is a major challenge for clinicians, considering there are no high sensitivity confirmation markers. The diagnosis is based on physical examination, neuropsychological tests, imaging studies and long term follow-up. Our results showed that both dementia and MCI were significantly underdiagnosed in Hungary, and the categorization of patients into dementia subtypes is also different from international data. The high incidence of miscellaneous dementia in international and Hungarian data may be due in part to diagnostic difficulty, but also presumably includes dementias and encephalopathies caused by reversible causes.

Efforts should be made to identify the type of dementia as accurately as possible, in which increasing the number of skull imaging studies may be helpful, because the course of each form of the disease is very different. Furthermore, there is an urgent need to clarify and correct the causes of median survival, which lag far behind the international data.

In addition to determining the correct diagnosis, it is important to start the available antidementia therapy as soon as possible, as this can significantly improve the survival of patients and the quality of life of them and their caregivers.

A significant proportion of patients are unlikely to be admitted to specialist neurological and psychiatric care, and the training of primary care providers could improve the number of cases recognized and taken into care. Furthermore, educating professionals about the applicability of available antidementia drugs could increase the proportion of those receiving therapy.

6. Publications

In relation to the present thesis:

Balázs N, Ajtay A, Oberfrank F, Bereczki D, Kovács T. (2021) Dementia epidemiology in Hungary based on data from neurological and psychiatric specialty services. Sci Rep. 11:10333., **IF: 4,38**

Balázs N, Bereczki D, Ajtay A, Oberfrank F, Kovács T. (2022) Cholinesterase inhibitors for the treatment of dementia: real-life data in Hungary. Geroscience. 44:253- 263., **IF: 7,713**

Balázs N, Kovács T. (2021) Heterogeneity of Alzheimer's disease [Az Alzheimer-kór heterogenitása]. Orv Hetil. 162:970-977., **IF: 0,54**

Balázs N, Bereczki D, Kovács T. (2021) Cholinesterase inhibitors and memantine for the treatment of Alzheimer and non-Alzheimer dementias. Ideggyogy Sz. 74:379-387., **IF: 0,427**

Other publications:

Balázs N, Milanovich D, Hornyák C, Bereczki D, Kovács T. (2019) Late-onset Niemann-Pick disease type C overlapping with frontotemporal dementia syndromes: a case report. J Neural Transm (Vienna). 126:1501-1504., **IF: 3,722**