

SHORT THESIS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY (PHD)

Clinical and epidemiological characteristics of primary
subarachnoid hemorrhage in Hungary and Japan

by Norbert Kozák

Supervisor: Prof. Dániel Bereczki and Sándor Szabó



UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF CLINICAL MEDICINE
DEBRECEN, 2015

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The Examination takes place at Department of Preventive Medicine, Faculty of Public Health, University of Debrecen, 22 of February, 2016, at 11 am

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1. Introduction and background

Primary subarachnoid hemorrhage (SAH) account for only 5% of stroke cases, but its impact is great because it strikes at a fairly young age and its mortality may be as high as 50%. Furthermore a significant proportion of the patients will have severe residual symptoms. Management of SAH cases is recommended in specialised centers where advanced diagnostic and treatment options are available: CT, CT angiography, MRI, DSA, interventional neuroradiology, neurointensive care unit, and neurosurgery.

Ruptured aneurysm is the cause of SAH in 85% of the patients. The so-called perimesencephalic SAH accounts for 10% of the cases. In the remaining 5% other sources can be verified, eg. arteriovenous malformation, dissection. Anterior communicating artery aneurysm (ACoA) ruptures most frequently, internal carotid artery (ICA) and middle cerebral artery (MCA) follows. It is well-known that ICA aneurysm is more frequent in women, ACoA in men. Intracranial aneurysms are not congenital, they develop during the course of life. Rupture is probably triggered by a sudden increase in the transmural arterial pressure eg. in hypertensive crisis or during

intense physical activity. Established risk factors of SAH are hypertension, smoking, excessive alcohol consumption and cocaine use. Familiarity can be observed in 10% of the cases.

After the hemorrhage itself vasospasm is the leading cause of death and disability in SAH patients. Angiographic vasospasm develops in up to 70% of the patients, whereas symptomatic vasospasm in 20 to 30% of the cases.

1.1 Incidence of subarachnoid hemorrhage

The incidence of SAH has ranged widely among the different regions of the world. The overall incidence of SAH was reported to be 9 per 100 000 person-years, however in Japan and Finland it is higher than 20. In the last decade incidence rates were published from different parts of Japan (Kumamoto Prefecture, Shimokita Peninsula, Izumo) confirming the high rates.

In most of the populations SAH is more frequent in women than in men. Male majority was observed in Finland. There was a plateau in men in southwest England, Sweden and in some parts of Japan. It means that the incidence increased with the age until a certain age then became stable. In Australia and New-Zealand bimodal distribution was observed in men with peak rates

among younger adults and the oldest old. In women rates increased continuously with age, the trend being attenuated after the menopause. De Rooij systematic review found that the preponderance of women starts in the sixth decade and after adjustment for gender incidence increased by a factor of 1.06 for each additional year (Poisson regression).

Óváry et al published crude incidence rate from Hungary: 4.75 per 100 000 person-years from 1997-98. Earlier (1959-68) Mérei and Bodosi from the city of Pécs: 5.5 per 100 000 person-years. This data comes from the pre-CT era and the authors supposed that this is an underestimation of the real occurrence.

1.2 Diurnal and seasonal variation of SAH occurrence

The risk of SAH is low during the night and around noon. This phenomenon may be associated with the circadian fluctuations of blood pressure. There was a peak in Tokyo at 10a.m. and a less pronounced peak at 18p.m., nadir between 1a.m. and 6a.m. In Izumo two statistically significant daytime incidence peaks were found: one between 6a.m. and 10a.m., the other between 4p.m. and 8p.m.

There is a long-standing debate regarding seasonality of SAH. A metaanalysis published in 2013 using data of more than 70 000

patients from 24 countries of 5 continents found that SAH is less frequent in the summer, than in the winter. It is most frequent in January, rarer in the months of the summer. In Japan similar results were found in Tokyo, Izumo and Yamaguchi prefecture. Many studies could not find significant result. First of all to be mentioned are two studies from the US with large patient populations, including 7700 and more than 50 000 patients respectively. However these studies used general hospital databases, not designed for epidemiological purposes. Hence missing data of patients died before reaching hospital. As for the cause of the possible seasonality less sunshine and humidity was supposed. Furthermore cold temperature may induce peripheral vasoconstriction with elevation of blood pressure. Another factor can be the seasonality in alcohol consumption and indoor smoking in winter. Data regarding seasonal variation of SAH in Hungary is missing.

1.3 Vasospasm

Vasospasm usually occurs at 4 to 14 days after SAH onset, most often at 6 to 10 days. Delayed ischemic neurological deficit (DIND) or symptomatic vasospasm is responsible for up to 50% of the mortality of patients surviving the acute phase of SAH.

Delayed cerebral ischemia (DCI) or neurovascular event are frequently used terms as well. Angiographic vasospasm without clinical deterioration occurs in up to 70% of the patients, whereas symptomatic vasospasm in 20 to 30%. The more significant the spasm the more probable the clinical symptom, however very pronounced narrowing of the vessel may be symptomfree and little narrowing may be accompanied by clinical symptoms. In a significant proportion of the cases with DCI (proved by CT) - in Dhar's study 25% of the patients - vasospasm cannot be verified. In the pathomechanism of the neurological worsening other factors may play a role too, eg. constriction and thrombosis of the arterioles, cortical spreading ischaemia. There is a debate regarding the terms and definitions to be used. In our study we used the term symptomatic vasospasm because during the data collection this phrase was widely accepted. We defined symptomatic vasospasm as a clinical entity that includes a new, delayed focal neurological deficit or mental status decline without evidence of any other cause in SAH patients.

1.4 Predictors of vasospasm

Treatment of vasospasm is still challenging, prevention would be optimal. Predictors would be helpful to screen for high risk patients. Several factors were studied as predictors of vasospasm, such as age, sex, amount of blood on CT (Fisher grade or other method), and admission status. Amount of blood on admission CT is the most established factor. The Fisher grade was proposed in 1980 and was widely accepted for a long period, however in the last decade it was questioned. It was proposed that not only the amount of blood is important in prediction of vasospasm but the location as well. There are data that suggest female sex is a risk factor for angiographic vasospasm; however the majority of the studies have shown no correlation between sex and the risk or incidence of vasospasm. There are controversial reports regarding age. Several studies suggest that young age is a predictor for symptomatic vasospasm. Other studies could not find significant connection, while in Lanzino's large study there were more symptomatic vasospasms in the older age groups, but there were no significant difference in angiographic vasospasm among the age groups. It is difficult to diagnose symptomatic vasospasm in patients with high Hunt-Hess grade, so we have to be cautious

with the interpretation of the results with admission status. The study designs, age limits and vasospasm definitions are different in the studies, making it difficult to compare their results and explaining at least partly the observed differences.

2. Aim of the study

1. To establish the incidence of SAH in Akita Prefecture, Japan using the Akita Stroke Register. To analyse its trends between 1989 and 1998, age and sex distribution, diurnal and seasonal changes and mortality.
2. To analyse the characteristics of SAH in Hungary in 2009 using data supplied by the hospitals about their inpatient services to the National Health Insurance Fund (OEP).
3. To analyse the characteristics of SAH in Debrecen between 1987 and 2004 using the SAH database of the Department of Neurosurgery University of Debrecen with special emphasis on the occurrence and predictors of symptomatic vasospasm.

3. Patients and methods

3.1. Japan - Akita Stroke Register

Akita Prefecture is located in the northern part of Honshu Island in Japan, and has a population of about 1,200,000. The stroke cases that had undergone CT examination in the prefecture are enrolled in a prospective stroke register, inpatients as well as outpatients. Those patients, who died before arriving at hospitals underwent autopsy or, since autopsy is rare in Japan for religious reasons, postmortem neuroimage confirmation. Since in Akita Prefecture all suspected strokes are referred to hospital and CT is performed, it is essentially a population-based register. SAH was determined by attending physicians based on clinical symptoms and neuroimage findings. Lumbar puncture was performed when the CT scan could not confirm SAH in spite of strong clinical suspicion. First-ever primary SAH cases that had occurred between the 1st of January 1989 and the 31st of December 1998 among Akita Prefecture inhabitants were involved in this study. Patients who reside in other prefectures were excluded. Neither the cases resulting from secondary SAH (trauma, coagulation disorder, neoplasm, etc.), nor the recurrences were involved. More than 85% of the patients

underwent angiography. Sites of aneurysms were categorised as following: internal carotid artery (ICA), anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), anterior communicating artery (ACoA), basilar artery (BA), and the junction of the vertebral and posterior inferior cerebellar arteries (VA-PICA). Evaluated characteristics of the patients were: sex, baseline age, consciousness level, focal sign (motor palsy), headache, stiff neck (physical finding), vomiting, origin of bleeding (aneurysm, AVM or other), hypertension (history or BP above 140/90 by consecutive), diabetes mellitus (history), heart disease (ischaemic heart disease, based on history), hypercholesterolaemia (history), smoking: yes, no, heavy (more than 20 cigarettes per day), alcohol consumption: yes, no, heavy (at least 2 go (1.8 dl) of sake or other beverage with the same amount of alcohol per day). If the patients were not capable of cooperation, relatives were asked for information.

3.2 Assessment of the Hungarian data

We performed a query in the electronic database of the Hungarian Health Insurance Fund (OEP) using the ICD-10 code I60 as a main diagnosis for the year 2009. I60 is the code for subarachnoid hemorrhage in ICD-10 (international classification

of diseases). The full 5-digit code involves localization and form (aneurysm or arteriovenous malformation) as well. Evaluated characteristics were: sex, age, diagnosis, hypertension as an additional diagnosis, radiological evaluation (CT or MRI), average hospital stay, case-fatality, regional distribution, monthly distribution. Data assessment was done by the number of hospital cases and number of the affected persons as well.

3.3 Vasospasm and its predictors in Debrecen

Data of primary SAH patients admitted or referred to the Department of Neurosurgery at the University of Debrecen between the 1st of January 1987 and the 31st of December 2004 were collected prospectively and entered in an anonymized database. Because University of Debrecen is a referring center of the region, patients are registered not only from Debrecen City, but also from several counties of the region. SAH was determined by clinical symptoms and neuroimaging findings (CT, angiography). Lumbar puncture was performed when CT scan could not confirm SAH in spite of strong clinical suspicion. Cases resulting from secondary SAH (trauma, coagulation disorder, neoplasm, etc.) were excluded. Evaluated patients' characteristics were: sex, age, presence of aneurysm, Fisher

grade on initial CT scan, hypertension, Hunt-Hess grade on admission, symptomatic vasospasm, and case fatality. If the patients were not capable of cooperation, relatives were asked for information. We defined symptomatic vasospasm as a clinical entity that includes a new, delayed focal neurological deficit or mental status decline without evidence of any other cause in SAH patients.

3.4. Statistical methods

The denominators for calculation of the incidence rates were the 1990, 1995 and 2000 census data of Japan in Akita prefecture. Incidence rates were standardised to the European Standard and to the World Standard Population. Confidence intervals were calculated according to the Poisson distribution. Continuous variables were compared by one-way ANOVA or Mann-Whitney test, categorical variables by χ^2 test or Fischer's exact test. Linear regression, i.e., modelling of the log incidence (natural logarithm) as a linear function of year, tested the time trends. Seasonal and diurnal changes were evaluated by χ^2 test. Univariate and multivariate logistic regression were applied to test predictive factors for symptomatic vasospasm. The following factors were tested as possible predictors: age (as a

continuous variable and also as dichotomized at 50 years of age), sex, hypertension, Hunt-Hess and Fisher grade on admission, site of aneurysm (anterior versus posterior circulation). All of these factors were included in the multivariate logistic regression analysis. Stepwise backward model was applied to find the independent predictors of symptomatic vasospasm. Statistical analyses were performed on Statistical Package of Social Sciences (SPSS) software, SPSS Inc.

4. Results

4.1. Japan – Akita

During the 10-year period from the 1st of January 1989 to the 31st of December 1998, 3257 first-ever SAH cases were registered, 1146 (35%) men and 2111 (65%) women. Mean \pm SD age: 62.2 \pm 13.2, 58.2 \pm 12.8 in men, 64.4 \pm 12.9 in women, respectively.

The crude annual incidence was 20, 33 and 27 per 100,000 in male, female and both-sexes combined. The incidence adjusted to the World Standard Population was 12, 17 and 15 per 100,000; to the European Standard Population 16, 23 and 20 per

100,000, respectively. The incidence was higher in women than in men above 55 years of age.

During the study period the crude incidence was stable in men but an increasing tendency was observed in women ($p=0.001$ $r=0.873$). After adjustment to the World or European Standard Population this tendency disappeared. The incidence increased according to the increasing baseline age in women till 75 years of age. In men there is a plateau above 55 years.

Female patients had significantly higher mean age; smoking and alcohol consumption were more frequent in men. Mean age significantly increased in both sexes: from 56.9 to 60.4 in men ($p=0.006$ $r=0.791$) and from 62.7 to 66.1 in women ($p=0.001$ $r=0.873$). There were no significant changes in the rate of hypertension, diabetes mellitus, hypercholesterolaemia, heart diseases, smoking (heavy or general) and heavy alcohol consumption during the observation. In the alcohol consumption of men there was a significant increase. The 28-day case fatality was 26.5% in men and 26.8% in women, respectively.

Aneurysm could be verified in 83.5% of the patients, 1% had arteriovenous malformation. 486 patients had no confirmed origin of bleeding. This group includes patients with negative or

missing angiography (because of poor state or other contraindications), also the so-called perimesencephalic SAH.

Separately analysing the angiographically proven aneurysmal cases the crude incidence is 16, 28 and 22 per 100,000 in male, female and both-sexes combined. 10, 14 and 13 per 100,000 adjusted to the World Standard Population; 14, 20 and 17 per 100,000 to the European Standard Population. The pattern of the incidence according to time, the baseline age and the risk factor distributions was similar.

Aneurysms of the internal carotid artery were significantly more frequent in women, aneurysms of the anterior communicating artery in men. We analysed certain clinical parameters according to the aneurysm sites. PCA aneurysms were excluded because of small numbers. Motor palsy was significantly more frequent in MCA and basilar artery aneurysm cases. Case fatality was worse if the posterior circulation is involved. There was no significant difference in the risk factor profiles (hypertension, diabetes mellitus, heart disease, hypercholesterolaemia, smoking, and alcohol consumption) or mean ages of the different sites.

There were two diurnal peaks: one is at 7 a.m. and the other at 5 p.m. ($p < 0.001$). The incidence was the lowest in the summer,

highest in spring in both sexes ($p=0.015$ for men, $p=0.063$ for women).

4.2. Hungarian data

1403 SAH hospital cases were recorded, it means 1028 SAH patients. 63.6% were women. The case fatality was 12.2%, 4.3% died in the first 24 hours. The average hospitalisation time was 6.47 days. 763 CT were done (74.2% of the patients). Hypertension was recorded in 61.3% of the patients. The incidence was increasing with age till the age group 51-60 years, beyond that decreasing. Female preponderance could be observed from the age group 21-40 years and was the most pronounced between 51 and 60 years. Patient number was the highest in Budapest, Baranya, Csongrád and Hajdú-Bihar counties. Case-fatality was lower in those counties where neurosurgery is available. In 531 patients the origin of bleeding could be verified. Aneurysm of the anterior communicating artery was more frequent in men, aneurysm of the middle cerebral artery (MCA) and internal carotid artery in women. In total MCA aneurysm was the most frequent. Arteriovenous malformation was present in 7.6% of the patients. SAH was

most frequent in January and February, rarest in April and August.

4.3. Predictors of vasospasm in the Debrecen SAH database

Between 1987 and 2004, 567 SAH cases were registered. In 457 patients we had unequivocal data whether clinical signs of symptomatic vasospasm did or did not appear. These patients were included in the present study. Female patients were significantly older and had hypertension more frequently. Case fatality was 32.5%. There was no significant change in case fatality during the observational period. Aneurysms were verified in 94.9% of the patients.

Symptomatic vasospasm developed in 22.5% of the patients, significantly more frequent in women.

Only SAH cases with proved aneurysm were included in the logistic regression models. Applying univariate logistic regression Hunt-Hess grade 2 (OR: 2.9 (1.4-6.2) $p=0.006$) and 3 (OR: 2.4 (1.1-5.3) $p=0.037$), and female sex (OR: 1.8 (1.1-2.8) $p=0.019$) were predictive for symptomatic vasospasm. In multivariate logistic regression (including age, sex, Hunt-Hess and Fisher grades, hypertension, aneurysm site) only female sex (OR: 1.8 (1.005-3.2) $p=0.048$) was predictive for symptomatic

vasospasm. Age was tested as a continuous variable and also as dichotomized at 50 years of age.

5. Discussion

5.1. Akita - Japan

The incidence of SAH in Akita Prefecture is similar to other regions of Japan. The incidence is higher in Japan than in other parts of the world, except Finland.

Similarly to other Japanese studies we found higher incidence in women, mainly in the older age group. A plateau was observed in men's incidence in Shimokita and in Kumamoto as well. We found an increase in women's incidence similarly to Izumo, while the incidence was stable in Shimokita in the same period (1989-98). We suppose ageing is the main factor in the increasing tendency in crude rates of women in Akita Prefecture. Because of the plateau in men the increasing age is a risk factor for SAH only in women. We have not observed significant changes in risk factors during the study period except the increasing age in both sexes and light alcohol consumption in men. The proportion of elderly people (>65 years of age) increased in Akita Prefecture to 23.55% from 15.65%, in

Shimane Prefecture (Izumo) to 24.8% from 18.18% between 1990 and 2000 (from 13.6% in 1980), according to census data. Also in Aomori Prefecture (Shimokita), where the incidence remained stable, to 19.44% from 12.95%, suggesting that other factors should be involved also.

The 28-day case fatality was stable during the study period similarly to Izumo. A metaanalysis found 17% decrease in mortality worldwide between 1973 and 2002. This is a significantly longer period than ours, and major regional differences were observed as well.

The low incidence observed in the summer fits to previous data, however in Akita SAH occurrence was highest in the spring. Studies done in Izumo and other regions suggest that the risk of SAH is low during the night and around noon. This phenomenon may be associated with the circadian fluctuations of blood pressure.

5.2. Hungarian data

We found that SAH is more frequent in Hungary than we thought before and SAH occurrence is higher in the cold months and rare in the summer.

The diagnosis of SAH and its final management is done at different wards or institutes in many cases. This fact explains the difference in the number of hospital cases and affected persons. Because of the characteristics of SAH (very severe headache, focal neurological signs) the patients always see doctors and practically all of them are admitted to hospitals. Therefore we can estimate the incidence using hospital data. In 2009 1028 persons were recorded with the diagnosis of SAH it means a 10/100 000 person-years crude incidence, close to the world average 9/100 000. Óváry et al. published Hungarian data previously: 4.75/100 000 in 1997-98, this data is half of the estimation above. Using OEP data from 1998 the estimated incidence would be 18/100 000. The high number may be the consequence of the diagnostics methods at that time: headache plus lumbar tap. Eg. misinterpretation of artificially bloody cerebrospinal fluid as SAH. I60 code had no special financial advantages so the high number can not be “financial morbidity”. By the increasing availability of CT examinations the incidence decreased.

According to our data in more than 20% of the patients CT was not performed. Although in some percent MRI was done this is

still a very high number. In Óváry's 1997/98 study 18% of the patient had no CT examination.

It is quite easy to diagnose SAH with the modern diagnostic methods and SAH patients are always admitted to hospitals. Previous studies suggest that 10-15% percent of the patients die before reaching hospitals, these patients are missing from our study, as well as from Óváry's study. It is possible that secondary SAH cases were recorded. But there is a different ICD-10 code (S0660) for traumatic SAH and this was not included in the query. Secondary SAH cases resulting from coagulopathy could be recorded in the database; however their number should be low. The high number of cases, low CT and case-fatality rates raise the suspicion of recording non-acute patients. But their number may be low because rehabilitation and chronic care wards were not included in the database query. There is a special code I6900 for the post SAH status but it can not be main diagnosis.

The case-fatality is low comparing to international data (European average is 44% but it changes between 8 and 64%), however we could get only hospital case fatality data and the average hospital time was only 6 and a half day. Therefore lower mortality is expected comparing to the usual

28days/1month mortality data. In Óváry's study the 28 days mortality was 33%.

The observed female preponderance fits data reported in other studies. Although the age distribution is different because in most of the studies the incidence increases with age. According to our data the gender difference is highest between 51 and 60 years of age. It is well-known that the occurrence of SAH accelerates in women comparing to men in the postmenopausal period. Aneurysms are not congenital, they develop later in life. The decreasing oestrogen levels change the connective tissue in not only the skin but in the vessels as well. Probably the flow is also different in women's vessels (smaller vessel, higher velocity, turbulent flow). After the menopause atherosclerosis accelerates too, resulting in vulnerability of the vessels. There are data from studies with high patient numbers that suggest SAH preventive effect of the postmenopausal hormone replacement therapy. We found that female preponderance starts earlier than in other countries, around 40 years of age.

In the 531 patients with recorded aneurysm location the distribution is different from the data in the literature. MCA aneurysm is more frequent, ICA (including the posterior communicating artery – PCoA) is less frequent. In Kassel's and

Yasargil's reports: MCA: 18-22%, ACI (with PCoA): 29-31%. In our data from Debrecen MCA is 33%, so this finding can be a real Hungarian characteristic. But occurrence of ICA is less comparing to the Debrecen data too. It is well-known that ACoA is more frequent in men, ICA in women. Frequency of hypertension can be established only with limitations because it was not a mandatory data to be report to the OEP. Therefore we can only state that at least 60% of the patients had hypertension. This is a high number comparing to western data: 28.3% in southern Sweden, 31-34% in France, 47% in the US.

There are higher patient numbers in the four counties with medical university. Final care of SAH patients is usually done in these centers. The case-fatality is lower in counties with neurosurgery wards because of the better care. Another reason can be that patients with poor condition are not transferred to these centers and die in other hospitals. SAH occurrence is highest in January and February, lowest in August, similarly to other countries.

5.3. Predictors of vasospasm in the Debrecen SAH database

In Debrecen 22% of the patients developed symptomatic vasospasm. From the evaluated factors (hypertension, sex,

aneurysm location, Fisher and Hunt-Hess grade) only female sex was found to be a predictor of symptomatic vasospasm.

Female preponderance is observed in most SAH study populations. Ruptured aneurysms are the cause of SAH in 85% of the cases. In the present study the rate was higher, probably due to referring bias. The case fatality did not change significantly during the observational period. This is in contradiction with the decreasing trend reported in the above mentioned metaanalysis.

The rate of symptomatic vasospasm was similar to data in the literature.

Although due to the earlier time period of the data collection we could not test the newer scales, our results support the necessity of re-evaluation of the original Fisher grading scale. In our study the location of the ruptured aneurysm was not predictive.

Our results suggest that female gender is predictive for symptomatic vasospasm. There are data that female sex is a risk factor for angiographic vasospasm, however the majority of the studies have shown no correlation between sex and the risk or incidence of vasospasm. There are controversial reports regarding age. Several studies suggest that young age is a predictor for symptomatic vasospasm, however in our study

young age did not predict symptomatic vasospasm. Smith et al concluded that sex, age, Hunt-Hess and Fisher grades are not predictive. Ryttefors et al did not find age to be a significant predictor for either angiographic or symptomatic vasospasm. In Lanzino's large study with 906 patients, using 5 age groups, there were more symptomatic vasospasms in the older age groups, but there were no significant difference in angiographic vasospasm among the age groups. Kale et al found that younger age (<50) predicted symptomatic and angiographic vasospasms, whereas sex, Hunt-Hess and Fisher grade on CT were not predictive.

In univariate analysis we found that Hunt-Hess grade 2 and 3 is risk factor for vasospasm. However it is difficult to diagnose symptomatic vasospasm in patients with high Hunt-Hess grade, so we have to be cautious with the interpretation. Even in our study in multivariate analysis Hunt-Hess grade lost its significance.

The study designs, age limits and vasospasm definitions are different in the studies, making it difficult to compare their results and explaining at least partly the observed differences.

The limitation of our study is the long period of data collection. Although the diagnostic procedures did not change during this

period, patient characteristics and routine treatment might have changed considerably between 1987 and 2004. However, the outcome of SAH did not change significantly during the observational period. Furthermore, not being available at the time of data collection, we had to stick to the Fisher grade and could not test the newer CT grading scales in our analysis. Advantage of our study is the high patient number and this is the first report not only from Hungary but also from Central-Europe regarding the occurrence and predictors of vasospasm in SAH patients.

6. New establishments

1. We established the incidence of SAH in Akita Prefecture, Japan. The crude annual incidence rate was 27 per 100 000, 20 in men, and 33 in women. Between 1989 and 1998 the incidence was stable in men, however there was a significant increase in women probably attributable to the aging of the Japanese population. In women the incidence peaked at 75 years of age, in men it reached a plateau after 55 years of age. Case-fatality was

26.7% and stable in the observation period. The incidence was lowest in the summer months. Two diurnal peaks were observed: one at 7 a.m. and another at 17 p.m.

2. Analysing the data supplied by the Hungarian hospitals about their inpatient services to the National Health Insurance Fund in 2009 we concluded that the incidence of SAH should be higher in Hungary than previously reported. There were still hospitals in 2009, where SAH patients were treated without CT examination. SAH was most frequent in the colder months and less frequent in the summer in Hungary too.
3. We are the first to report occurrence of symptomatic vasospasm from Hungary and Central-Europe: 22% in Debrecen. From the evaluated factors only female sex could be proved as a significant predictor. Our results support the necessity of re-evaluation of the Fisher grade.



Registry number: DEENK/199/2015.PL
Subject: Ph.D. List of Publications

Candidate: Norbert Kozák
Neptun ID: CB8A3R
Doctoral School: Doctoral School of Clinical Medicine
MTMT ID: 10036733

List of publications related to the dissertation

1. **Kozák, N.**, Bereczki, D., Szabó, S.: Predictors of symptomatic vasospasm after subarachnoid hemorrhage: a single center study of 457 consecutive cases.
Turk. Neurosurg. "Accepted by Publisher" (2015)
DOI: <http://dx.doi.org/10.5137/1019-5149.JTN.14408.-15.1>
IF: 0.576 (2014)
2. **Kozák, N.**, Hayashi, M.: Trends in the incidence of subarachnoid hemorrhage in Akita Prefecture, Japan.
J. Neurosurg. 106 (2), 234-238, 2007.
DOI: <http://dx.doi.org/10.3171/jns.2007.106.2.234>
IF: 1.99





List of other publications

3. **Kozák N.**, Szabó S., Ajtay A., Bereczki D.: Adatok a magyarországi subarachnoidealis vérzésekről: A kórházak 2009. évi jelentései alapján készült elemzés.
Ideggyógyász. Szle. 64 (11-12), 394-398, 2011.
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4. Bereczki, D., Kollár, J., **Kozák, N.**, Viszokay, K., Barta, Z., Sikula, J., Magyar, M.T.: Cortical spreading edema in persistent visual migraine aura.
Headache. 48 (8), 1226-1241, 2008.
DOI: <http://dx.doi.org/10.1111/j.1526-4610.2008.01183.x>
IF: 3.081
5. **Kozák N.**, Csiba L.: Az epilepsziakezelés diétás vonatkozásai.
Ideggyógyász. Szle. 60 (5-6), 234-238, 2007.
6. Wéber, I., Puskár, Z., **Kozák, N.**, Antal, M.: Projections of primary afferent fibers to last-order premotor interneurons in the lumbar spinal cord of rats.
Brain Res. Bull. 71 (4), 337-343, 2007.
DOI: <http://dx.doi.org/10.1016/j.brainresbull.2006.10.003>
IF: 1.943

Total IF of journals (all publications): 8,078

Total IF of journals (publications related to the dissertation): 2,566

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

28 September, 2015



Acknowledgements

I would like express my gratitude to my supervisors, **Professor Dániel Bereczki** and **Sándor Szabó** for their continuous help and support.

I am grateful to **Professor László Csiba** for the oppurtinity to join the Department of Neurology.

I am thankful to **Kazuo Suzuki** who was my tutor in Japan and helped me later as well and to **JICA** (Japanese International Cooperation Agency) that supported my stay at the Research Institute for Brain and Blood Vessels in Akita.

I am grateful to **András Ajtay** for his work with OEP data.

I am thankful to **my family** for the support and patience.