

Role of Self-administrated Questionnaires in identifying primary headaches and measuring its effect on quality of life

PhD thesis

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1. Introduction

Headache is one of the most common reason why people see a doctor. Primary headaches include migraine, tension type headache, cluster headache and „other” primary headaches.

Migraine affects approximately 10% of population, its prevalence is 6% in men and 18% in women, and occurs mainly in young, active ages. It is a very expensive neurological disease and causes poor health-related quality of life. Based on clinical experiences, the disability caused by migraine is bigger than the disability caused by the most common primary headache, the tension type headache, and the effect of migraine on quality of life is comparable with the effect of the most painful but much rarer primary headache, the cluster headache. Migraine takes the third place among diseases that can cause disability, and induces both physical and mental impairment for patients.

Despite of these facts, migraine is still underdiagnosed and undertreated. Only less than half of the patients get a medical diagnosis of migraine in their life, and only one third of patients use some migraine specific treatment for their migraine. There are several causes of it, the most important of these that many people suffering even with severe headache do not seek help from a physician. Most of the patients who ask medical help visit their general practitioner because of their headache, for that very reason physicians working in primary care have an important role in recognising migraine. Primary headaches do not have reliable biological marker, the base of their diagnosis is the detailed medical history, presentation of symptoms and the negative neurological examination.

In order to facilitate the detection of migraine, several questionnaires have been developed. One of them is the ID-Migraine Questionnaire („Identification of Migraine Questionnaire”), which asks the patients whether their headaches caused disability, nausea and photophobia in the previous three months. According to the ID-Migraine, a patient suffers from migraine if she or he gave minimum two „positive” answers from these three questions. The ID-Migraine has been proved a reliable and valid tool for screening migraine. It is important to emphasize, that no questionnaire has diagnostic value alone, the „gold standard” always the clinical diagnosis made by a doctor.

There are two forms of quality of life questionnaires, generic and disease-specific questionnaires. The most known generic quality of life questionnaire is the Short Form Health Survey (SF-36), which examines 8 quality of life domains, 4 physical (physical functioning: PF, role-physical: RP, bodily pain: BP, general health: GH) and 4 mental (vitality: VT, social functioning: SF, role-emotional: RE, mental health: MH). The previous quality of life questionnaires, validated on foreign languages, didn't show significant differences between the effects of different types of primary headaches on quality of life, despite of the clinical experiences. Moreover, patients felt that these questionnaires do not ask about many important aspects/domains which influence quality of life.

2. Objectives

- On the one hand, our goal was to create and validate a migraine screening questionnaire in Hungarian language which would be used easily and quickly by the patients in the every day medical practice. To take a long view, our goal was to develop a questionnaire, which makes it easier to identify migraine patients not only in the headache centres, but also in primary care. This led us to develop the Migraine Diagnostic Questionnaire (the MDX Questionnaire).
- On the other hand, our aim was to validate the migraine screening ID-Migraine Questionnaire in Hungarian language, which have been developed originally in English and validated later in several languages with good results. Our aim was to improve the identification of migraine in the future in Hungary with this questionnaire, similarly to the MDX Questionnaire.
- Our further goal was to create and validate a headache-specific quality of life questionnaire in Hungarian language, not only for migraineurs – contrary to the previously validated headache-specific quality of life questionnaires – but also for other primary headaches. That led us to develop the Comprehensive Headache-related Quality of life Questionnaire (CHQQ), which examines in more detail those domains that have important role for quality of life in headache patients. Our aim with the CHQQ was to determine the effects of different primary headaches on quality of life.

3. Methods

3.1. The Migraine Diagnostic Questionnaire (the MDX Questionnaire) study

Our study was carried out at the Headache Service of the Department of Neurology, Semmelweis University in 2011-2012 among patients suffering from primary headaches. Patients filled out the questionnaires themselves during their medical appointment. Clinical diagnoses of headaches were determined according to the International Classification of Headache Disorders (ICHD-II) criteria. Based on the clinical primary headache diagnosis, we created four groups: migraine, tension type headache, cluster headache and „other” primary headaches. We excluded patients with probable migraine and probable tension type headache and patients with rare adult migraine subtypes. There were no further exclusion criteria. The study was approved by the local ethics committee and all patients provided written informed consent.

The sample consists of 306 patients with mean age of 39.1 ± 13.3 years. Most of the patients were women ($n=242$, 79%). The clinical primary headache diagnoses according to the IHS criteria among the 306 patients were as follows: 227 migraineurs (74%), 55 patients (18%) suffering from tension type headache, 17 patients (6%) with cluster headache and 7 patients (2%) with „other” primary headaches. In addition, 17 patients also had migraine among patients with non-migraine primary headache diagnosis, hence 244 patients had migraine altogether. Among the 17 migraineurs, the primary headache clinical diagnoses were as follows: 10 had chronic tension type headache, 6 had episodic tension type headache and one had cluster headache. During the statistical analysis of the questionnaire, migraineurs ($n=244$) were the positive control, while pure non-migraineurs were the negative control. The primary clinical headache diagnosis was tension type headache in case of 39 patients, cluster headache in case of 16 patients and „other” primary headaches in case of 7 patients. Among the total sample, 72 patients had chronic headache.

The MDX Questionnaire items were developed based on the International Headache Society (IHS) diagnostic criteria and clinical experiences collected in headache clinics. The MDX Questionnaire contains 9 „yes” or „no” questions, these questions asking about disability caused by headache, accompanying symptoms and efficacy of drugs used for acute treatment of headache. The questionnaire also asks the number of

headache days the patient experienced in the previous month and the number of days when the patient used analgetics for headache.

For statistical analysis of the questionnaire we summarized the number of „yes” answers. The „gold standard” was the clinical diagnosis made by our headache specialists according to the IHS criteria, after recording medical history of the patients and detailed physical examination. The clinicians were not aware of the questionnaire results at the time of the examination, so this has not influenced the clinical diagnosis.

It is a very frequent observation in the clinical practice that one patient can suffer from more than one headache at the same time, it was an expectation also when we planned this study. During the statistical analysis of the MDX questionnaire the patient was identified as migraineur if he or she had migraine among the primary and/or secondary clinical headache diagnosis.

The distribution of the total scores of the MDX questionnaire in the diagnostic subgroups was investigated with Kolmogorov-Smirnov test. Since the data did not show normal distribution, the differences between the total scores in the diagnostic subgroups was analysed with Kruskal-Wallis ANOVA test. We used version 10 of Statistica program.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and missclassification error (MC) of the MDX questionnaire were calculated. In addition, we determined the „cut off” value of the questionnaire and its’ receiver operating curve (ROC).

3.2. The Hungarian ID-Migraine Questionnaire study

Patients between 18 and 65 years of age, suffering from primary headache, presenting at the Headache Service of the Department of Neurology, Semmelweis University or the Headache Service of Esztergom Hospital in 2012-2014, and reporting two or more headaches in the previous 3 months were involved. Every patient took part in our study who regularly visited our headache outpatient department for minimum two years, willing to participate in our study and they gave written informed consent to this. We excluded patients suffering from probable migraine or probable tension type headache and rare type of adult migraine. There were no further exclusion criteria. The study protocol had been approved by the ethics committee of Semmelweis University.

Patients filled out the Hungarian translation of the ID-Migraine Questionnaire. The validation sample consisted of 380 patients. Clinicians were blinded to the result of the ID-Migraine Questionnaire, so it didn't influence the clinical diagnosis. Patients completed the MDX Questionnaire also, but it was not included as a reference tool in the validation process of ID-Migraine Questionnaire. The „gold standard” during the validation of the Hungarian ID-Migraine Questionnaire was the clinical diagnosis made by our headache specialists, according to the ICHD-3 β diagnostic criterias. As in the original English version, the Hungarian version of the ID-Migraine Questionnaire was considered positive for migraine if a patient answered „yes” at least to two of the three screening questions.

A patient was defined as migrainous if he or she had migraine as primary and/or secondary clinical headache diagnosis. Based on the primary clinical headache diagnosis, we determined the ID-Migraine Questionnaire's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and missclassification error (MC) values. These parameters were calculated for the individual items of the ID-Migraine Questionnaire, as well. We also calculated these values in subgroups of patients according to sex, age (≤ 44 years and >44 years) and disease duration (≤ 12 years and >12 years). In addition, we determined the ID-Migraine's ROC-curve also.

Among the 380 headache sufferers, 40 patients completed the ID-Migraine twice, and among them, we calculated test-retest reliability, using Cohen's Kappa.

We used an Excel spreadsheet for data input, and an online statistical package (VassarStats, <http://vassarstat.net/>) to calculate the ID-Migraine Questionnaire's validity parameters, confidence intervals, missclassification errors and test-retest reliability.

3.3. The CHQQ study

Consecutive outpatients visiting the headache centre of the Department of Neurology, Semmelweis University, in 2008-2010, who fulfilled the IHS criteria for migraine with and without aura, or either episodic or chronic tension type headache took part in the study. We excluded patients suffering from rare adult migraine subtypes and probable migraine or probable tension type headache. Patients whose analgesic consumption reached the criteria of analgesic abuse were also excluded, as were patients who also had concomitant chronic pain syndromes, untreated hypertension, and untreated or

severe kidney or liver disease. Other concomitant treated disorders were not exclusion criteria, but their possible effect on quality of life was not taken into account in the statistical analysis. All patients had headache as the main complaint at the time of the study.

During the development of the CHQQ the main aim was to better focus on unique effects of headaches on quality of life, compared to previous headache-specific quality of life questionnaires, and reveal the involvement of physical, mental and social dimensions of quality of life. Another important consideration was to emphasize those aspects that are crucial not only for clinicians but for the patients, as well.

The CHQQ contains 23 questions that ask about the previous 2 weeks. All questions have five possible answers (5-point Likert scale), ranging from the absolute absence of restriction to maximal restriction. After scoring, the values are transformed to a 0-100 point scale, the absence of restriction being equal to 100 points and the full restriction to 0 point. Total scores and the three dimensions (physical, mental and social) of the CHQQ were calculated. General quality of life was measured with the validated Hungarian version of the SF-36 questionnaire.

Patients filled out the questionnaires after their medical examination. The patients' headache characteristics and other clinical data were recorded during their clinical interview. Headache severity was assessed by the patient (visual analogue scale (VAS); 0-100 mm) and also by the specialist during the clinical interview (IHS rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). Headache diagnoses were made by the same headache specialist during the outpatient visit, using the IHS criteria.

We tested the reliability and the validity of the psychometric properties of the CHQQ. We assessed the convergent validity by the correlation of our instrument with the SF-36 questionnaire. We assessed the criterion validity by examining the correlation of the patients' headache characteristics with our instruments' scores. When we calculated discriminative validity, we compared the results of the CHQQ in the two diagnostic groups, migraine and tension type headache. In the case of assessing the criterion and convergent validity of the CHQQ, we used Spearman's rank correlation coefficients, and Mann-Whitney test in the case of discriminative validity of the CHQQ. In order to assess the structure of our instrument we performed an analysis of item-dimension correlation using Spearman's rank correlation coefficient (content validity). Statistics

were calculated using Statistica 8.0 software. The level of significance was set to $p < 0.05$. The study was approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University.

4. Results

4.1. Results of the Migraine Diagnostic Questionnaire

Patients filled out the questionnaire easily and quickly. In the diagnostic subgroups the total scores of the MDX were significantly different ($p < 0.0001$, Kruskal-Wallis ANOVA). The highest mean scores were measured among migraineurs (7.1 ± 1.5) and the lowest mean scores in the tension type group (3.7 ± 1.4). According to Post hoc Dunn tests, migraineurs' scores were significantly higher than scores of tension type, cluster and „other” primary headache sufferers, and cluster headache sufferers had significantly higher scores than patients with tension type headache. Out of the 9 questions the question regarding disability caused by headache showed the highest sensitivity (0.98) and NPV (0.65), and the question asking about vomitus had the highest specificity (0.87) and PPV (0.93) values. MC was the lowest (0.18) in case of the question asking about nausea.

The missclassification rate of the MDX Questionnaire was the lowest (0.11) in case of minimum 5 „yes” answers out of the 9 questions. The area under the ROC-curve was 0.876 (95% CI 0.823-0.929, $p < 0.0001$). In case of minimum 5 „yes” answers, the MDX Questionnaire's sensitivity was 0.96, specificity was 0.61, PPV was 0.91 and NPV was 0.81.

In addition to the minimum 5 „yes” answers, which was the accepted cut off point in our study, 235 (96.3%) out of the 244 clinically diagnosed migraineurs had positive MDX questionnaire for migraine. In the total migraine sample size 9 subjects (3.7%) were false negative patients. In the group where the primary clinical diagnosis was migraine ($n=227$), the questionnaire showed migraine in 219 (96.5%) patients; the number of false negative patients were 8 (3.5%). From the 62 patients clinically diagnosed as not migraineurs 38 (61.3%) had negative results for migraine with the questionnaire. However, from these 62 patients 24 (38.7%) had false positive results for migraine with the MDX; from them 12 had cluster headache, 10 had tension type

headache and 2 had „other” primary headache according to the clinical diagnosis. From the 39, clinically diagnosed tension type headache patients 10 (25.6%) had positive questionnaire for migraine. From the 16, clinically diagnosed cluster headache patients 12 (75%) had positive questionnaire for migraine, and from the 7 clinically diagnosed as „other” primary headache patients 2 had positive questionnaire for migraine.

4.2. Results of the Hungarian ID-Migraine Questionnaire

A total of 380 patients completed the Hungarian version of the ID-Migraine Questionnaire. Eighty % were female and 20% were male, the median age was 36 years, the interquartile range was 19.8 years. The median disease duration was 10 years, the interquartile range was 16 years.

The number of clinically diagnosed migraineurs was 309; among them 190 had only migraine, whereas 119 patients had another headache diagnoses beside migraine. The total number of non-migraine patients was 71; the primary diagnosis was tension type headache in 45 patients, cluster headache in 19 patients, and „other” primary headache in 7 patients. Among the 380 patients, 257 had only one type headache, namely: 190 patients had only migraine, 44 had only tension type headache, 16 had only cluster headache and 7 had only „other” type of primary headache. The other 123 patients had more than one type of primary headache at the time of the study.

Among the 380 patients 334 had positive ID-Migraine score. Among the 309 clinically diagnosed as migraineurs 293 had positive ID-Migraine score. Among the 45 patients clinically diagnosed with tension type headache 23 had positive ID-Migraine score, as did 16 of the 19 patients whose clinical diagnosis was cluster headache. Among the 7 clinically diagnosed as „other” type of primary headache 2 had positive ID-Migraine score.

Based on the whole sample (n=380), the quality scores of the Hungarian version of the ID-Migraine Questionnaire were the following (at least 2 „yes” answers from the 3 questions): sensitivity: 0.95 (95% CI, 0.92-0.97), specificity: 0.42 (95% CI, 0.31-0.55), PPV: 0.88 (95% CI, 0.84-0.91), NPV: 0.65 (95% CI, 0.5-0.78), MC: 0.15 (95% CI, 0.12-0.19).

Fourty of the 380 patients also completed the ID-Migraine during a follow-up visit. We determined the test-retest reliability of the ID-Migraine Questionnaire among these 40

patients. The median interval between filling out the ID-Migraine for the first and second time was 90.5 days, the interquartile range was 475 days. At the time of the first completion, 36 of the 40 patients had a positive ID-Migraine. At the second time, 34 of the 40 patients had a positive test. The kappa coefficient of the ID-Migraine was 0.77, indicating a substantial agreement between the assessments.

All of the items of the ID-Migraine (nausea, photophobia and disability) had high sensitivity and PPV (>0.8). We found the highest sensitivity for disability (0.97), nausea showed the highest PPV (0.9). By contrast, we found significantly lower scores for the NPV and specificity compared to sensitivity and PPV, and compared to the previous validation studies with the ID-Migraine. Regarding to the clinically relevant subgroups (according to sex, age and disease duration), sensitivity and specificity of the ID-Migraine was the same in female and male patients, the PPV was noticeably higher, whereas the NPV and MC were noticeably lower in females than males. There were no other substantial differences between the subgroups.

The ID-Migraine was positive for migraine in 51% of patients clinically diagnosed as tension type headache sufferers, 84% of patients clinically diagnosed with cluster headache and 29% of patients clinically diagnosed with „other” type of primary headache. This high false positive proportion might be related to the low specificity and NPV of the Hungarian ID-Migraine. Among patients whose clinical primary headache diagnosis was tension type headache ($n=45$), the cause of high false positive proportion with the Hungarian ID-Migraine might be some clinical diagnostic error. With more detailed examination of these patients with the MDX Questionnaire, we found that many patients might also have migraine beside their tension type headache. The high false positive rate among patients clinically diagnosed as cluster headache might be related to the fact, that many of these patients had symptoms which are characteristic for migraine, and cluster headache sufferers were overrepresented in our sample.

4.3. Results of the CHQQ

The CHQQ was statistically analysed in a sample of 202 patients. From the 202 patients 169 were female and 33 were male. The mean age was 35.1 years (SD 11.53; 18-68). In the whole sample, 168 patients (83.9%) were migraineurs according to the clinical diagnosis and 34 patients (16.8%) had tension type headache.

The CHQQ demonstrated excellent reliability, with Cronbach's alpha being 0.913 for the whole sample, 0.892 in the subgroup of migraineurs and 0.928 in the subgroup of tension type headache sufferers.

In the present study more severe clinical parameters of headache were related to a worse quality of life measured by the CHQQ (showing lower scores with the CHQQ). The strength of the negative correlations was weak to moderate, just some of them reached statistically significant degree, and the tension type patients showed the weakest relationships.

The content validity of our instrument was adequate when we determined the item-dimension correlations.

When we assessed the convergent validity of the CHQQ, we found that the total score of our instrument correlated significantly positively with all SF-36 dimensions in the whole sample and in the diagnostic subgroups. The exception was the total score in tension type patients that was not correlated with SF-36's social functioning domain. The three dimensions of CHQQ had significant correlations with the majority of SF-36's domains. The strength of most correlations were moderate (0.3-0.5) in the whole sample and in the migraine group, while there was a high number of strong (>0.5) correlations between CHQQ scores and SF-36 domains among the tension type headache patients.

When we determined the discriminative validity of the CHQQ we demonstrated that tension type patients had numerically higher scores (better quality of life) for all items, dimensions and total scores of CHQQ compared to migraineurs. The differences between the two diagnostic subgroups were strongly significant in most cases.

Later CHQQ was validated with good results in a Serbian population, and we tried it with similarly good results among patients suffering from cluster headache and medication overuse headache.

5. Conclusions

5.1. The Migraine Diagnostic Questionnaire

The good results of the MDX Questionnaire suggest that it is a useful tool for migraine screening. This questionnaire is unique because there was no migraine screening

questionnaire validated in Hungarian language before our study. Thus, the underdiagnosis of migraine might be decreased with the MDX Questionnaire not only in headache centres but probably in primary care also. However, a more precise assessment of the MDX Questionnaire would be desirable using further studies in representative samples from the Hungarian general population.

5.2. The Hungarian ID-Migraine Questionnaire

The sensitivity and PPV of the Hungarian ID-Migraine Questionnaire were similarly good compared to previous validation studies of the ID-Migraine Questionnaire. Therefore, we propose that the Hungarian ID-Migraine is a useful tool for screening migraine. However, the specificity and NPV of the Hungarian questionnaire were numerically lower compared to previous validation studies of the ID-Migraine. This might be related to the high proportion of false positive results among patients suffering from tension type and cluster headache. Further testing of the instrument is required, preferably in a sample from the general population; among this sample probably the questionnaires' specificity and NPV would be higher. Our results suggest that the use of Hungarian ID-Migraine Questionnaire might decrease the underdiagnosis of migraine in the future.

5.3. The CHQQ

Previous headache-specific quality of life questionnaires were validated only among migraineurs, and did not show significant differences between the effects of different types of primary headaches on quality of life. We validated the CHQQ, developed by us, with good results not only among migraineurs, but also among patients suffering from tension type headache, and we tried it with good results among patients suffering from cluster headache and medication overuse headache. Such headache-specific quality of life questionnaire in Hungarian language previously was not available that would be suitable to discriminate the effects of different types of primary headaches on quality of life in such a detail like our newly developed instrument. Therefore, CHQQ has a unique value in identifying headache patient's health-related quality of life.

6. Publications

6.1. Journal articles relevant to the thesis

- Csépany É, Tóth M, Gyüre T, Magyar M, Bozsik G, Bereczki D, Juhász G, Ertsey C. (2018) The validation of the Hungarian version of the ID-migraine questionnaire. *J Headache Pain*, 19 (1):106.
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- Jankovic S, Andjelkovic M, Zaric R, Vasic M, Csépany É, Gyüre T, Ertsey C. (2016) The psychometric properties of the Comprehensive Headache-related Quality of life Questionnaire (CHQQ) translated to Serbian. *SpringerPlus*, 5:1416.

6.2. Other journal articles

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