Examining the Quality of Life in Primary Headaches

PhD Thesis

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1. Introduction

1.1 Health related quality of life

Quality of life (QOL) is a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationship and their relationship to salient features of their environment.

Health-related quality of life (HRQoL) is a more circumscript entity. Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. HRQoL represents the overall effect of illness and its therapy, as reported and evaluated by the patient. Accordingly, a distinction between overall HRQoL and disease-specific HRQoL is necessary. Overall HRQoL is a concept that includes physical and mental functioning and well-being, social and role disability, and general health perceptions of the individual. On the other hand, disease-specific HRQoL describes the particular impact of a selected condition on HRQoL.

Patient reported outcomes (PROs) include all information, which is communicated directly by the patient and describes his/her health and emotional status, or medical conditions, and the consequences thereof. Beside the 'hard' indicators – i.e. mortality, morbidity – which are traditionally applied for measuring the efficiency of health care activities, PROs describing the patients' subjective experiences – including life quality measurements – are gaining more and more attention. Practical experiences confirm – mainly in case of chronic diseases– that better values, shown by objective indicators used in medical work, are not necessarily accompanied by the patients' sense of feeling better. On the other hand, in case of several medical conditions, the quality of life is an independent predictor of disease progression and/or outcome.

1.2 Measuring health-related quality of life

Measuring HRQoL has become a widely accepted and popular method for assessing health status, it is a relevant and quantifiable outcome of care, therapy quality and effectiveness. The standardized evaluation of HRQoL makes it possible to quantify the burden of illness. Although measuring health related quality of life can be useful in individual persons, it is particularly useful in assessing the impact of disease in groups of patients and it is often used as end point tool in clinical studies. Further, it is also helpful in pharmacoeconomic evaluations and appropriate allocation of health care resources. The subjective evaluation of

the impact of a disease on the individual's quality of life has become possible with the development of HRQoL instruments and the demonstration of their statistical and psychometrical properties. HRQoL questionnaires are among the most commonly used PRO measurement tools. HRQoL scales are used to complement available measurements by incorporating the patient's point of view. The primary advantages of using such scales in addition to clinical rating scales is the reflection of the patients own assessments of their health, which often differs considerably from clinicians or even carers views.

There are two basic types of HRQoL questionnaires: generic or disease-specific questionnaires. Generic HRQoL questionnaires measure overall HRQoL. They include questions that represent those aspects of health that are important for the majority of people. Thus, these instruments permit the comparison of the impact of one illness with that of others and also with values of those who are well. They can measure the effect of various healthcare interventions and therefore can be useful, among others, in analysing cost-efficiency or planning resource allocation in health economics studies. Generic instruments may, however, be unresponsive to changes in specific conditions. There are numerous generic quality of life instruments in use, the most widely used being the 36-Item Short Form Health Survey (SF-36). Disease-specific HRQoL questionnaires focus on problems associated with single disease states, allow comparisons of illnesses which share the leading symptoms, and can be helpful in selecting the most appropriate therapy for the patient and monitoring its efficiency. Moreover, they may better reflect the particular impact of a selected condition. On the other hand, these questionnaires are not suitable to compare the impacts of different conditions with different symptomatologies.

1.3. Psychometric properties of a HRQoL questionnaire

QOL instruments usually study more domain**s** of QOL. A domain refers to a specific area of behaviour or experience, such as work performance, social functioning, sleep, leisure activities, etc. The domains usually cover the three main dimensions of HRQoL: physical, mental and social. Like in the case of other scales, the properties of HRQoL scales should be established in the population studied before the scale can be used for further investigations. The validation of a questionnaire requires testing its psychometric properties, most importantly its reliability and validity. Reliability is the degree to which a test consistently

measures what it aims to measure. The methods of assessing reliability include test–retest method, use of two alternative questionnaires and measuring the internal consistency. Measuring the internal consistency requires calculating either the split-half reliability, or the inter-item correlation. The inter-item correlation is determined by the Cronbach's alpha coefficient. Internal consistency is generally considered adequate if Cronbach's alpha exceeds 0.7, but in clinical setting an alpha exceeding 0.9 is the minimum requirement. Validity refers to the degree to which an instrument can accurately assess the specific concept that the research is attempting to measure. A high-quality QOL instrument is required to demonstrate different forms of validity, such as criterion validity, construct validity and content validity. Criterion validity is usually defined as the extent to which scores of an instrument are related to a criterion measure. In headache research, the clinical characteristics of the individual's headaches (such as the frequency, severity or duration of the attacks) are frequently used as criterion measures, and criterion validity is assessed by measuring the correlation of the patient's headache characteristics with the questionnaire's items, dimensions and total score. Construct validity refers to an agreement between a theoretical concept ('construct') and the instrument designed for measuring it. Convergent and discriminative validity are two subcategories of construct validity. Convergent validity shows the correlation with another, already validated instrument. Discriminative validity is measured by comparing the results of the instrument in two diagnostic groups. Content validity expresses the degree to which the underlying construct (QOL) is comprehensively sampled by the instrument's items. Responsivity means that the instrument is able to follow and measure changes in the HRQoL (caused for example by a medical treatment). Besides the adequate psychometric properties, the length and ease of use of a questionnaire are important aspects of its usability. A validated instrument can only be used in the original language in which the validation studies were done. Before using in another language, the instrument has to be validated in the new language.

1.4 Burden of headache and measuring HRQoL in headache

Headache is one of the most frequent complaints in medical practice. Primary headaches constitute a public health problem, affecting 46% of the adult population globally, causing a significant amount of disability and poor HRQoL. The most common primary headache is

tension type headache (TTH), which global prevalence exceeds 40%, while the prevalence of migraine is approximately 12%. 2% of the population has medication overuse headache (MOH), but its relative frequency is much higher in secondary and tertiary care (over 30% in headache centers). According to moderate estimates at least 3.5 million Hungarian people have regular headaches. For comparison, there are 30 accredited headache centers in Hungary, which treat yearly approximately 20-30000 patients. The third costly neurological disease in the European Union is primary headache.

There is a significant amount of scientific evidence about the negative effect of episodic and chronic migraine, cluster headache (CH), TTH and chronic daily headache on generic and headache-specific QOL. Studies with generic HRQoL instruments have established that the impact of migraine on patients' health status and quality of life may be similar to, or even greater than, that of other chronic disorders such as osteoarthritis, diabetes, low back pain, depression, or congestive heart failure. The effects of acute and prophylactic migraine treatment on QOL have also been documented. The most commonly used generic instrument for measuring HRQoL in headache ist the SF-36. Since the 1990s several headache-specific QOL instruments have been developed. These include the Migraine-specific Quality of Life Questionnaire (MSQ2.1), the Migraine-Specific Quality of Life measure (MSQOL), the 24-hour Migraine Quality of Life Questionnaire (24-hour MQoLQ), the Qualite´de Vie et Migraine (QVM), and the Migraine Disability Assessment Score (MIDAS). The 6-item Headache Impact Test (HIT-6) was designed to measure headache impact, a concept that is strongly related to QOL.

The headache-specific QOL instruments were mainly developed to follow the status of migraineurs. Although they were used several times in other types of headache, most of them had not been validated in these headache types. Only MSQ2.1 and HIT-6 have been psychometrically validated for chronic migraine and MSQOL for TTH, but none have been validated in other headache types. Despite the obvious differences in the clinical picture and the patients' complaints QOL instruments measured a much smaller difference than expected, when investigating QOL in different headache types. The headache specific MSQ2.1 questionnaire, which is widely used in headache research, did not show any difference between the QOL profiles of CH patients and migraineurs. Moreover, a clinically effective therapy was not necessarily reflected by an improvement of the QOL scores. These

observations raised the possibility that the previously used QOL instruments do not fully capture headache patients' perceptions and they are not enough responsive to detect the difference between different headache types and to follow the changes of state.

2. Aim

The aim of our studies was to assess the impact of common headache types on HRQoL. First we investigated the health-related and condition-specific quality of life in episodic cluster headache. After that, for the reasons detailed in the introduction, we aimed to develop a new comprehensive headache-specific questionnaire, which assesses several aspects of QOL and which is useable in common headache types. We then examined the psychometrical properties of our new questionnaire, called Comprehensive Headache-related QOL Questionnaire (CHQQ), in migraineurs, TTH patients and MOH patients. To assess the responsiveness of the CHQQ for following QOL of headache patients during headache treatment we tested the questionnaire on a sample with MOH.

3. Methods

3.1 Patients

Consecutive outpatients visiting the headache centre of the Department of Neurology, Semmelweis University, who fulfilled the International Headache Society (IHS) for migraine with and without aura or tension type headache (either episodic or chronic) or episodic cluster headache or medication overuse headache took part in the studies. During the psychometric testing of the draft version of the Comprehensive Headache-related QOL Questionnaire data of 25 outpatients visiting the headache centre of the National Institute of Neuroscience with the diagnose of episodic migraine were also included. We excluded patients suffering from the rare adult migraine subtypes (hemiplegic migraine, basilar-type migraine, retinal migraine and complications of migraine). In order to minimize the chance of misdiagnosing the patients, we also excluded patients with the diagnosis of probable migraine and probable TTH. Patients with significant somatic or mental diseases were excluded. Other concomitant treated disorders were not excluding criteria, but their possible effect on QOL was not taken into account in the statistical analysis. Mild to moderate depression was not an exclusion criterion. The studies were approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University.

3.2 Presentation of the applied questionnaires

Generic QOL was measured by the SF-36 questionnaire. This is one of the most frequently used generic QOL instrument, it was validated in 50 countries. The SF-36 yields an eight-scale profile of functional health and well-being. The 36 items of SF-36 are aggregated in eight scores, each representing 2–10 items. Four items [physical functioning (PF), role physical functioning (RP), bodily pain (BP) and general health (GH)] represent physical health and four [vitality (VT), social functioning (SF), role emotional functioning (RE), mental health (MH)] are related to mental health; accordingly, physical and mental composite scores can also be calculated. The original version of the SF-36 (also validated in Hungarian) does not count calculate any dimensions or a total score. It measures only the scores of the eight domains, thus producing quality of life profiles which are often represented in graphical form. The later version, the SF-36v2 allows calculation of physical and mental dimensions. Data collected with the first version can be converted to the second version only after a study on a large sample in the general population. This was not made for the Hungarian version, therefore the second version is not validated in Hungarian language.

Disease-specific HRQoL was measured by MSQ2.1 in the study which assessed the impact of CH on QOL. MSQ2.1 contains 14 item and measures three dimensions of headache impact. Seven questions ask about the extent of limitation in daily activities caused by migraine- this is the MSQ's so-called role-restrictive area. Four questions ask about how often are these activities limited- this is the role-preventive domain. Three questions probe the emotional impact of migraine. MSQ2.1 was found to be reliable and valid in assessing QOL in migraine. It has also been used in CH. More recently, MSQ2.1 was validated for clinical use in episodic and chronic migraine and was found to demonstrate significant differences between these, with chronic migraine sufferers having lower values in all dimensions.

In our further studies we investigated the psychometric properties and responsiveness of the CHQQ, the new questionnaire which was developed by our working group. The 23-item CHQQ examines the impact of headache on QOL in detail. The questions cover the 4 weeks before the data recording. 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 points. Total score and the three dimensions (physical, mental and social) are calculated; they are the mean values of the relevant transformed item scores, i.e. the item scores are not weighted. It is also possible to use the questionnaire as a profile, in this case the scores of each item should be represented in graphical form. This can be useful among others to assess the effectiveness of a special therapy.

3.3 Data recording

Generic QOL was measured with the validated Hungarian version of the SF-36 questionnaire in all studies. Headache-specific quality of life was measured with MSQ2.1 in the first study, which investigated the health-related and condition-specific quality of life in episodic cluster headache. In the other studies, after our working group developed the new Comprehensive Headache-related QOL Questionnaire, headache-specific quality of life was measured by this new instrument. The patients completed the questionnaires in the Headache Unit, after their outpatient visit. Missing data were not complemented. The patient's headache characteristics and other clinical data were recorded during their outpatient visit. The average headache severity was assessed by the patient (VAS; Visual Analogue Scale 0-100 mm continuous version) on a sheet accompanying the CHQQ, and also by the headache specialist during the clinical interview (HIS rating scale, 0=pain free, 1=mild, 2=moderate, 3=severe). Headache diagnoses were made by the same headache specialists during the outpatient visit, using the IHS criteria. Depression was not formally tested during the visit. The HRQoL data were not used in the diagnostic and therapeutic evaluation of the patients during their medical visits.

3.4 Statistical methods

Statistics were calculated using Statistica software, versions 8.0 to 11.0. The level of significance was set to $p<0.05$. As the data distribution of most HRQoL domains was not Gaussian, we used nonparametric tests in all studies. Wilcoxon signed rank tests were used to check differences within the groups. Spearman's non-parametric tests were used to check for correlation between the QOL instruments and between HRQoL scores and patient characteristics. Differences between groups were assessed with either Kruskal–Wallis ANOVA with Dunn's multiple comparisons tests or Mann–Whitney tests.

3.5. Validation process

According to the internationally accepted recommendations, we investigated the reliability and validity (criterium, convergent and discriminative validity) of the questionnaire during the psychometric testing. The detailed description of these psychometric properties are described in chapter 1.3. We assessed the reliability of the questionnaire by calculating the internal consistency (determined by the Cronbach's alpha coefficient). Convergent validity was examined by calculating the correlation of the CHQQ's items with subscales of the SF-36 measure. The correlation of the patients' headache characteristics (e.g. headache severity, attack frequency, amount of analgesic consumption) with the questionnaire's items was used to assess criterion validity. Discriminative validity was assessed by comparing the results of the instrument in the different diagnostic groups. The responsiveness of the CHQQ was tested in a pilot study, by measuring the changes of quality of life due to complex treatment in a sample of MOH patients.

4. Results

4.1. Examination of quality of life in episodic cluster headache

In our first study about HRQoL in headache we set out to assess overall and disease-specific HRQoL in episodic CH patients during the cluster period and outside the bout. Thirty-five patients with episodic CH were involved in the study. The results were compared with those of a group of migraineurs and a control group from the general population. Both comparator groups were matched for sex and age.

General HRQoL

During the cluster period, CH patients had lower scores in all SF-36 domains than non-migraineur controls. The difference was statistically significant in six domains (role physical, bodily pain, general health, vitality, social functioning and mental health). CH patients also scored significantly lower than migraineurs in the bodily pain and social functioning domains. After the termination of the cluster period, CH patients' scores improved, this improvement was significant in the role physical, bodily pain and social functioning domains. There was no statistical difference between CH patients outside the bout and headache-free controls. There was no correlation between SF-36 scores and most

of the characteristics of CH patients. Migraineurs scored lower than controls in all SF-36 domains; the differences were statistically significant for physical functioning, role physical, bodily pain, general health and social functioning scores.

Headache-specific HRQoL

Patients during the CH period scored the lowest on all three MSQ 2.1 subscores. There was a significant difference between CH patients and controls as well as between migraineurs and controls. The difference between CH patients' scores and those of migraineurs was not significant. After the bout, CH patients' subscores improved dramatically and were similar to the headache-free control values. There was no correlation between MSQ2.1 scores and the characteristics of CH patients.

As expected, among the items of physical health, bodily pain score of SF-36 correlated with all MSQ2.1 subscores: more severe pain was associated with more pronounced limitations in role and emotional functioning. Limitations in the role physical domain also correlated with loss of functioning in all MSQ2.1 subscores.

SF-36's physical functioning score correlated with emotional functioning on MSQ2.1. The general health score showed no correlation with MSQ 2.1. Of the four SF-36 subscores related to mental health three (vitality, social functioning and mental health) positively correlated with emotional functioning, and two (vitality and role emotional functioning) with the role-function preventing aspect of CH. Surprisingly, there was no correlation between physical functioning and the role functioning items of MSQ2.1 or between the emotional functioning subscores of the two instruments.

Discussion

In our study, generic and headache-specific HRQoL were found to be seriously impaired during the cluster period. This impairment was at least as severe as in migraineurs for most HRQoL domains; bodily pain and social functioning were significantly worse in CH. MSQ2.1 and SF-36 were not sensitive enough to the difference between the QOL profiles of CH patients and migraineurs.

Before this study, there was only a limited amount of data concerning overall quality of life in CH. In an Italian study HRQoL of CH patients was investigated by the SF-36 during the

active periods and the results were compared with Italian normative data. CH was associated with a significant decrease in six of the eight scales (role physical, bodily pain, general health, social functioning, role emotional and mental health). It is of interest that in our study five of these scales (role physical, bodily pain, general health, social functioning and mental health) were also significantly worse, and physical functioning was not statistically different from controls in both studies. Italian CH patients had worse emotional role functioning than controls whereas Hungarian patients scored lower on the vitality subscore. On the whole, these data indicate that the HRQoL impairment in CH is quite uniform in different cultural and linguistic contexts.

Generic instruments make it possible to compare HRQoL in different medical conditions. Based on literature searches, CH patients seem to have a very unfavourable profile. All SF-36 subscores of the present CH population were significantly lower than those of patients with previous myocardial infarction. CH patients had significantly worse scores in all SF-36 dimensions except physical functioning than patients who had survived peritonitis. CH patients had more severe bodily pain, lower vitality, worse social functioning and mental health than patients with surgically treated hip arthrosis, peripheral artery disease, or coronary artery disease.

Headache related QOL was previously not studied in CH. Because a general headache specific HRQoL instrument did not exist, in our study we used the MSQ2.1. MSQ2.1 has been widely used to study migraine-specific quality of life. In our study, MSQ2.1 was sensitive to HRQoL improvement of the present CH population during and after the bout. However, it was surprising that limitations measured by MSQ2.1 caused by CH were not significantly more severe than those of migraineurs, as would have been expected from personal accounts of patients who suffer from both headache types. The relative insensitivity of MSQ2.1 to the consequences of CH may be explained by the item selection process during the development of MSQ, which aimed at achieving a highly migraine-specific measure. We felt that these two instruments may not capture some essential aspects of CH. Among others, these observations also motivated us to develop a new headache specific HRQoL instrument.

4.2. Development and validation of the Comprehensive Headache-specific Quality of life Questionnaire

4.2.1 Development process of the new headache-specific questionnaire

The development of the questionnaire consisted of the following steps: relevant item identification, development of a draft version, psychometric testing of a draft version and development of the final version.

First one of our team conducted open interviews with 25 persons suffering from the most important primary headache types (10 migraine, 10 TTH and 5 CH patients). The questions for these interviews were based on the experience of five clinicians and literature reviews of QOL in headaches and other pain conditions. A question was considered a potential item if at least two clinicians and two patients from each diagnostic group felt the respective issue was important. Twelve of the 37 original questions were found redundant or insignificant and therefore removed, resulting in a 25-item draft version.

In a second step, 11 migraineurs from a larger group studied for the effect of migraine were asked to complete the draft version and were then interviewed about it. These interviews were used to determine whether each individual understood the items, felt them meaningful and whether they felt the answer categories were sufficient. Minor changes of content and format were applied accordingly.

In the next step, the psychometric properties of the item scores, dimension scores and total score of the 25-item questionnaire were tested in a group of 117 migraineurs. The questionnaire demonstrated good reliability, with Cronbach's alpha being 0.893. Criterion validity was adequate, with headache severity being correlated with most of the items. Convergent validity was adequate; most "physical" items of the new questionnaire showed significant correlations with the bodily pain and role physical SF-36 subscales and most "psychical" and "social" items were correlated with mental health and social functioning SF-36 subscales. Two items were problematic and therefore not included in the final version. One of them had by far the biggest proportion of missing answers, the other one had a very low item-total correlation. The reliability and validity assessments confirmed that the resulting 23-item questionnaire was adequate for further testing.

4.2.2 Validation of the Comprehensive Headache-specific Quality of life Questionnaire in different headache types

4.2.2.1 Migraine and tension type headache

A total of 202 patients (169 females, 33 males, mean age 35.1 ± 11.5 years) were involved in the study. 168 patients (83.2%) were migraineurs and 34 patients (16.8%) had TTH (11 episodic and 23 chronic).

The questionnaire 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 TTH patients. The physical, mental and social dimensions also showed good reliability in the whole population and also in the diagnostic subgroups (Cronbach's alpha values 0,801-0,874). By assessing the criterion validity, HRQoL scores were negatively correlated with headache characteristics in both subgroups. In the subgroup of migraineurs, headache severity (measured both with a visual analogue scale and the IHS scale) showed strong, negative significant correlation with the questionnaire's dimensions scores and total score. Headache frequency did not correlate significantly with the dimensions scores and total score. The other headache characteristics showed significant, mild to moderate negativ correlations with the dimensions scores and total score. In the subgoup of TTH patients, clinical data showed significant correlations with a much smaller number of items. Headache severity (measured both with a visual analogue scale and the IHS scale) showed mild negative correlation with physical and social dimension either in this subgroup. By assessing the convergent validity, in the subgroup of migraineurs the dimension scores and total score showed significant, mostly moderate correlation with the domains of SF-36, except for the social dimension, which did not correlate significantly with role emotional functioning SF-36 domain. In the subgroup of TTH, the dimension scores showed mostly significant, mild to moderate positive correlations with the scores of SF-36. There were no significant correlations between physical dimension and bodily pain SF-36 domain, between mental dimension and role emotional functioning SF-36 and between the social dimension and physical functioning. In the subgroup of TTH, the total score showed moderate to strong correlations with all SF-36 scores, except for social functioning. Discriminative validity was assessed by comparing the QOL scores of the two subgroups. All dimension scores and also the total score were significantly lower in migraineurs than in TTH.

4.2.2.2 Medication overuse headache

We involved 68 MOH patients (53 women and 15 men; mean age 42.1 ± 14.2 years). The majority of the patients had a clinical headache diagnosis of chronic migraine (51 patients, ie. 75%); 15 had chronic TTH and two had chronic daily headache not otherwise specified. Forty-four patients (65%) were overusing simple NSAIDs, 11 combined NSAIDs, while 10 had triptan- and 3 ergot-overuse at the time of the study.

The reliability of the questionnaire was adequate (Cronbach alpha = 0,869 for the whole questionnaire) in this group of MOH patients. When examining the criterion validity of the instrument, we found negative correlations between the clinical data and CHQQ scores of the patients, as we had expected. Significant, mild to moderate correlations were observed between headache severity (measured both with a visual analogue scale and the IHS scale) and the questionnaire's social dimension and total score. The questionnaire's dimensions and total score were not significantly correlated with the other clinical data. In order to compare the two QOL questionnaires' performance, we also examined the criterion validity of the SF-36 in this sample. We found significant, but weak negative correlations between headache severity (measured both by VAS and IHS scales) and SF-36's bodily pain dimension. The patients' age, headache and attack frequency showed mild, but significant negative correlations with SF-36's physical functioning domain. Surprisingly, we found significant positive correlations between disease duration and 4 of the 8 SF-36 domains (bodily pain, vitality, social functioning, and mental health). During the examination of convergent validity the dimensions of the questionnaire showed positive and almost always significant correlations with the SF-36 domains. The total score of the questionnaire showed significant, mostly mild to moderate correlations with all SF-36 domains; it was strongly correlated to the bodily pain domain of the SF-36. During the examination of discriminative validity we compared the QOL of MOH patients and chronic TTH patients. All dimensions scores and the total score were lower in MOH patients than in chronic TTH patients; the difference was significant except for the mental dimension. SF-36 scores of MOH patients were also lower, the difference was not significant in three of the four SF-36 mental domains (social functioning, role emotional functioning, mental health).

4.2.2.3 Examination of the questionnaire's responsivity in medication overuse headache after withdrawal treatment

The questionnaire's responsivity was tested in a pilot study. 15 of the original 68 MOH patients were involved (13 females, 2 males, mean age 39.7 ± 12.5 years). The quality of life of the MOH patients at baseline was compared to our previously obtained QOL values of 177 patients suffering from episodic migraine.

In the study we investigated the changes in the headache's clinical characteristics (headache and attack frequency, duration and severity of headache, analgesic consumption) and the changes in QOL (Wilcoxon tests). Futher we analysed the correlation between the change in clinical characteristics and QOL (Spearman's tests). When analyzing the correlations between the improvement of clinical variables and QOL, the improvement was expressed as the percentage of the baseline value. The patients were enrolled to a complex treatment programme consisting of acute medication withdrawal, preventive pharmacological treatment, structured advice and lifestyle intervention. The baseline QoL profiles and clinical characteristics of the involved 15 patients were not significantly different of the whole MOH patients group. After the treatment period the clinical characteristics of patients' headaches improved significantly. The quality of life also improved, all three dimensions and total score of CHQQ showed a significant increase. The correlations between the change in clinical characteristics and that of CHQQ's scores were not significant with the exception of the correlations between the improvement of headache severity and the improvement of the CHQQ total score.

4.2.3 Discussion

According to the internationally accepted recommendations, we investigated the reliability and validity (criterium, convergent and discriminative validity) of the questionnaire during the psychometric testing.

We calculated the internal consistency to assess the reliability of the questionnaire. Cronbach's alpha was adequat in all the diagnostic subgroups, in several subgroup it's value exceeded the very conservative level 0.9, which represents an excellent reliability. The use of test–retest analysis, ie. the repeated application of the instrument would have been ethically incorrect in our studies, because the majority of our patients clearly needed a

change in their acute medications, and a significant portion also needed prophylactic therapy.

By assessing the criterion validity, according the expectations, the clinical data of patients with headache showed negative correlations with the QOL scores. In all diagnostic subgroups QOL scores correlated mostly and strongest with pain intensity. This confirms the finding, which has been observed by other working groups, too, that pain intensity is the main determinant of QOL in headache. Surprisingly, QOL scores showed less correlations with headache and attack frequency. The strength of the correlations we observed (weak to moderate) was comparable to those found in other validation studies, and can be explained by the conception of QOL, which is based on the patients' subjective interpretation, while the clinical data can be considered more objective. In our studies, clinical data were gathered from the patients' headache diaries. In the field of headache research, by a general consensus, the patients' headache diary is considered to be objective.

It is worth noting, that the SF-36 domains showed less and weaker correlations with clinical data, and in the subgroup of MOH patients, we found significant positive correlations between disease duration and 4 of the 8 SF-36 domains. This suggests, that according to our intention, the CHQQ is more sensitive to the relationship between QOL and clinical data, than the generic instrument SF-36.

By assessing the convergent validity we examined the correlation of the different patient subgroups' quality of life scores with the domains of the SF-36. Most correlations were of weak to moderate strength, which was similar to those found in previous validation studies and studies using validated questionnaires, including our own earlier study.

By assessing the discriminative validity we found that the questionnaire is able to disclose the differential effect of headache types on quality of life. Confronting the diagnostic subgroups' headache specific quality of life significant differences were measured by our questionnaire. As expected, QOL was significant worse in migraineurs than in TTH patients and in MOH patients than in chronic TTH patients. These findings suggest, that the discriminative validity of CHQQ is adequate, and it is able to detect differences between the impact of different headache types.

Further we observed and found that the responsivity of our questionnaire is adequat. In a pilot study the complex treatment of medication overuse headache patients resulted in

improvement of the headache characteristics and simultaneously in highly significant changes of quality of life. Only a few similar studies in MOH have been done as yet, and the applied methods have not measured QOL improvement in all cases.

The length and ease of use of a questionnaire are important aspects of its usability. In our studies the questionnaire did not present any difficulty for the patients and we observed a high response rate, which indicated that the length of this questionnaire would probably not be a significant limiting aspect of its clinical use.

In summary, the psychometric properties of the new questionnaire were adequat in all diagnostic subgroups. The reliability and validity of CHQQ were appropriate; the questionnaire was capable to specify and follow the impact of headache on QOL and it was useful in monitoring the effectiveness of headache therapy. Firstly among the quality of life questionnaires in use, we validated the questionnaire formaly in the most important headache types: migraine, TTH and MOH. The aim of our working group is the widespread use of the new questionnaire as well in clinical practice as in headache research. In our current studies the new questionnaire is just being validated in other languages (English and Serbian). Further, we have already preliminary data of a validation study in cluster headache. Our studies were performed on patients from specialized headache centers. According to international experiences, patients with serious headaches are overpresented in these centers. Therefore, for a more accurate assessment of the questionnaire's usefulness, we are preparing a study which will investigate a sample of the normal population. We are also planing studies which evaluate the effect of prophylactic and acut treatment on QOL.

5. Conclusion

Health-related quality of life (HRQoL) is one of the most commonly used patient-reported outcomes. We examined HRQoL in different headache disorders using generic and headache-specific questionnaires. First we investigated the quality of life (QOL) in cluster headache (CH) in details. During the active period of CH, patients had significantly lower generic and headache-specific HRQoL than healthy controls. The impact of CH on HRQoL was comparable with that of migraineurs; some domains were more affected than in migraineurs. After the termination of the cluster period the HRQoL of patients was similar

to that of headache-free controls. Our study was the first, which investigated condition specific HRQoL in CH.

After that, we developed a new headache-specific HRQoL questionnaire, called Comprehensive Headache-related Quality of life Questionnaire (CHQQ), which aims to assess the patients' HRQoL in a more detailed fashion.

First we examined the psychometric properties of CHQQ in the two most common and important primary headache types, ie. migraine and tension-type headache (TTH). The reliability and validity of the questionnaire were adequate in these headache types. The questionnaire detected significant differences in the effect of migraine and TTH on HRQoL. This difference was in accordance with the clinical experience, as migraineurs had lower scores than TTH patients. We then performed a validation study of the questionnaire in patients suffering from medication overuse headache (MOH). Again, the reliability and validity of the questionnaire were adequate in this headache type.

In a pilot study, we studied the responsiveness of the questionnaire in a group of MOH patients. The complex treatment of these patients resulted in the improvement of the headache characteristics and simultaneously in highly significant improvement in the QOL as measured by the new questionnaire.

Taken together, our results indicate that the questionnaire may be useful in assessing the QOL of patients suffering from different forms of primary and secondary headaches, and also in monitoring the effect of headache treatments on QOL.

6. List of publications

Articles related to the thesis

Gyüre T, Csépány É, Hajnal B, Kellermann I, Balogh E, Nagy Zs, Manhalter N, Bozsik Gy, Ertsey C. (2014) The Comprehensive Headache-related Quality of Life Questionnaire shows significant improvement after withdrawal treatment in medication overuse headache: a pilot study. Ideggyogy Sz, 67(5–6):169-176.

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Other, relevant publications

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