

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

Examination of certain characteristics of headaches in East  
Hungary

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## 1. INTRODUCTION AND AIMS

Primary headaches – mainly tension-type headache and migraine – affect a significant portion of the population. Headache is one of the most frequent complaints in general practice and in the neurological outpatient setting despite the fact that similarly to studies in other countries, about half of migraine patients never see a doctor in Hungary as well. Of those referred to a neurologist by their general practitioners, the reason for referring is headache in 20-30% of cases. The problem frequently remains unresolved mostly due to difficulties in diagnosis and treatment.

Organic as well as psychogenic causes may result in pain. By the underlying cause two patient groups can be formed: organic causes explain pain in the first group but not in the second. Depression is more prevalent in headache patients than in the headache-free population. The co-existence of a primary headache and depression in the same patient might be a coincidence due to the high prevalence of these conditions, but there might be a causal relationship between them, or headaches and depression might have a common background.

Quality of life of the headache patient is affected not only by the characteristics of pain (frequency, duration, severity) but also by the disability caused by headache and the associating mood disorder. Recognizing coexisting mood disorder and disability helps to make the best treatment choice for the acute and preventive treatment of headaches.

Headache is underrepresented in the Hungarian neurological literature. Less than 1.2% of papers published in the first 50 volumes of the journal Clinical

Neuroscience/Ideggyógyászati Szemle, the major official journal of Hungarian neurologists, focused on headache despite the fact that headache is among the most frequent complaints in neurological consultations. In the first phase of my work, with the extension of our previous handsearch and with the use of electronic bibliographic databases, we evaluated the presence of headache as the main topic in articles of the Hungarian medical literature, and we also analyzed the presence of the results of Hungarian headache research in international journals.

There is a lack of information about the distribution of primary headaches in Hungary. For practical reasons it is important to know how patients with primary headaches distribute in a specialized headache outpatient clinic. We also analyzed if tension type headache indeed affects everyday activity less than migraine. In the second phase of my work therefore we analyzed the characteristics of those patients with primary headaches who consulted a single specialized headache outpatient service in East Hungary.

We assumed that headache-associated depressive symptoms are determined by several factors including the gender and the age of the patient, the frequency and the intensity of pain, and the severity of headache-related disability. We also assumed that this relationship differs among different types of headaches, and between patients with headache and non-headache pain. Headache attributed to disorders of the neck (cervicogenic headache) can be considered a disease bearing some characteristics of primary headaches (as far as the location of the pain is concerned) as well as of low back pain (as far as etiology is concerned, i.e. a syndrome due to the disorder of the spine and the paravertebral structures). Therefore we used cervicogenic headache as a model to test if location or etiology is a more important factor in determining the association between depression and disability in pain. We hypothesized that location of pain has

more importance therefore the relationship in cervicogenic headache will follow the pattern seen before in primary headaches. In the third phase of my work I will present the results of a 2-year prospective study in which we evaluated the relationship between headache associated depressive symptoms and disability by analyzing over 900 consecutive cases.

## 2. METHODS

### *2.1. Methods of the literature search*

We identified full publications on headache by handsearching all volumes of the journal *Clinical Neuroscience/Ideggyógyászati Szemle* from 1950 till the end of 2003. Electronic searches were performed to find Hungarian papers focusing on headache using the bibliographic databases of the Hungarian National Library of Healthcare (Hungarian Medical Bibliography, HMB) and the American National Library of Medicine of the National Institutes of Health (MEDLINE and OLDMEDLINE). Results of handsearch and electronic searches were cross checked for the journal *Clinical Neuroscience/Ideggyógyászati Szemle*.

### *2.2. Methods of the epidemiological survey*

All consecutive patients with primary headaches referred to the Neurology and Headache Outpatient Clinic, City Health Service of Debrecen, between February 2002 – April 2003 were asked to fill in a questionnaire on headache characteristics and the migraine disability score (MIDAS) form. Headache diagnoses were assigned using the criteria of the Headache Classification Committee of the International Headache Society.

### *2.3. Relationship of depressive symptoms and disability*

All consecutive patients with either migraine, tension-type or cluster headache, consulted by two neurologists in a 2-year period between February 1, 2002 and January 31, 2004 were asked to fill in a questionnaire containing the age and gender of the patient, the duration of the headache history, the frequency, the duration, the severity and other characteristics of pain. Consecutive patients below 60 years of age with low back pain but free from primary headache, examined by the same two neurologists, were included as a non-headache pain patient group. A healthy control group was recruited from a local cardiovascular screening program who declared themselves healthy and free of headache or other pain. The MIDAS questionnaire was used to evaluate the impact of headache on work-, household- and social activities. Severity of depressive symptoms was evaluated by the Beck Depression Inventory.

### *2.4. The association between location of pain, depressive symptoms and disability*

As a part of the prospective study on headaches, all consecutive patients with low back pain or cervicogenic headache examined between February 1, 2002. and January 31, 2004. completed the above mentioned questionnaires. The diagnosis of cervicogenic headache was assigned using the clinical criteria of the Headache Classification Committee of the International Headache Society.

### *2.5. Statistical methods*

Data are presented as means $\pm$ SD or medians with 25 and 75 percentiles. Frequencies were compared by the chi-squared test. Normality of continuous variables was checked by the Shapiro-Wilk test. The Mann-Whitney test, the

Kruskal-Wallis ANOVA and the Spearman correlation tests were used in the analyses. Multiple comparisons p values were calculated for pairwise comparisons when the Kruskal-Wallis ANOVA found significant difference among the groups. The general linear model was used in multivariate analyses. Factors proved to be significant predictors in univariate tests were included in the multivariate analyses. Statistical significance was assumed if  $p < 0.05$ . Analysis was performed using Statistica for Windows v.6.1 (StatSoft, Tulsa, USA).

### 3. RESULTS

#### *3.1. Results of the literature search*

During the 54 years of the journal *Ideggyógyászati Szemle* 32 full publications were published with major interest on headache. The major area was migraine in 13, cluster headache in 6, secondary headaches in 4 articles, and general aspects of headaches in 5 publications. One paper focused on tension type headache, characteristics of migraine and tension type headache were compared in 2 articles, and the relationship between migraine and secondary headaches was discussed in 1 paper.

Since 1985 there was at least one paper published on headache almost each year, but articles on headache were published much rarely before that. For example in the period of 1966-1984 the volumes published over 19 years did not contain a single paper on headache.

In the NLM database (MEDLINE) we found 488 references. By checking each of them we excluded those with no Hungarian authors and those with major topics other than headache. After exclusions there were 66 publications left,

published between 1955-2003. Two-thirds of these papers were either on clinical (n=32) or experimental (n=12) aspects of migraine. There were no papers focusing on tension-type headache. Cluster headache was the major focus of 4 articles, secondary headaches were the major topic in 10, whereas the general aspects of headache in 8 publications. The number of MEDLINE indexed papers on headache with Hungarian relevance increased considerably since 1990. This increase was not due to publishing more papers in MEDLINE indexed Hungarian journals but due to the increase in publication activity of Hungarian authors in international journals.

We found 295 references in the HMB database. After excluding the irrelevant publications, we were left with 132 documents published in 41 journals. The major topic was migraine in over 40%, general aspects of headache in 33%, and secondary headaches in 15%. Five articles concentrated on tension type headache, 4 papers compared tension type headache to other headaches, 6 articles focused on cluster headache and 1 further paper compared cluster headache to other headaches.

Of the 425 articles of *Ideggyógyászati Szemle* published between 1954-1964 375 are enlisted in the OLDMEDLINE database. Papers published after 2002 are to be found in the MEDLINE database. In the journal volumes published between 1954-1964, we found 7 papers by handsearch on headache. Of the 7 articles 2 were published in supplements. Four of the remaining 5 were enlisted and found in the OLDMEDLINE database. After 2002 the single paper on headache found by handsearch was also identified by MEDLINE.

Publications of the journal *Ideggyógyászati Szemle* appear in the HMB database since 1990. Bibliographic data of those 16 full text papers identified by

handsearch in the period of 1990-2003 were all found by electronic search of the HMB database.

### *3.2. Results of the 2-year prospective study*

The results of the 2-year prospective study will be presented in 3 analyses. First we summarized the characteristics of patients admitted to a single headache outpatient unit. In the next step we analyzed the relationship between the severity of depressive symptoms and disability in primary headaches. Finally, we attempted to give answer to the question if the location of pain or the pathomechanism of pain has more importance in determining the relationship between the level of disability and the severity of depressive symptoms. To examine these 3 questions we analyzed different parts of the database.

### *3.3. Results of the epidemiological study*

During the period of the study 327 patients attended the headache neurology outpatient clinic with primary headache. Sixteen per cent of the patients were male, with no age difference between genders (men:  $38.3 \pm 13.6$ , women:  $38.9 \pm 11.8$  years; mean  $\pm$  SD). Of the patients 42% had migraine, 31% had tension-type headache, 0.9% had cluster headache and 26% had combination headache. We defined patients with combination headache as those who had more than one type of headache. These patients had typical migraine or tension-type headaches, and either both types of headaches appeared in the same patient, or a headache with the clinical characteristics of headache attributed to the disease of the cervical spine was associated with tension-type headache or migraine. Of those 213 patients who had migraine either in a clear form or as part of combination headache symptoms 24 (11%) had migraine with aura. Of

those 154 patients who had tension-type headache either in a clear form or as a part of a combination headache, 49 (32%) had episodic and 105 (68%) had chronic tension-type headache.

Of the patients 191 (59%) could be categorized as those with episodic headaches and 41% with chronic daily headache (CDH). Of the pure migraine cases the majority (130/138, i.e. 94%) belonged to the episodic category, whereas of the pure tension-type headaches 75/102 (75%) were chronic. Sixty per cent (50/84) of those with combination headaches had CDH. CDH was found in 34% among men, and in 42% among women. The proportion of those with CDH between genders did not reach the level of statistical significance ( $p=0.24$ ). The age of women with chronic and episodic types of headache were similar ( $40.1\pm 12.9$  and  $38.0\pm 11.3$  years,  $p = 0.12$ ), whereas men with CDH were almost 10 years older than men with episodic headaches ( $44.6\pm 12.9$  and  $35.1\pm 12.9$  years,  $p=0.015$ ). Chronic migraine (CM) as defined by the proposed 2003 classification of the International Headache Society could be diagnosed only in 8 of the 213 patients with migraine headache even if we did not exclude those with analgesic overuse. CM patients were young (mean age: 36 years), and 6 of the 8 patients had their headache for more than 10 years. These patients had severe disability: their mean and median MIDAS scores were 52 and 51, whereas the corresponding values for chronic tension-type headache were 51 and 33.

The majority of patients had a headache history longer than 1 year in both the episodic and the chronic subgroups. Headaches occurred more frequently in tension-type and combination headaches than in migraine both among men and women. As expected, tension-type headache was associated with less severe pain than migraine in both genders.

Both the median values and the ranges of days with impaired work-, household- and social activities were higher for those with than for those without tension-type headache, both in those who had and who did not have migraine in association with tension-type headache.

Migraine attacks were treated by aspirin, paracetamol or other nonsteroid anti-inflammatory drugs (NSAIDs) in 88% of the cases. Ergotamine tartarate was recommended for 9% whereas triptanes were used by 13%. Of the migraine patients 15% were on preventive therapy. For such purpose tricyclic antidepressants (n=16), beta blockers (n=6), selective serotonin reuptake inhibitors (SSRIs, n=5), calcium channel blockers (n=4) and valproate (n=1) were used.

Episodic tension type headaches were treated with NSAIDs in 76%. Preventive treatment with antidepressants was administered in 45% of those with episodic tension-type headache. Of the 106 chronic tension-type headache patients 77% were recommended NSAIDs, and 63% were on preventive medication. For preventive medication tricyclic antidepressants were most frequently used (36%), SSRI's were administered in 25% of the cases.

#### *3.4. Relationship between the severity of depressive symptoms and disability in primary headaches*

The mean age of the 635 subjects was 39 years, and about two-thirds of the study subjects were women. There was a statistically significant difference among groups for the Beck score and the MIDSAS score as well (Kruskal-Wallis ANOVA,  $P < 0.0001$  in both comparisons). Using the standard cutoff values of the BDI, moderate or severe depressive symptoms were found in 32% of the tension-type headache group, in 14% of the migraine group, and in 18%

of the patients with low back pain. There was a statistically significant difference among groups for pain frequency and pain intensity as well (Kruskal-Wallis ANOVA,  $P < 0.0001$  in both comparisons).

We checked if gender, age, pain frequency, pain intensity and disability have significant effect on the severity of depressive symptoms separately in healthy controls, in patients with low back pain, in patients with headache and in the total study population. As in headache patients as well as in the total study population all of these factors had significant effect on the Beck score (female gender, higher age, more frequent and more intense pain, and more severe disability were associated with more severe depressive symptoms), all of these factors were entered in a multivariate model to test which factors remain significant (i.e. which are independent predictors of depression severity) after controlling for the effect of other factors.

Although the level of disability and age are the most significant determinants of the severity of depressive symptoms in headache patients, the frequency of pain, and gender also had significant effect in the total headache group. Disability is the most important independent predictor of the severity of depressive symptoms in all of the headache subgroups, but not in low back pain. Age is also a significant or at least a marginally significant predictor in chronic tension-type headache and in migraine without aura, but not in the low back pain subgroup. In contrast to the headache subgroups, pain intensity and frequency, but not disability and age, were significant independent predictors of the severity of depressive symptoms in patients with low back pain.

### *3.5. Location of pain and the depression-disability relationship*

In this analysis we compared patients with low back pain to those with cervicogenic headache. Of the 298 subjects there were 113 men and 185 women. Mean age of the low back pain group was 5 years older ( $p < 0.001$ ) and there were more women in the headache group and more men in the low back pain group ( $p < 0.001$ ). In the total study population of 298 subjects, the severity of depressive symptoms (i.e. the BDI score) marginally significantly differed between men and women (mean $\pm$ SD, men: 11.8 $\pm$ 8.4; women: 14.4 $\pm$ 10.4, Mann-Whitney test  $p = 0.043$ ) and there was a marginally significant correlation between age and the BDI score (Spearman  $R = 0.11$ ,  $p = 0.048$ ). Neither gender ( $p = 0.14$ ), nor age (Spearman  $R = -0.005$ ,  $p = 0.93$ ) had an effect on disability (i.e. the MIDAS score) in the total population.

There was no statistically significant difference in the frequency and intensity of pain and in the severity of depressive symptoms between the 2 patient groups, whereas those with low back pain were more disabled in their everyday activities than those with cervicogenic headache ( $p = 0.017$ ).

In univariate tests disability in low back pain patients depended on pain frequency ( $p < 0.0001$ ) and on the severity of depressive symptoms ( $p = 0.0013$ ), whereas gender, age and pain intensity were not associated with the MIDAS score. In cervicogenic headache in addition to pain frequency and the severity of depressive symptoms, pain intensity was also associated with the severity of disability, whereas age and gender – similarly to low back pain – were not related with the level of disability. In univariate tests depression was significantly associated with pain frequency, pain intensity and the level of disability both in low back pain and in cervicogenic headache.

We used general regression models to test which are the factors that, after controlling for the effect of other factors, independently determine disability and depression in patients with low back pain and with cervicogenic headache. As age and gender distribution differed between the two patient groups, and both factors had an effect on the severity of depressive symptoms in the total study population, we entered these factors in the multivariate models. The other predictors were pain frequency and intensity. Determined by the dependent variable, either the severity of depressive symptoms (i.e. the BDI score) or the level of disability (i.e. the MIDAS score) were included as possible predictors.

Age and gender are not significant independent predictors of disability in either group. In low back pain only frequency of pain, whereas in cervicogenic headache pain frequency and the severity of depressive symptoms remained the significant independent predictors of disability. After controlling for the effect of other variables the BDI score was not an independent predictor of disability in low back pain.

Gender and age are not independent predictors of the BDI score in either group. Pain frequency, and pain intensity are independent predictors of the severity of depressive symptoms in low back pain as well as in cervicogenic headache. In addition to these factors, the level of disability is also a significant independent predictor of the severity of depressive symptoms in patients with cervicogenic headache.

## 4. DISCUSSION

### *4.1. Headache in the Hungarian medical literature*

According to our initial survey till 1999, less than 1.2% of papers published in the first 50 volumes of the journal *Clinical Neuroscience/Ideggyógyászati Szemle*, the major official journal of Hungarian neurologists, focused on headache. This rate has not changed when the handsearch was extended to 2003. This underrepresentation might be caused by the difficulties in diagnosing primary headaches – especially tension type headache – with traditional neurological methods: in most cases there are no focal neurological signs on physical examination, imaging techniques usually result in normal results and these diseases can not be exactly diagnosed by neuropathological methods.

Despite of all these, after the lack of interest until the mid-1980-ies, headache became a frequent topic in the Hungarian medical literature: after 1990, in the HMB database there are over 110 publications in over 40 different journals with headache as a main topic. Most articles focused on migraine, and there is an obvious lack of papers on tension type headache despite of its high prevalence.

Bibliographical data of articles on headache published after 1990 can be identified by electronic searches of the Hungarian and international bibliographic databases using carefully constructed but simple search strategies. An increasing presence of Hungarian headache research was found in international journals in the last 2 decades.

### *4.2. Findings of the epidemiological survey*

In the present study we used the MIDAS questionnaire, originally developed to score disability in migraine patients. This questionnaire scores headache

frequency, severity, and number of days affected by the headache in work, household and social activities. Similarly to other recent reports we also felt it justified to score disability not only in migraine but in other types of primary headaches by this instrument. According to our study tension-type headache has a significant impact on daily activity. Although the chronic form of tension-type headache has a more important effect on the quality of life than the episodic form, the number of days lost from work did not differ significantly between those with episodic tension-type headache and migraine in our sample ( $p=0.35$ , Kruskal-Wallis ANOVA). From this survey we concluded that the functional impact of tension-type headache is usually underestimated.

In our survey 84% of those who consulted the headache neurology outpatient service with primary headaches were women, i.e. the proportion of men to women was 1:5. This high proportion of women probably does not reflect the distribution of primary headaches in the whole population. It was reported in several populations that men are more reluctant to consult their headaches than women. Among our 24 cases of migraine with aura, men and women were almost equally distributed (11 men and 13 women), whereas in the migraine without aura subgroup of 189 patients there were only 15 men, i.e. the male:female ratio was 1:12. As in a population survey performed by others in our region the male:female ratio was 1:2 for migraine with aura and 1:3 for migraine without aura, we can conclude that men are generally less likely to consult their headache unless headaches are associated with other clinical symptoms. Cultural and social factors might explain that among our patients there were several times more women than men with migraine and tension-type headache, reflecting that men are more reluctant to seek consultation for their headaches than women in the Hungarian population as well.

The age distribution of our patients deserves attention. Over 90% of our patients were in the active working age group and only 2.5% of our patients were over 65 years of age. Although it was reported that the prevalence of migraine is highest in persons between the ages of 25-55 years, it was also found that a consistent proportion of elderly people have primary headaches and consultation with a specialist was particularly recommended for patients with moderate or severe attacks, or with CDH. The lack of elderly patients in our sample was striking, and further studies should be performed to find the reason for this low consultation rate in this age group.

#### *4.3. Depressive symptoms and disability in primary headaches*

Pain is often associated with depression: in a neurological outpatient setting the odds of having depression were increased to over two-fold in those with pain. Moderate or severe depressive symptoms were reported by 21% of our headache patients and by 18% of those with low back pain, confirming the high prevalence of comorbid depression in patients with pain. It should be emphasized, that both the headache and the low back pain patients of the present study are probably more severe sufferers of pain than those who do not seek medical help for their symptoms. Therefore the conclusions of the study may not be generalized for the total headache and low back pain population.

Among our patients those with chronic tension-type headache scored higher on the Beck scale than migraine patients, although the episodic tension-type headache group had similar score than the total migraine population. Pain frequency was a stronger predictor of depressive symptoms than pain intensity in headache patients in univariate as well as in multivariate testing.

The determinants of the severity of depressive symptoms in headaches and in low back pain differed in our study. Whereas disability and age were the significant predictors of the severity of depressive symptoms in primary headaches, these factors were not independent predictors in low back pain after controlling for the other factors. Pain intensity and to a lesser extent, pain frequency were the most important independent determinants of the severity of depressive symptoms in low back pain.

#### *4.4. Location of pain and the depression-disability relationship*

To study the relationships between pain, depression and disability, in the present study we compared non-malignant conditions. In the chapter above we discussed that this relationship differs between patients with primary headaches and those with low back pain. We chose pain conditions which are prevalent in the population. Similarly to several international studies, low back pain and headache frequently causes disability in the Hungarian population as well: in a population survey disabling back pain and headache pain was present in 6.7% and 7.2% of those over 16 years of age.

Pain is associated with disability and depression. In a Hungarian population based study pain-related disability affected one third of the adult population, and depressive symptomatology was present in 30% of those reporting pain associated disability. It is of question, whether the interrelationship among pain, depression and disability depends mostly on pain characteristics (intensity and frequency), pain etiology (like pain related to malignant or non-malignant causes, primary or secondary pain syndromes), or pain location (like headache or non-headache pain).

In the current analysis we tested whether the relationship between depression and disability in cervicogenic headache has its special pattern, or it resembles to that seen in primary headaches or to that in low back pain. In contrast to patients with primary headache, in patients with low back pain, frequency and intensity of pain were, but disability was not a significant independent predictor of the severity of depressive symptoms.

The difference in predictors of the severity of depressive symptoms in primary headache and non-headache pain subjects suggested a different mechanism for developing depression in primary headaches and in low back pain. Therefore, in the current study we tested if pain location (i.e. headache or non-headache pain) or the etiology of the pain (i.e. primary headache or a pain of vertebral origin irrespective of its location) has a more important role in determining the association between depression and disability in pain syndromes. In cervicogenic headache we found that, similarly to what we reported in primary headaches, disability was a significant determinant of the severity of depressive signs. However, in cervicogenic headache the severity of depressive symptoms was also affected by the severity and frequency of pain – which is a characteristic of low back pain but not of primary headaches. Therefore we conclude that cervicogenic headache bears the characteristics of primary headaches as well as that of low back pain in a way, that both pain location (i.e. headache) and the etiology of pain (i.e. spinal disorder) represent its effect in determining the relationship between pain characteristics, depressive symptoms and disability.

## 5. PRACTICAL CONCLUSIONS

Based on our results and concentrating on practical significance, we can conclude the following:

- Depressive symptoms occur more frequently in headache patients than in the headache-free population.
- As depression often accompanies headache, when examining a headache patient special attention should be paid to the recognition of comorbid depression.
- Comorbid depression is associated with female gender, higher age, and higher frequency of headaches.
- The diagnosis of suspected mood disorder could be supported by using simple screening methods, like the original or the abbreviated versions of standard depression inventories, but the final diagnosis of major depression needs psychiatric evaluation.
- Quality of life of the headache patient is affected not only by the characteristics of pain (frequency, duration, severity) but also by the disability caused by headache and the associating mood disorder.
- Recognizing coexisting mood disorder and disability helps to make the best treatment choice for the acute and preventive treatment of headaches. For the double effect, in headache and comorbid depression, antidepressants should be the first choice among the medications proved to be effective in the prevention of primary headaches.
- In the epidemiological survey the lack of men and especially of the elderly was striking. The reason for this should be further investigated.
- In primary headaches the severity of depressive symptoms is determined by the level of disability, and to a lesser extent by the age of the patient.
- The determinants of the severity of depressive symptoms are similar across subtypes of primary headaches.

- In contrast to patients with primary headaches, the severity of depressive symptoms is associated with the frequency and the intensity of pain, and not with the level of disability in patients with low back pain.
- In pain syndromes both the location and the pathomechanism of pain may have a role in determining the relationship between depressive symptoms and disability.

## 6. LIST OF PUBLICATIONS

6.1. *The PhD thesis is based on the following full length publications:*

Bereczki D, Gesztelyi G. Az Ideggyógyászati Szemle első 50 évfolyamának közleményei. *Clin Neurosci/Ideggy Szle* 1999;52:318-324.

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