THESIS FOR THE DOCTOR OF PHILOSOPHY (PH.D.) DEGREE

STROKE EPIDEMIOLOGICAL INVESTIGATIONS IN CENTRAL-EASTERN EUROPE

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1. INTRODUCTION

1.1. Justification of the research subject

Stroke is the third leading cause of death and the most important cause of long term disability in Western countries. Considerable decrease in stroke mortality has been observed in developed countries until recently probably due to better control of hypertension and other risk factors in the population. In contrast to other countries of the industrialized world, Hungary had a dramatic increase in mortality between 1970-1992. Among European countries Hungary had the highest increase in cerebrovascular mortality, and was the only country where this increase was higher than that of cardiovascular mortality between 1970-85.

Comparing trends in 27 countries Bonita et al (1990) found that in the period of 1970-1985 countries of the former Eastern block had the highest increase in stroke mortality. Although in some of these countries, like in Hungary, stroke mortality rates started to decrease in the last decade, in others, like Romania and Ukraine the trend is either high stable or still increasing. Decreasing trends in stroke mortality in Western countries were assumed to be associated with a better control of risk factors, especially hypertension and it has also been reported, that although stroke mortality has decreased, the total number of strokes (i.e. incidence) was stable or even increased. We might assume that the decrease in stroke mortality is at least due to the decrease in stroke severity: a better control of risk factors could have resulted in a tendency of increase in milder strokes in countries with effective primary prevention. Despite the high stroke morbidity and mortality, prospective epidemiological studies have been scarcely done in Central-Eastern European countries, and most available data are from official mortality reports.

1.2. Aims

Because of lacking accurate epidemiological data we found it important to perform epidemiological investigations in the Central-Eastern European region. Our investigations had three directions. First, we developed a stroke database in a stroke unit of the Debrecen University (Debrecen, Hungary). This unit had been established at the Department of Neurology in 1974, i.e. it was among the first stroke units in Europe. Second, we performed a population based study of stroke incidence and mortality in the city of Uzhgorod, Ukraine. Third, we

compared hospital stroke services in 3 cities of 3 former Eastern block countries: Debrecen (Hungary), Uzhgorod (Ukraine), and Târgu Mureş (Romania).

1.2.1. AIMS OF THE DEBRECEN STUDY

We report basic characteristics of a stroke unit established in 1974 at the neurological department of a university hospital in Eastern Hungary. To check if one stroke unit bed for 10.000 inhabitants covers the need of the catchment area we compared the number of stroke patients treated at the stroke unit to the number of stroke patients treated in the same calendar year at all departments of internal medicine covering the same catchment area. With our analyses we wanted to get answers to the following questions:

- How many patients with acute cerebrovascular disease (CVD) are treated at the stroke unit during a calendar year ?
- What is the distribution of different stroke types?
- Is there any difference between men and women in age and in case fatality?
- What is the application rate of different diagnostic methods at the stroke unit?
- How do hospitalized stroke patients distribute between the stroke unit and wards of internal medicine?
- How compares stroke death in hospital to the reported number of stroke deaths in the population of the catchment area?
- Is the size of the present stroke unit (1 bed per 10.000 inhabitants) sufficient for the treatment of all acute stroke patients of the catchment area?

1.2.2. AIMS OF THE POPULATION BASED STUDY IN UZHGOROD

According to the statistics of the World Health Organization stroke mortality is extremely high in former Eastern block countries, among them in Ukraine. Stroke mortality in Ukraine was constantly high in the 1981-1998 period, with a value of standardized mortality rate over 200/100.000. In contrast to this high value several local studies reported relatively low stroke morbidity from the region, with numbers close to the data of some West European countries. For example for 1992 the age standardized death rate for cerebrovascular diseases (ICD-9 430-438) was 305 for men and 225 for women in Ukraine, whereas Pashkovskii reported that in the 1992-1994 years the incidence of cerebrovascular diseases (including ischemic and hemorrhagic strokes) ranged from 156/100.000 in the Western Cherniwtzi (Chernowitz) region to 213/100.000 in the South-Eastern region of Harkiv. The proportion of

hemorrhagic strokes (intracerebral and subarachnoid hemorrhages) was 15.9% in West Ukraine and 19.3% in the South-Eastern part, respectively. Although stroke mortality is not reported in the paper of Pashkovskii, it is extremely improbable, that stroke mortality (an average of 215/100.000 for 1992-1994 for Ukraine according to WHO data) would equal incidence (224/100.000 for Ukraine for the same period) which should be the case if both the WHO data and the numbers reported by Pashkovskii are valid. The WHO data for cerebrovascular mortality seems too high even if we consider that in Ukraine the death cause given on death certificates was erroneous in 5-40% of cases for cardiovascular diseases. As both the mortality and the incidence data were based on official reports and no prospective population based study has been performed yet in this region, we performed a prospective epidemiological study in the West Ukrainian city of Uzhgorod to accurately evaluate stroke incidence, stroke services and 30-day and 1-year case fatality.

1.2.3. AIMS OF THE MURES-UZHGOROD-DEBRECEN COMPARATIVE STUDY

We analyzed hospital stroke services in 3 cities (Târgu Mureş, Uzhgorod and Debrecen). As hospital data do not yield accurate epidemiological data, the most important aim of this study was not the gain of epidemiological data but the survey of the current situation of stroke services in 3 Central-Eastern European countries. We set out to establish a database of acute hospital stroke care in a region where only a small number of studies were performed if studies were done at all.

2. METHODS

2.1. Methods of the Debrecen Stroke Database

We investigated basic demographic data, the distribution of diagnoses, the application rate of traditional and recent diagnostic methods, the length of hospital stay, and the rates of case fatality for one calendar year at a university hospital stroke unit. The catchment area of the university hospital was the city of Debrecen and the village of Nádudvar, both located in Eastern Hungary with a total population of 220.000 inhabitants.

The stroke unit

The stroke unit, physically located at the Department of Neurology, has 23 beds of which 7 have intensive care facilities. At least 3 board certified neurologists and 2 residents work for the unit, and a neurologist is available 24 hours a day.

Among diagnostic methods clinical laboratory and CT is available 24 hours a day. Color duplex ultrasound, transcranial Doppler and transthoracic echocardiography can be performed within 24 hours of admission. Magnetic resonance imaging (MRI), magnetic resonance angiography, digital subtraction angiography and transesophagal echocardiography can be performed by appointment, usually within 10 days. In selected cases single photon emission computed tomographic and positron emission tomographic examinations can also be performed. Although physiotherapists work for the unit on a daily basis, presently there is no separate rehabilitation ward within the stroke unit. Rehabilitation is organized after the acute care at a different hospital after consultation with rehabilitation specialists.

Admission criteria to the stroke unit

In principle, from the catchment area all adult patients with acute stroke are eligible for admission to the stroke unit. Admission in practice, however is limited by the capacity of the unit. There is no upper age limit for patient admission, childhood stroke (<14 years of age) is treated at the department of pediatrics. According to local agreements patients with parenchymal hemorrhage are transferred to the stroke unit from other wards. Most stroke patients with a coexisting severe other medical condition (extremely elevated serum glucose level, severe cardiac, renal or hepatic disease) are admitted to one of the three wards of internal medicine.

Extraction and analysis of data

Retrospective analysis was performed using data from medical records of all patients with acute cerebrovascular disease (N=522) discharged from the stroke unit between January 1, 1995 and December 31, 1995. Data were recorded using a software prepared for an AT personal computer. Almost 100 parameters per patient were numerically coded including medical history, risk factors, clinical signs of stroke, results of laboratory, ultrasound and computer tomographic (CT) investigations, clinical diagnosis, length of hospital stay and condition at discharge from the ward. In addition to the database of the stroke unit, the electronic database of all departments of internal medicine of the university hospital with the same catchment area has been searched for patients discharged with stroke as the main or accompanying diagnosis [International Classification of Diseases (ICD-10) codes I60, I61, I63, I64 and I67]. To get stroke mortality data for the population of the catchment area, mortality records were searched in

the database of the population registry of the Central Statistical Bureau for all stroke deaths (ICD-9 codes 430-438) in the catchment area in the year of 1995.

2.2. Methods of the Uzhgorod study

DEFINITIONS AND CASE IDENTIFICATION

The study period lasted from October 1, 1999 to September 30, 2000. During this period we intended to register all stroke cases in the city. Stroke was defined as rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Case fatality was defined as death due to any reason within 30 days of stroke onset. Cases were identified from seven sources. (1) Hospital records prospectively collected for the study in all 4 hospitals where acute stroke patients are treated. (2) The registry of calls of the emergency neurology service. (3) The registries of the city's neurology outpatient service. This includes a registry of all neurologist home calls, a registry of outpatients who are seen at the city outpatient neurologist's office and a separate registry for stroke cases. (4) The district registries of the general practitioner (GP) zones. The 55 GP districts of the city are organized into 4 area zones. Each zone has its chief physician and a registry. All death cases in the zone are recorded in this registry. (5) The registry of the department of statistics located at the city hospital keeps records of all death cases of the city. This is monthly updated from the records of the City's Registrar's Office. (6) Autopsy records of the hospitals and of the county forensic department. (7) For follow up, a regular personal contact was maintained with all 55 GPs and their nurses. According to local regulations all stroke cases that meet the health care system are supposed to be recorded in at least one of these registries. The registries were checked, and the GPs were contacted by myself. The age distribution of the population of Uzhgorod, separately for men and women was obtained from the local census bureau. Values given for year 2000 were used in calculations.

Case certification

Case certification for hospitalized patients was performed by the hospital neurologists/neurosurgeons. For those who were treated at home, two neurologists (one of the neurological emergency team, and one of the city outpatient neurologists) confirmed clinically the case of stroke. Therefore even for non-hospitalized stroke patients at least 2 neurological examinations were performed. Case certification was basically performed by clinical examination.

Results of computer tomography (CT) and cerebrospinal fluid (CSF) examination were recorded when performed. Quality of case ascertainment was checked according to the five key indicators given by Asplud et al.

Recorded data

Basic demographic data (age, sex), the affected brain region, date of stroke and date of death were recorded for all patients. For fatal cases it was also noted whether autopsy was performed. For hospitalized patients a standard datasheet was filled out by the neurologist in charge including risk factors, time from stroke onset to admission, clinical signs, diagnostic and therapeutic interventions, condition at discharge and recommended secondary preventive measures.

Follow up

I kept track of all identified cases, hospitalized or not, and maintained personal contact with all 55 (later 52) GPs of the city, as well as with the emergency medical service and the city outpatient neurological service. The registry of the emergency service as well as that of the city outpatient neurology service were regularly checked. The latter included all home calls for neurological reasons, and cases with calls for stroke were checked. Files of all stroke patients were checked at the GPs' offices to decide if the patient was dead or alive on the 30th day and at 1 year after stroke independent of the actually registered cause of death.

2.3. Methods of the Mures-Uzhgorod-Debrecen study

Method of data collection

A standard case report form (CRF) was developed and used in the languages of the participating countries. To find a balance between the amount of information to register and the time available, a 4-page form was designed. The first page has the most important demographic data, the risk factors and the category of the cerebrovascular disease. On the second and third pages admission and discharge conditions are recorded: neurological signs, blood pressure and heart rate. The last page contains information on the application and results of diagnostic methods, on the specific treatment for stroke, on recommendation for secondary prevention, on discharge conditions, and follow-up information.

Data collection started after an initial training for the participating physicians on October 1, 1999 and patient inclusion lasted for 1 year, until September 30, 2000. We planned to include data of all consecutive patients hospitalized for acute cerebrovascular disease in 3 cities: Târgu Mureş (Romania, 165.000 inhabitants), Uzhgorod (Ukraine, 126.000 inhabitants) and Debrecen (Hungary, 210.000 inhabitants). Physicians (residents or young neurologists, supervised by the local project leaders) in each participating department were asked to fill in the admission part of the form immediately after admitting the patient with acute cerebrovascular disease. Neurologists in charge of the wards treating stroke patients were asked to fill in the discharge part of the form. The forms were collected by the study coordinators of the centers. It was regularly checked against the hospital registries if CRFs for each patient had been filled in. If missing forms were identified the form was subsequently filled in based on the patient documentation by a specially trained neurologist. In a previous study we tested and found that stroke scale scores could be estimated with acceptable reliability from medical records.

Demographic characteristics and risk factors

The patients' age, gender, identification number, the contact information of the patient and his/her nearest relative and his/her family doctor were recorded. It was also registered whether at the time of stroke the patient lived alone, with family, or in hospital/institution. The date and time of stroke onset and that of admission was also recorded. Information was collected on risk factors and medical history**:** diabetes, hypertension, previous stroke or transient ischemic attack (TIA), heart disease/arrhythmias, peripheral artery disease, psychiatric illness, alcohol consumption, smoking and history of stroke in the family.

Based on the physical examination and on the results of imaging studies the current acute cerebrovascular disease was categorized by the affected region and by the main stroke subtype as follows. Affected region: right hemisphere, left hemisphere, brainstem/cerebellum, multiple areas; stroke subtype: ischemic stroke, parenchymal hemorrhage, TIA, subarachnoid hemorrhage (SAH), other. Based on the recorded data a more detailed characterization of stroke subtypes will also be possible.

Recording neurological status on admission and at discharge

Although stroke scales are not recommended to measure stroke outcome, they are appropriate to use in clinical trials to evaluate stroke severity and to detect changes in clinical signs. Physical examination for the study was performed on

admission to the acute stroke unit and the clinical signs were scored on 19 items containing the items of the Mathew scale, the NIH stroke scale, the Orgogozo scale, the Scandinavian neurological stroke scale and the unified MCA stroke scale. In our previous study we found that all of these scales are sensitive enough to detect changes in neurological signs in the first week of stroke.

Interrater comparison of scoring neurological signs by the scales

Unbiased intraclass correlation coefficients (ICC-U) via the analysis of variance method were calculated to evaluate interrater reliability for all stroke scales. The project leaders of the 3 centers of the study examined 23 patients and scored the 19 items of neurological signs independently. Thirteen patients were evaluated by all 3, and a further 10 patients were scored by 2 examiners. Examination of the same patient by the 2 or 3 examiners was performed within 60 minutes. Interrater reliability for the four scales are summarized in Table 1. There was a good agreement among the scores given by the three examiners: ICC-U ranged from 0.85 for the NIH scale to 0.96 for the Scandinavian stroke scale. Therefore we concluded that severity of stroke signs can be compared among the centers by any of the scales.

Diagnostic interventions

To evaluate stroke subtypes and etiology, cranial CT, carotid Doppler and cardiac evaluation (electrocardiography and echocardiography) are recommended tools. In addition to these, the application and the results of some laboratory investigations (cerebrospinal fluid examination and hematocrit, hemoglobin, white blood cell count, platelet count, serum triglycerides, cholesterol, HDL-C, LDL-C, and plasma fibrinogen) were also recorded.

Therapeutic interventions

Treatment given specifically for stroke as well as recommended secondary preventive measures were recorded. The CRF specifically included items on the application of heparin (or its derivates), aspirin, ticlopidine or clopidogrel, mannitol, glycerol or other specified treatment, including surgery. The „other" category was used to record rtPA, neuroprotective or any other treatment used for treating stroke in a given center. For secondary prevention the recommendation for antiplatelet or anticoagulant treatment and carotid endarterectomy (CEA) were recorded.

Follow up items

The status of the patient at discharge was recorded by the Glasgow outcome scale. The living arrangement planned at discharge was recorded as at home alone, at home with family, discharge to other hospital, or discharge to nursing home. Follow-up was planned for 30 days and at 1 year. The Glasgow outcome scale and the living arrangement was recorded at both times. If the patient died the date of death was also noted on the CRF.

Method of follow up

The primary method for follow-up was a telephone call to the family or the family practitioner. Further information was obtained by checking the hospital electronic database. If information could not be obtained, a questionnaire was sent out to the patients by mail or a personal visit was performed at the patients home.

3. RESULTS

3.1. Results of the Debrecen database

The first analysis was performed after 1 year. Of the 686 patients 104 did not have cerebrovascular disease, 77 had chronic cerebrovascular disorder. Of the 505 patients with acute ischemic or hemorrhagic stroke 136 had stroke or TIA in their history. The proportion of hemorrhagic strokes was 15.8%. Acute stroke distributed evenly between genders.

In the second analysis acute stroke cases during a full calendar year (1995) were evaluated. Of the patients with acute CVD 11.9% had transient ischemic attack (TIA), 72.2% had ischemic stroke, 13.4% had parenchymal hemorrhage and 2.5% had subarachnoid hemorrhage. Among the 522 patients with acute CVD 104 had stroke and 38 had TIA in their case history. Case fatality was 18.6% for the total group and 21.1% for stroke (i.e. after excluding patients with TIA).

The mean age of patients with acute CVD was 67.5±12.8 years (mean±SD, range: 17-94 years). The mean age of men was 2.3 years younger than that of women (66.4±11.3 and 68.7±14.2 years, p=0.044), and the peak of distribution was between 60-70 years for men and between 70-80 year for women. Sixty-three percent of men and 46% of women were younger than 70 years of age. Of the patients 10.5% was younger than 50 and 17.8% was over 80 years of age.

Case fatality did not differ in acute CVD between men and women (56 out of 270 men and 41 out of 252 women, p=0.19). When age distribution in fatal cases were analyzed separately, the age difference between men and women was found to be 6.1 years (67.8 years for men and 73.9 years for women, p=0.034), a much larger difference than in the total group. Among fatal cases 29.3% of women but 50% of men were below 70 years of age.

Average length of hospital stay did not differ between genders and was 11.96 days for men and 11.58 days for women; 37% of patients were discharged within one week of admission and less than 6% of patients stayed longer than 30 days. The median length of stay was 4 days for fatal cases (range: 1-71 days) and 9 days (range: 1-88 days) for survivors.

Computer tomography, duplex carotid ultrasound, cerebrospinal fluid examination and electroencephalography were performed in 79%, 77%, 7% and 2% of the patients, respectively.

To estimate the proportion of hospitalized stroke patients of the catchment area treated at the stroke unit the database of the University Hospital was searched for stroke patients treated at the department of neurology (i.e. at the stroke unit) and at all departments of internal medicine. Of these patients with the diagnosis of acute CVD 58% were treated at the department of neurology and 42% at the departments of internal medicine. The mean age of cerebrovascular patients in the university database was 64.5±14.9 years, and case fatality for the medical wards varied between 14.3 – 26.3%.

Data of stroke mortality of the catchment area were obtained from the database of the Central Statistical Bureau. In the year of study (1995) 228 stroke deaths were reported in the catchment area, whereas 97 stroke deaths occurred at the stroke unit and 76 at the departments of internal medicine. With the assumption that population statistics based on death certificates are accurate, these numbers mean that 42.5% of all stroke fatalities occurred at the stroke unit and another 33.3% at the departments of internal medicine, therefore less than 25% of stroke deaths occurred either at other hospitals not included in our survey or at non-hospital settings.

The Debrecen Stroke Database currently contains data of over 3500 consecutively admitted patients with acute cerebrovascular disease. Of the 3556 patients 86% had ischemic cerebrovascular disease, 12% had intracerebral

hemorrhage, 2% had subarachnoid hemorrhage. The application rate of CT increased over the years, with 89% in the whole patient group. Mean age was 68,9±13,9 for women and 65,7±12,1 years for men, 42% of men and 33% of women were below 65 years of age.

3.2. The Uzhgorod study

Characteristics of the population and the patients

According to the Uzhgorod census office, in year 2000 the city had 125482 inhabitants. In the 20th century there was significant migration in and out of the city, but there was no considerable migration and change in the ethnic structure of the population in the last 20 years. The current population is a mixture of Ukrainian, Russian, Hungarian, Polish, and Slovakian ethnicity, therefore the city is not representative of the ethnic structure of Ukraine as a whole.

During the 12 months of the study 352 acute stroke cases were identified, 188 men and 164 women. Men were almost 6 years younger than women (60.8 ± 12.8 versus 66.6 ± 11.6 years, $p < 0.001$), 38% of women whereas 58% of men are below 65 years of age. In fatal cases the age difference is even larger, close to 9 years (63.5 ± 12.4 versus 72.5 ± 10.4 years, $p = 0.001$). There were no women below the age of 35 and no men over the 85 years age limit. 30-day case fatality did not differ significantly between men and women. Computer tomography was performed in 145 of the 234 patients treated at hospital and in none treated out of hospital. Forty three of the patients had cerebrospinal fluid (CSF) examination, electrocardiography was performed in 223, carotis Doppler in 12 and echocardiography in 10 of the 234 hospitalized patients. Of the 82 death cases 27 had autopsy. As only 41% of all stroke cases had CT examination, it was not possible to reliably analyze stroke subgroups in this register.

Characteristics of treatment settings

Exactly two-thirds of the patients were treated in hospital settings. Those treated at home, either in the closer supervision of the outpatient neurology service or in the care of the GP after an initial instruction by a neurologist, were more than 10 years older in average than those who were hospitalized ($p < 0.001$). There were 4 patients who died either before the emergency service arrived or during transport by the ambulance.

30-day and 1-year case fatality in different settings

Case fatality is significantly higher in those subgroups that did not get hospital care ($p < 0.001$). Overall 30-day case fatality was 23.3%, with lowest values for hospitalized patients (15.4%) and highest values for those who were left in the care of the GPs. This difference in case fatality among the different settings probably reflects differences in prognostic factors at the time of the initial neurological examination when decisions for higher level care were made for patients with more hopeful prognosis.

Case fatality at 1 year was 23% in hospital-treated and 52% in home-treated patients. Two-thirds of deaths between 30 days and 1 year after stroke occurred in the 65-84 years old age group. At 30 days and at 1 year 42 and 59 of the 114 home-treated and 36 and 53 of the 234 hospitalized patients were not alive ($p = 0.0001$). Case fatality of those who survived their stroke for more than 30 days was still significantly higher by 1 year after stroke in home-treated than in hospitalized patients (23.6% and 9.3%, $p = 0.0028$).

3.3. Result of the Mures-Uzhgorod-Debrecen study

Interrater reliability for stroke scales was checked for 3 examiners and 5 scales by examining 23 patients. Unbiased intraclass correlation coefficients were calculated and good agreement was found for all scales ($p < 0.005$). We concluded that any of the scales is appropriate to compare stroke severity among the centers involved in the study.

When we analyzed the retrospective applicability of stroke scales we compared scoring of the acute patient by the admitting neurologist to the score given by a neurologist based on the medical records. Good agreement was found between the scores of the admitting physician and the neurologist who scored the patient by the medical records ($p < 0.005$ for all 5 stroke scales).

The detailed analysis of the Mures-Uzhgorod-Debrecen study is currently ongoing. The 3 cities are comparable in size, and the size of their population is optimal for epidemiological investigations. The proportion of hospitalized stroke patients per 100.000 population is the largest in Debrecen (263/100 000), and the smallest in Târgu Mureş (158/100 000). These data do not necessarily reflect differences in stroke incidence among the cities. Rather, they reflect different hospitalization rates in the 3 cities. This possibility is supported by the fact that

patients in Debrecen are 6 years older than those in Târgu Mureş, and 10 years older than those in Uzhgorod. It can be assumed therefore that in Debrecen older patients with milder clinical signs also get into hospital. Men are 3-4 years younger than women in all 3 cities. The proportion of CT examination is over 90% in Debrecen, and this rate is below optimal values in the other 2 cities. Hospital case fatality was the lowest in Uzhgorod (13,7%), and the highest in Târgu Mureş (20,3%), but this difference more probably reflects differences in stroke severity among hospitalized patients, and not the differences in the quality of stroke services in the 3 cities.

The rate of cerebral hemorrhages is higher in Târgu Mureş (18,1%) and Uzhgorod (16,7%) than in Debrecen (11,1%). The rate of 17-18% is high compared to reports from other countries. This does not mean that the population of Târgu Mureş and Uzhgorod is more prone to hemorrhages than the population in Debrecen. Two factors might be responsible for potential bias. If more severe cases get to hospital then among those, cerebral hemorrhage is more frequent than in the total stroke population. The other factor can be the low CT rate. Without CT severe ischemic strokes could have been misdiagnosed clinically as hemorrhagic strokes.

The detailed analysis of the data of this comparative study is ongoing. We shall be able to compare the characteristics of stroke, the application of diagnostic and treatment methods, and to analyze relationship between stroke outcome and the former factors.

4. DISCUSSION

4.1. The Debrecen Stroke Database

From population based studies it is known that hospital discharge records do not reflect accurately the incidence of stroke in the population. This is - at least partly - due to the rate of non-hospitalized stroke victims. Patients with rapidly lethal strokes or those with rapidly reversible or mild symptoms are the most probable candidates for avoiding hospital care. The rate of non-hospitalized stroke patients can be estimated by comparing population based and hospital records and is considerable. Data are not necessarily accurate for mortality as well. Though recent European studies reported a considerable proportion of false positive and false negative cases in death certificates they found that in aggregate numbers official mortality rates are close to truth. From our analysis

we can only say that if official mortality statistics are accurate, 75% of stroke deaths occurred at the departments involved in the survey. Assuming that stroke mortality is underestimated by 25% using data from death certificates we can calculate that 60% of stroke deaths in the catchment area occurred either at the stroke unit or at the departments of internal medicine. Therefore, at least for fatal stroke cases hospitalization rate in Hungary is not lower than that reported for other European countries. As far as patients with non fatal strokes are concerned no accurate data can be given on the rate of hospitalization until a population based survey is performed including all family practitioners as well in the catchment area.

The 67.5 years mean age in our group was between the 63.8 and 75.1 years in 9 Western European hospitals, lower than the 73.2 years in the Tel Aviv stroke registry, higher than the 61.1 and 60.3 years for men and women in the Lausanne stroke registry, and somewhat higher than the 65.4 and 66.1 years for men and women in the population based Framingham study. Similarly to our results, the peak frequency was between 65-74 years in a Saudi Arabian database. The somewhat lower mean age of our patients compared to the data of most European hospitals might be explained by the general condition of the Hungarian population: according to data of the World Health Organization the life expectancy in Hungary is almost 10 years less than that in Switzerland (69.0 and 78.2 years, respectively).

Depending on local practices of rehabilitation, average length of stay varies severalfold among stroke units. For accurate comparisons therefore not in-hospital mortality but case fatality at a certain time point after stroke onset (e.g. at 1 week, at 1 month or at 1 year) would yield comparable data. For technical reasons, average length of stay and in-hospital case fatality data are given in our first study. Hospital rate of case fatality in a similar study with a similar size of catchment area was 21%, a similar value to ours. The proportion of patients dying in the hospital ranged between 4-46 percent among 9 Western European hospitals. Case fatality among patients with parenchymal hemorrhage was 51.4% in our group, considerably larger than in recent reports. In the study of Howard et al (1991) in-hospital mortality in 1970 was 18.6% for acute CVD, 45% for parenchymal hemorrhage and 24% for cerebral infarcts. As these values dropped significantly from 1970 to 1987, it could be expected that with improved primary care stroke mortality rate would decrease further in Hungary in the next decades: between 1980 and 1996 the 1% decrease in total mortality

in the Hungarian population was already accompanied by a 20% decrease in cerebrovascular mortality.

For a reliable stroke databank a high (70-80%) neuroimaging investigation rate is required. The 79% rate in the first year of our study for patients with acute CVD is therefore acceptable and similar to that of other hospital based stroke registries. The CT rate increased to over 90% by 2000. Proportion of parenchymal hemorrhages differ from study to study and in population based or unselected case series studies the value ranges from 5 to 17% among patients with acute stroke but is around 10% in studies where all patients had CT investigations. The proportion of parenchymal hemorrhages in our survey is relatively high (13.4%), but this was expected due to the local admission policy as most patients with diagnosed parenchymal hemorrhage were transferred to the stroke unit from other departments.

The mean length of stay in our study is at the lower end of the 11-39 days range found in 9 hospitals in Western Europe which is probably due to the fact that post-stroke rehabilitation is organized outside the setting of the acute stroke unit. Based on the number of stroke patients treated at the departments of internal medicine we can calculate that if the average length of stay (i.e. 12 days) could be decreased by 25% at the stroke unit, then the present size of the unit would be able to treat the number of patients that were treated by the departments of internal medicine. However, until reasonably sized rehabilitation units are organized this aim is not realistic.

In the present study data from three databases were used and compared. The most detailed of these is the regularly updated stroke databank of the stroke unit maintained by board certified neurologists. The database of the University Hospital is handled by administrative personnel using medical reports from all departments mostly for accounting purposes towards insurance companies. The third database is that of the Central Statistical Bureau, independent of the University Hospital and based on death certificates. Information in these databases might be somewhat different due to different coding conventions, differences in the amount of available information and different levels of accuracy. Therefore comparing data from these different databases involves some error that should be considered during the interpretation of the results.

4.2. The Uzhgorod study

Evaluation of the quality of case ascertainment

To evaluate the reliability of our study we used the five criteria recommended by Asplund et al. The first indicator is the proportion of fatal cases identified by the study compared to that reported in official statistics. In our study we found 352 stroke cases and 82 deaths within 30 days of stroke onset. For the year 2000, the official health statistics registered 228 stroke cases by ICD-10 codes as follows: I60 (subarachnoid hemorrhage): 14 cases; I61 (intracerebral hemorrhage): 42 cases; I63 (cerebral infarction): 144 cases; I64 (stroke not specified): 28 cases. Of these cases only 31 were recorded to have died of stroke. In the previous year (1999), similarly, only 218 stroke cases (141 of them ischemic) and 30 stroke deaths were recorded. We found 2.6 times more stroke deaths and 54% higher stroke incidence than recorded by the official statistics. As the stroke register-to- routine mortality ratio is much higher than the limit of 0.75 set by Asplund et al, identifying fatal cases seems acceptable in our register.

The second criterion is the proportion of fatal stroke cases not admitted to hospital. Although this proportion varies from country to country depending on the local practice of stroke care , the proportion of fatal stroke cases not admitted to hospital should be over 10%. In our register 46 of the 82 deaths (56%) occurred outside hospital. As none of the 21 MONICA populations reported higher proportion of out-of-hospital than in-hospital fatalities, we feel we found most stroke deaths that occurred outside the hospital settings.

The third indicator suggested by Asplund et al, was the case fatality rate as incomplete coverage of nonfatal events leads to overestimation of case fatality. With the 23% 30-day case fatality our register would rank 8th among the 21 MONICA populations, therefore we do not think that too many nonfatal events were missed in our register.

The forth criterion is the proportion of surviving stroke patients cared for outside the hospital. If this proportion is low, it reflects less than optimal case ascertainment. This proportion ranged 0-16% in the 21 MONICA populations and was 20% in our registry. Therefore we assume that we identified most of those stroke survivors who were treated out of the hospital.

The fifth criterion is the proportion of fatal cases examined by a physician before death, or subjected to autopsy in fatal cases. In our study, as well as in the MONICA study, stroke was defined by clinical investigation. Autopsy was performed in all 4 cases when death occurred on route to hospital. All 82 fatal cases therefore were subject to medical investigation or autopsy. Due to local coding traditions, stroke deaths reported on death certificates is very low (31/year). A large number of fatal cases in our register were coded as "death due to old age" in the official statistics, reflecting that in this region of Ukraine stroke is not a preferred label for cause of death on death certificates. Therefore, in the region of study not over- but underreporting of stroke cases might distort official statistics. This might be a problem in those cases where the patient dies without medical examination and autopsy. This could have happened in the oldest age group in our study, as the age specific crude incidence and mortality numbers are lower in the age group of 85 years and older than what could be expected. Although the low incidence and mortality found in this oldest age group might be due to chance because of the small number of such old people in the population, it also cannot be excluded that some stroke cases in this age group were not seen by the health care system. However, even if stroke cases and stroke deaths occurred unrecorded in this age group, they were not registered by the health system and fatal cases were not coded as death due to stroke in the death certificates.

Due to conflicting information between WHO mortality data and local stroke incidence reports for Ukraine we set forth to perform a prospective, population based survey of stroke incidence and 30-day and 1-year case fatality in a West Ukrainian city of Uzhgorod. Such data are lacking for Ukraine, the available WHO data are based on death certificates and to our knowledge no similar study has been performed yet in this East European country. Even a recent large scale European survey of 22 countries does not include stroke incidence and case fatality data from Ukraine.

The reliability of death certificates has long been debated, and questions were raised about the accuracy of studies dependent of such source of information in general, and specifically in Ukraine as well. Therefore instead of the analysis of health authority reports we chose to perform a 1-year survey of all levels of health care for stroke in a city of 126.000 inhabitants. Thorvaldsen et al reported that there is a systematic overreporting of stoke deaths in the official vital statistics of former USSR countries. We indeed found that stroke incidence was much lower than could have been expected based on WHO mortality data.

Theoretically, the low stroke incidence and mortality found by us in this West Ukrainian city might be due to the inadequate identification of stroke cases in the population. However, using the quality criteria of Asplund et al it is not probable that insufficient case ascertainment is responsible for the low incidence and mortality data found by us. The only critical age group is that over 85 years of age. A disproportionate lack of older people might be suggested by the low frequency of cases over 85 years of age. However, this is true mostly for men, and it is not probable that a large number of missed stroke cases in this age group could have significantly distorted our results. The relatively low representation of the age group over 85 years of age (especially for men) might reflect the late effect of World War 2: the current age group of 85-95 years were 25-40 years old during the war. According to the data of the regional statistical bureau in year 2000 only 173 men whereas 448 women were of the age of 85 years or older in the city of Uzhgorod. The GPs see all patients – including stroke patients - in their district, and in case of a suspected stroke they have to call the emergency service or consult the city outpatient neurologist according to local traditions and legal reasons. It can not be excluded that in rare cases the GP treats the stroke patient without consulting the neurologist. However, as the manager of the study (L. M.) kept regular connection with all 55 GPs of the city, it is highly unlikely that a considerable number of stroke patients could have been lost for this survey. It is also possible that in some cases neither the GP nor the emergency service is called when stroke occurs in patients over the age of 85 years. As in fatal cases in this age group the cause of death is usually coded other than stroke - even in cases which were seen before death by the health care system - such cases are not only missed in our register but in official statistics as well.

The 23.3% value for 30-day case fatality is similar to the values reported for Denmark (20-25%), Slovenia (21%) or the United Kingdom (20%). In our survey 33% of stroke patients were not hospitalized, which is close to the reported numbers for Croatia (35%), or Oxfordshire (40%), but higher than the values reported for most European countries. The mean age of stroke patients in our survey (63.4 years) was similar to values reported for Switzerland (63), Turkey (65.5), Slovenia (63.2) and Estonia (64).

The crude stroke incidence of 280/100.000 in our register is close to values reported for several Western European countries like Austria (200-250/100.000) or Germany (170-250/100.000); somewhat higher than the numbers given for

Belgium, Denmark and Portugal (200/100.000) and lower than the number of 300/100.000 for Sweden and Croatia. Age standardized incidence and mortality data are easier to compare, therefore we calculated these numbers using the European and the world standard population as well. The incidence standardized for the European population was 341/100.000 in our survey, close to the values of Auckland, New Zealand (350/100.000), Perth, Australia (361/100.000), Rochester, USA (362/100.000), Umbria, Italy (374/100.000) or Oxfordshire, England (379/100.000). The mortality standardized for the world population was 69/100000 per year in our study, a value comparable with those found in Eastern European MONICA populations.

From these comparisons we conclude that for any of the above parameters we could find one or more West European countries with parameters similar to that of Ukraine. Our results cast doubt on the accuracy of WHO data of high stroke mortality of Ukraine as well as on the generalizability of the east-west gap of stroke epidemiological data, and support the assumption of Alter et al, that much of the reported variation in stroke mortality and incidence rates between populations may be attributed to methodological issues.

4.3. Evaluation of the Mures-Uzhgorod-Debrecen study

As stroke is a major public health problem in former Eastern block countries, it is essential to have reliable information on current health care needs and practices. The optimal method to get accurate data is a population based study. Of the 3 centers it was possible to perform such a study only in Ukraine. From that survey it is known, that not all acute stroke patients are hospitalized and the hospitalized stroke patients differ in age and in stroke outcome from those who are treated at home. Therefore, a drawback of the current study is the lack of population based data. The proportion of non-hospitalized stroke patients might differ from country-to-country, and might depend on local traditions and conditions. For example, by comparing stroke deaths in national statistical registries and hospital records in Hungary we estimated that in 1995 less than 20% of stroke deaths could have occurred outside hospital settings, whereas in West Ukraine about one third of stroke patients are treated at home. In Romania, although the exact rate of hospitalization is not known, a considerable number of patients with mild stroke are never hospitalized but treated by neurological outpatient services. As a hospital based survey, the current study is not

appropriate to directly compare stroke incidence and mortality in the 3 centers and conclusions only on hospitalized patients can be drawn.

In spite of the disadvantages of hospital based stroke studies, the current project will give accurate information on the current practice of stroke inpatient care in these 3 cities of Central-Eastern Europe. It will be possible to compare these data to other hospital based stroke registries, e.g. to registries of countries with more favorable stroke mortality. The application of 5 frequently used stroke scales makes it possible to compare initial stroke severity with several other databases and the hypothesis might be tested if hospitalized strokes are indeed more severe in those countries where stroke mortality is higher. Characteristics of special patient groups (e.g. those with altered consciousness, or those with aphasia) can be compared among the 3 centers as well as with other databases. Comparison of the distribution of various risk factors will also become possible.

In addition to research purposes the study will have direct practical use: the data arising from this study might help health care authorities in this region to define the most important measures for primary prevention, to more accurately define hospital care needs for stroke patients, and to identify the most important issues in quality assurance in stroke care. Treatment in stroke units resulted in a more favorable outcome compared to treatment on general wards. The information of this study will provide information needed to organize stroke units and a more efficient health care system for stroke patients with the aim of decreasing stroke mortality in this region.

5. PRACTICAL IMPORTANCE OF THE RESULTS

- From our data collected in Debrecen it is obvious that with the current stroke morbidity and 12-day hospital stay it is not enough to plan one hospital bed for stroke per 10.000 inhabitants to cover the need for all stroke patients. In addition to increase the number of stroke-beds, the rehabilitation and nursing capacity should also be increased.
- Our data provide information needed for planning hospital (i.e. stroke unit) development, inpatient and home nursing services, and special areas for rehabilitation (speech therapy, psychiatric consultations).
- Further data analysis will give us information on the relationship between risk factors, demographic characteristics and stroke outcome in the region.
- Analysis of risk factors and current practice will inform us on the most important tasks in the field of primary stroke prevention.
- In comparative studies we found it reliable to use retrospectively stroke scale scores to evaluate initial stroke severity.
- We were the first to perform a population based stroke epidemiological study in the country of Ukraine. Similar results have not been published before from this region.
- The results of our study at the turn of the century will be a reference for later epidemiological studies in all 3 Central-Eastern European countries, and for comparisons with data from other regions.
- Our data will give baseline information for later evaluations of local changes, and for defining health care quality assurance tasks in all 3 cities.

6. SUMMARY

We examined characteristics of a stroke unit in East Hungary with a catchment area of 210.000 inhabitants. We established the Debrecen Stroke Database in 1994, which by the end of year 2000 contains data of over 3500 consecutively admitted patients with acute cerebrovascular disease. We do not have accurate information on the number of non hospitalized stroke patients, but by comparing 3 data sources (i.e. the stroke unit database, the database of the university hospital with data of stroke patients treated outside the stroke unit, and the database of the official stroke mortality records of the catchment area) we estimated that at least 75% of fatal strokes are hospitalized, and 60% of hospitalized stroke cases are treated at the stroke unit, and 40% are treated at departments of internal medicine. Hospital treated stroke patients in Debrecen are younger than the European average. Men are significantly younger than women, and this age difference is more pronounced in fatal cases. Of the diagnostic methods the application rate of CT corresponds to the European standard, and it increased to over 90% during the 6 years of the study. The proportion of cerebral hemorrhages somewhat decreased over the years, but it is still higher than in Western European countries. Hospital case fatality did not change considerably during the 6 years of the survey.

The population based study in Uzhgorod did not support the extremely high mortality data in Ukraine reported by the WHO. One third of stroke patients do not get to hospital in Uzhgorod, and these patients are 10 years older and have worse short- and long term prognosis than those who are hospitalized. Based on the results it is obvious that analysis of only hospitalized stroke cases does not yield reliable information on stroke morbidity and mortality of a region.

The detailed analysis of the Mures-Uzhgorod-Debrecen study is ongoing. Due to the study design we could analyze only hospitalized stroke cases in the 3 cities. The application rate of diagnostic methods differ among the cities, and there is considerable difference in case fatality as well. This probably reflects different traditions for hospitalization and not real differences in stroke characteristics or in the level of stroke services. This is supported by the fact that there was significant difference among the 3 cities in the age of the patients and in the rate of presumed hemorrhagic strokes. Further analyses have to be done to decide if initial stroke severity indeed differs among the cities and if differences in risk factors and treatment also have a role in differences in outcome.

7. LIST OF PUBLICATIONS

The thesis is based on the following full papers:

1. **Mihálka L**, Bereczki D, Fekete I, Csaba B, Csépány T, Csiba L. Egy klinikai cerebrovascularis osztály egyéves betegforgalma - az adatkezelés módszerei, demográfiai és letalitási adatok. ***Clin Neurosci/Ideggy Szle*** 1997;50:233-239
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