The epidemiology of stroke and the organisation of stroke care in the light of epidemiological data in Hungary
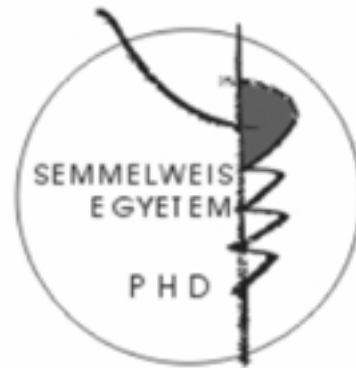
Doctoral Thesis

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1. Introduction

Of the adult neurological diseases, cerebrovascular diseases have a leading role, regarding both frequency and significance. About 50% of neurology departments' patients are admitted due to stroke or TIA. According to the WHO definition, stroke is any sudden onset of focal or global neurological deficit, that persists for more than 24 hours, or causes death within 24 hours, and that has no other proven background, than disturbances in cerebral circulation. Although stroke mortality has deceased in the worlds industrialised countries steadily since 1915, till the 60`s with a yearly average of 1.5 %, in Eastern Europe, thus in Hungary, the mortality statistics from the 1950`s to the end of the 80`s registered a significant increase, which since has again decreased due primarily to the development of acute stroke care. Presently, in our country, there are 25-28 000 hospital admissions due to acute stroke annually, and about 12 000 deaths are registered as a result of stroke on an annual basis.

Over the past three decades, many population-based epidemiological studies have been made in different ethnic groups in various countries of the world, which have demonstrated significant differences in stroke incidence, in relation to mortality and case-fatality rates. Low stroke mortality can be seen in Western Europe, North America and Japan, while the mortality rate is extremely high in Eastern Europe for example, such as in Hungary. During the incidence examination of the *Monitoring Trends and Determinants of Cardiovascular Disease* (MONICA) a similar degree of differences were found among those, bellow 65 years of age.

Figure 1. Standardised stroke deaths per 100 000 residents in Hungary and in the EU from 1985-2000. (WHO Database)
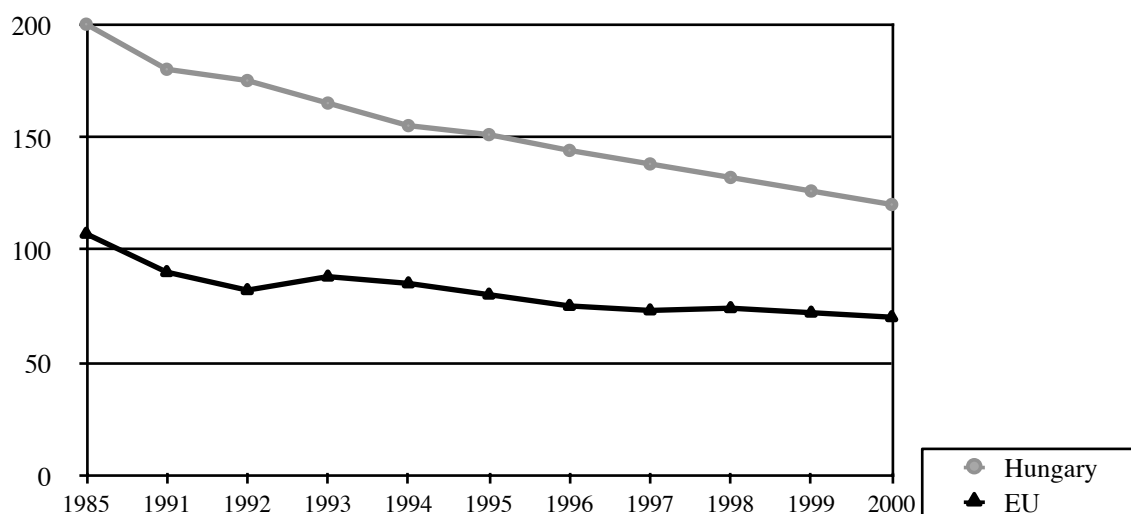
Figure 1. shows the changes in stroke mortality in our country and the European Union prior to the millennium per 100 000 inhabitants. Despite the positive trend experienced from the mid 80`s, during our study the cerebrovascular mortality has still always been at least twice the amount as in Europe`s developed countries.

Another unresolved issue at the time of our examination were the role of stroke units and stroke teams in acute care. Previous studies confirmed the positive impact of specialised and organised acute stroke care in disease outcome. Organised stroke care can mean either, separate stroke units with independent staff, or stroke teams working in other departments. Although both forms of care have been proven to be effective, a growing number of studies suggested, that the stroke units are more efficient. However, these studies often detected such groups of patients, that did not prove the benefits of organised care, and there was no difference when comparing case-fatality and favourable outcome.

These contradictions raise the possibility that the significance and effectiveness of the stroke departments and stroke teams are different according to region and country, and confirm that beyond a given countries basic reliable stroke epidemiological data estimates, the importance of the descriptive local examination of stroke-care efficiency is invaluable.

2. Goals

My doctoral dissertation has triple aim. On the one hand, based on the results of national epidemiological studies, I would like to give an overall and accurate picture of the Hungarian epidemiological data measured during our studies, through stroke incidence estimates, as well as acute stroke events one month case-fatality rate.

In the analyst epidemiological part of my dissertation, which is also supplemented by the results of a Japanese-Hungarian scientific cooperation, I will present in detail my conclusions, resulting from data acquired during our studies, about stroke mortality, stroke incidence and the population and ethnic difference in stroke outcome predictors and of their explanation. Finally, based on our data, I will analyse the impact that the national stroke centres work has on stroke outcome in our country.

3. Methods

3.1. The Hungarian Stroke Database

The raw material of my dissertation was provided by a standardised Hungarian stroke questionnaire, based on an earlier cooperation, the European Stroke Database`s (ESDB) Project questionnaire, that also defined the structure of the Hungarian Stroke Database. With the national cooperation of 11 regional stroke centres (Győr, Sopron, Szombathely, Nagykanizsa, Székesfehérvár, Vác, Miskolc, Balassagyarmat, Salgótarján, Kecskemét, Gyula) all acute stroke or TIA patients data were recorded in our registry, coming from the coming from the catchment area of these centres, over 18 months, from 1997-1999.

3.2. Patient selection

Stroke unit admitted patients data were recorded separate to those admitted to other departments in study hospitals, who were seen to in a consultative manner by the stroke department's specialists, as stroke teams. We defined stroke based on the WHO definition. In each case we recorded whether it was a first or recurrent stroke.

The centres monthly sent stroke data were compared to the GYÓGYINFOK database. (BNO 9th revision. According to classifications 430-434 and 436), and we requested those centres where there was discrepancy between the number of patients admitted to the hospital to those in the database, to rectify the irregularities. The checking of patient numbers, and the whole duration of the investigation was conducted under the current requirements for the protection of patients' rights, only the care supplying institutes were allowed   to identify their patients using the databases information.

3.3. Collected data

Besides the demographic data collected in the database, the data also included the clinical features of stroke or TIA, previous vascular risk factors, classification of stroke according to pathomechanism, and the 28-day outcome. Risk factors included hypertension, atrial fibrillation, diabetes mellitus, ischemic heart disease, current smoking and alcohol consumption.

We determined the stroke subtypes according to pathomechanism, as cerebral infarction (CBI), primary intracerebral hematoma (PIH) , and subarachnoid hemorrhage (SAV). In the absence of brain imaging studies or pathological findings, we considered the specific stroke event non classifiable (NO).

The stroke outcome was measured by the 28 day case-fatality rate, as well as hospitalisation rate on the 28th day. The questionnaires were filled in by the participating centres' neurologists.

3.4. Stroke incidence in Hungary

In the calculation of raw and age standardised stroke incidence we only took into account first stroke events. According to the 1991 census data, the examined Hungarian centres fully covered stroke care for 1.527.752 inhabitants. With respect to the high-proportion of non-classified subtype strokes (17.7%), and in the interest of a more precise subtype specific incidence rate calculation, we selected those 3 centres, where the number of classified cases reached 95%, and calculated a new incidence rate, based on the catchment area of these centres.

3.5. Calculation of stroke incidence in Japan

Akita Prefekture had a population of 1.227.049, according to the 1995 census data. The 37 hospitals responsible for the area`s care, have all been involved in the Akita Stroke Database since 1983. All stroke events are classified taking into account the regions key stroke epidemiological importance for the most accurate data possible, using CT, MRI or pathological examination, or post-mortem imaging, if the vent that religious causes did not allow for pathological examination.

The chief epidemiologist doctor of this project compared the database to the admissions' database of the 37 hospitals monthly, in order to reveal and make up for any missing data.

3.6. The comparison of stroke units and stroke teams in Hungary

Acut stroke units, stroke departments, were defined as having separately allocated stroke beds with specially trained staff as well as stroke neurologists. The treatment guidelines were determined by the 1996 AHA guidelines which relate to acute patient care. These patients received regular Salicylate, provided they suffered ischemic stroke, in addition the acute treatment was directed at 1) early mobilisation, 2) deep vein thrombosis prophylaxis, 3) the control of any possible fever and hyperglycaemia. In the event of potential cardiogenic origin cases the patients received anticoagulation. Intensive, semi-intensive monitoring was carried out in the vast majority of the patients within the first 24 hours.

Those patients, who were admitted to other departments for lack of capacity on stroke units, were examined by the same multidisciplinary team members of the hospitals stroke unit, but on a consultation bases. Just like in the stroke units, CT, MRI

examinations were carried out routinely among these patients. Stroke patients lying in other departments were examined by stroke specialists at least 4 times: on admission, after 24 hours, after one week and on the 28th day. The transferring of patients to other departments or other hospitals did not affect the content and data of the following examinations, telephone follow-up was possible if needed.

3.7. Statistical analysis

3.7.1. Stroke incidence

For incidence calculation, we used the 1991 Hungarian and 1995 Japanese census data, and standardised to the European population. The age-specific and age-standardised confidence intervals (CI) were calculated according to the Poisson distribution.

3.7.2. Demographic data, risk factors and stroke subtype comparison, as well as outcome predictors

We compared the demographic data, such as age, gender, ethnicity, with ANOVA, using Tukey-test for post hoc pairwise comparison. The risk factor profile and stroke subtypes were analysed using the Pearson's Chi-square test, the significance levels of these risk factors were corrected according to Bonferroni, eliminating any misleading effect of multiple calculations. We examined the outcome predictors with multiple logistic regression models, were (1) age, (2) gender, (3) previous stroke, (4) atrial fibrillation, (5) hypertension, (6) diabetes mellitus, (7) ischemic heart disease, (8) smoking, (9) regular alcohol consumption, (10) impaired consciousness on admission and (11) stroke subtype where the covariates.

3.7.3. Comparison of stroke units and stroke teams

To analyse the impact of stroke care in organised, specialised stroke units on the outcome, we also used multiple logistic regression models, where the covariates were (1) gender, (2) age group, (3)impaired consciousness experienced on admission, (4) stroke subtype and (5) the admissions department. We calculated all variables for the odds ratio (OR) and the 95% CI.

3.7.4. Statistical software

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS) 10.0 and 11.0 software.

4. Results

4.1. Demographic data in Hungary

When comparing genders in the domestic population there was a 4-5 year deviation: the average age of men who suffered stroke is 4-5 years less than among women. However, both the women's and men's average age at the time of the study was over retirement age (Table 1).

Table 1. Age of stroke patients in Hungary.

	men	women
Average	65	69
Median	66	71
Mode	72	76
Standard deviation	12	12,33

4.2. Circumstances of hospitalisation

In our study hospitals, the highest rate of patients were admitted to stroke units. There were also a significant number of patients treated on internal medicine or neurological departments (Table 2).

For comparison reasons it is important to note, that the case-mix index for the various admissions departments were about the same.

Table 2. The distribution of stroke patients according to admissions departments.

admission departments	N
Stroke unit	6340
Internal medical ward	1164
Neurology	1072
Intensive care unit	88
Emergency ward	50
Neurosurgery	9

admission departments	N
Stroke unit	6340
Rehabilitation	2
Private hospital	1

4.3. Early mortality data

Post stroke mortality was significantly higher in the national database (GYÓGYINFOK) which contains data for the whole country, than in our database.

Table 3. Number of stroke cases in Hungary in 1998 (based on the GYÓGYINFOK database).

	N	early mortality (%)
Stroke units	7 668	16,9
Other wards	27 834	18,56
Total	35 502	18,22

The significantly lower case fatality rate in stroke unit patients, while comparing national data, was striking (P<0.001), confirming the key importance of acute stroke care (Table 3).

4.4. Results of the Japanese-Hungarian comparative analysis

During the 18 months of the study, we registered 12.397 stroke cases in the Japanese-Hungarian combined database, including 9658 first ever strokes. The stroke patient's average age in Hungary was significantly lower in both genders: 64 and 67 years in men (p<0,001), 69 and 71 in women (p<0,001).

Table 4. details the distribution of age, gender and stroke subtypes in the studied population: in addition to average age, there was a significant difference in men to women ratio and stroke subtypes.

Table 4. The studied population distributed by stroke subtype, age and gender.

	Akita	Hungary	p
	(N=2991)	(N=6667)	
Age (average, ± SD)	69.52 ± 12.10	66.44 ± 12.60	<0.001
Gender (male), (%)	1609 (53.8)	3336 (50.0)	0.001
Stroke subtype, N (%)			
PIH	792 (26.5)	519 (7.8)	<0.001
CBI	1843 (61.6)	4875 (73.1)	<0.001
SAV	356 (11.9)	94 (1.4)	<0.001
NO	0 (0)	1179 (17.7)	

4.4.1. Stroke incidence

The raw incidence rates by age and geographic region are shown in figure 2. Stroke incidence increased in both populations by age, especially over the age of 70, and men and a higher risk of stroke in both populations.

Comparing the raw incidence rates in these two countries, the Hungarian data, without exception was higher than the estimated rates in Japan, in all age groups.

Figure 2. Stroke incidence per 100 000 inhabitants by geographical region and age groups.

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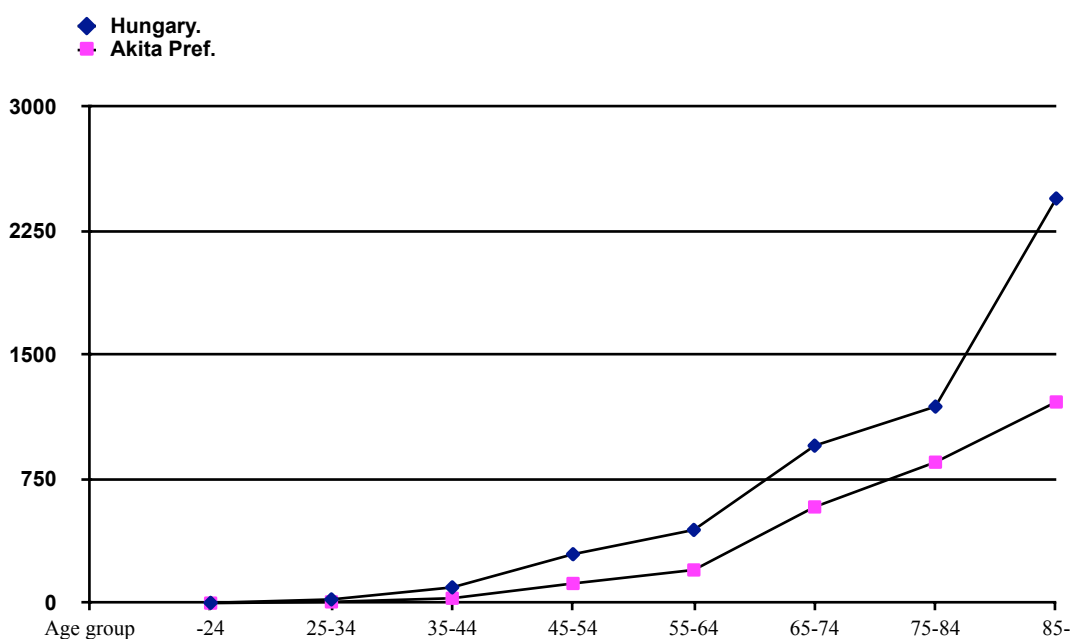
Raw and standardised incidence rates by stroke subtypes and geographic regions are shown in table 5. We measured significantly higher incidence of PIH and SAV in Japan, while the frequency of CBI was significantly higher in our country. These differences were also backed up by the three Hungarian centres' separate analysis, that reached higher than 95% of classified stroke events.

Table 5. Raw and age-standardised stroke incidence rates by stroke subtype

	Akita	Hungary	Selected centres in Hungary
PIH			
raw incidence	43.4	23.6	27.7
95% CI	39.7 - 47.1	21.1 - 26.0	20.0 - 35.6
age standardised	34.0	19.5	23.4
95% CI	30.7 - 37.2	17.3 - 21.7	16.1 - 30.4
CBI			
raw incidence	101.2	216.0	250.4
95% CI	93.4 - 104.6	208.7 - 213.3	226.6 - 274.3
age standardised	75.2	171.1	200.3
95% CI	70.3 - 80.0	164.5 - 177.7	178.9 - 221.6
SAV			
raw incidence	19.4	4.4	4.75
95% CI	16.9 - 21.9	3.4 - 5.4	1.5 - 8.0
age standardised	15.3	3.8	4.3
95% CI	13.1 - 17.5	2.8 - 4.7	1.1 - 7.4
Not classified			
raw incidence	-	53.1	14.2
95% CI	-	49.4 - 56.8	8.5 - 19.9
age standardised	-	45.4	11.9
95% CI	-	42.0 - 48.8	6.7 - 17.11

*selected centres in Hungary: the three Hungarian centres, where the number of classified stroke cases reached 95%.

4.4.2. Case-fatality rates

Table 6 shows case-fatality rates by region and stroke subtype, with significantly lower results in Japan. However, the case-fatality rates of CBI, SAV and all stroke events for those patients in Hungary, who were admitted to accredited stroke units, were not significantly different from those in Japan.

Table 6. Subtype specific case-fatality rates by region.

	Akita	Hungary (stroke units)	P
PIH	15.6	33.9 (32.4)	<0.001 (<0.001)
CBI	7.4	9.2 (8.4)	0.008 (0.057)
SAV	28.9	39.8 (33.3)	0.031 (0.421)
Total	11.8	13.3 (12.6)	0.023 (0.238)

4.4.3. Outcome predictors

Advanced age, impaired consciousness at admission, SAV and male gender predicted higher rate of case-fatality in both populations. However, atrial fibrillation, hypertension, diabetes mellitus and PIH only worsened the chances of survival among the Hungarians. These latest predictor's effects were not influenced by whether the patients were treated in stroke units, or other departments. In contrast CBI resulted a unanimous lower case-fatality rate in both populations.

4.5. The comparison of stroke units and stroke teams

A total of 8743 stroke events were recorded during the 18 month of our study in the Hungarian centres. Patients admitted to stroke units were significantly younger with an average age of 64 years, compared to the 67 year average of those stroke patients admitted to other departments, (p<0,001) and these patients' 28 day case-fatality rate was also significantly lower: 12,6% opposed to 15,2% (p=0,002).

However, if we compared the case-fatality rates by age group, the positive impact of treatment at a stroke unit was only detectable up until the age of 60, ceasing to exist above this age.

Table 7 details the outcome predictors. The advantage of stroke unit care was confirmed for the whole study population by multiple logistic regression model. (OR 1.701; CI:1.025-2.822).

Table 7. Outcome predictors. Multivariate logistic regression model.

	P	OR	95% CI
Type of care (stroke unit)	0.047	1.701	1.025-2.822
Age	< 0.001	1.444	1.355-1.538
Gender (female)	<0.001	0.736	0.633-0.855
Impaired consciousness at admission	< 0,001	3.759	3.497-4.042
Hemorrhagic stroke	< 0.001	1.157	1.067-1.253

OR and 95% CI larger than 1 predicts higher case-fatality rate.

Stroke unit care did not improve the case-fatality rate among those patients who were not independent (mRankin>=2) prior to their stroke: 17,8% compared with 20,3% (p=0,163). There were also similar results among those over 60, using multivariate analysis (case-mortality ratio: 14,8%, or 15,9% ; p=0,250). The beneficial effect of stroke unit care on case-fatality rates could be justified among those under 60`s and formerly independent (modified Rankin scale <2) (case-fatality rate 6.8% vs. 12.2%, p=0.001, OR: 1.110-3.245).

However, patients above 60, or those not independent prior to their stroke, more often left the hospital by the 28th day, if treated on stroke units. Meanwhile, this effect was not confirmed among those, who were formerly independent, and over 60

5. Conclusions

The necessity of a unified strategy in a comprehensive national professional program was formulated in Hungary in 1992, which took form in the National Stroke Program. The primary objective of the program was reached, as stroke mortality

decreased. In addition to the improvement of mortality rate, it would also be in interest to analyse how the program lived up to expectations with regards to other well-known indicators in stroke care.

5.1. The Hungarian database basic information

According to epidemiological data, the average age of stroke patients in our country is significantly lower, than in the Western European countries. Worldwide, in similar stroke databases, there is a higher overall average age in women. At the same time, the high case-fatality rate among young men, asides from public health factors, raises the role of sociological factors as well. Further testing of this seems essential in the future.

Despite the organisation of stroke centres, during our study, according to GYOGYINFOK data, 3 / 4 of stroke cases were not admitted to stroke units, even throughout the country, but explicitly among the centres participating in the study, there was a clearly lower early case-fatality rate among the patients in these centres (12.1%, compared to 18,56%). These results indicate the effectiveness of these experienced and motivated teams in our study hospitals.

The justification of the organisation of these stroke units have been demonstrated by a number of previous studies. In our own data, the lower case-fatality, and better functional outcome justifies the existence of stroke units. At the same time, due to our analysis, it is clear, that only suitably equipped specialised wards are able to fulfil their tasks.

5.2. Hungarian-Japanese comparative epidemiological studies

Our prospective epidemiological study built on large databases demonstrated a significant difference, in both stroke subtype specific incidence in case-fatality rates, and in the studied populations. This observation corresponds with the result of those previous comparative studies, that compared different periods of time, or different age groups. As a result of our cooperation, with regards to both populations, we were able to carry out incidence estimates, based on reliable and representative data. At the time of our study, no other Eastern-European stroke epidemiological study was larger than ours.

In addition, our international cooperation demonstrated a difference in outcome predictors between regions and populations as well, and there have been no similar findings in any previous comparative studies.

These results are essential for the planning of effective stroke prevention and acute care programs of public health, in a given population.

5.2.1. Stroke incidence

The age-standardised subtype specific incidence rates showed large differences in the studied populations. A lower incidence of PIH and SAV was measured in Hungary, while the incidence of CBI was twice as high as the values measured in Japan. The incidence rate of all stroke events in Hungary were higher than in Japan in all age groups, and this difference was particularly high under the age of 65. In the later context, taking into account the difference in life expectancy between the two country`s population (80 years in Japan, 69 years in Hungary), it explains the Hungarian stroke patients lower age average, even if the difference in the average age was considerably lower than could be expected due to the differences in life expectancy.

The higher incidence of hemorrhagic strokes in Japan could be a good explanation for the lower than expected average age in Akita, since these stroke subtypes (PIH, SAV) affect a younger population.

Neither of the studied countries health care neglected the hospital admission of elderly patients, a fact which allowed both the determination of average age and exact incidence calculation.

The differences in the incidence of cerebral infarcts could be explained by differences in the prevalence of vascular risk factors in the two populations, however a similar correlation for hemorrhagic strokes cannot be assumed. Hypertension, as the most important predictor for PIH, was more frequent in the Hungarian population, although the incidence of PIH was significantly higher in Japan, even if the subtype specific incidence rate was calculated from the data of the three selected stroke centres. Factors, effecting the degree of hemorrhagic stroke events, such as the prevalent use of salicylic acid in the given population cannot explain the observed variation alone. An even more significant difference was shown in the comparison of incidence of SAV: in Japan, the age standardised incidence was four times higher, and this was confirmed by the data analysis of the three selected stroke centres in Hungary as well. It is well-known from the literature, that both the PIH and SAV occur more frequently in the Asian, African-American, and Hispanic-American population. The results of these studies have called attention to the fact, that there are more important factors influencing stroke incidence. Dietary and lifestyle habits may cause equally significant differences in a given populations, besides genetic predisposition, and most likely our present research supports this. The incidence of PIH and SAV in Hungary

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corresponded with the incidence rates, measured in the Western-European population, and this determination in relation to PIH is definitely surprising. At the same time, the incidence of CBI was about more than twice in our country.

5.2.2. Case-fatality rate

The 28 day case-fatality rates by stroke subtypes in Hungary was higher in each subtype, most pronounced in PIH. As the Hungary stroke patients were treated either by accredited stroke units , or stroke teams, we had the opportunity to analyse the impact of organised stroke care on the outcome after stroke. When comparing the Hungarian stroke units with the Japanese hospitals during the same time period, there were no significant differences in the 28th day case-fatality rates for CBI and SAV. This proves that the 28 day case-fatality rate strongly depends on the level of acute care, giving us a further guideline to develop the capacity of the existing stroke centres.

5.2.3. The 28 day outcome predictors

Despite many previous large clinical trials, to date there are a lot of unanswered questions in connection with acute stroke outcome predictors. In previous publications, when examining the role of predictors, there were controversial results regarding the importance of these factors. The results of our present study suggest, that the determinants of early outcome may differ in various populations, different geographical regions and most of all, with different standards of acute stroke care. This may explain the inconsistencies revealed in the results of previous studies in addition to the methodological problems, or the differing definition of certain variables producing misleading results.

From a public health point of view in Hungary, to reduce stroke incidence and stroke mortality, we must confirm and develop the prevention of ischemic stroke, since the higher incidence of all strokes is the consequence of higher incidence of ischemic strokes. In addition, we must also aim to expand the capacity of the stroke units, as the positive impact of organised stroke care was evident during our study. The way forward in Japan lies in the prevention of hemorrhagic strokes.

5.3. The stroke units and stroke teams effect on stroke outcome

Although our present studies verified the stroke units' positive impact on stroke outcome, the extent of this were very different in various patient groups. Patients, admitted to stroke units, had a higher chance of survival if they were under 60, or were independent prior to their stroke. The specialised care, provided by the stroke units in

these two patient groups, however, did not affect the proportion of patients requiring hospital stay at the end of the 4th week.

Meanwhile, those over 60 or not independent prior to their stroke, often left the hospital before the 28th day, as long as they were treated at stroke units, although the 28 day case-fatality of these patient groups did not depend on the type of care.

From our study it follows, that the stroke unit provided care cannot be reproduced in other hospital departments, even if the patient`s hospital treatment is overseen by the same clinicians. Moreover, despite what we experienced during mortality comparison, we could not distinguish any patient groups, whose stroke unit care would not have been some kind of an advantage in their disease outcome. This fact, namely, that the stoke units' work surpasses the stroke teams effectiveness, has the utmost importance.

Our study received high priority in assessing the impact and effectiveness of the National Stroke program launched in 1991, as well as in the designation of the program's further goals and tasks.

6. List of publications

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