A CROSS-SECTIONAL STUDY ON THE QUALITY OF LIFE IN MIGRAINE AND MEDICATION OVERUSE HEADACHE IN A HUNGARIAN SAMPLE: UNDERSTANDING THE EFFECT OF HEADACHE CHARACTERISTICS

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A MIGRÉN ÉS A FÁJDALOMCSILLAPÍTÓ-TÚLFOGYASZTÁSHOZ TÁRSULÓ FEJFÁJÁS, VALAMINT A FEJFÁJÁS-KARAKTERISZTIKA ÉLETMINŐSÉGRE GYAKOROLT HATÁSA MAGYARORSZÁGI BETEGMINTÁN VÉGZETT KERESZTMETSZETI VIZSGÁLAT ALAPJÁN

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Background and purpose – Previous studies using generic and disease specific instruments showed that both migraine and medication overuse headache are associated with lower health-related quality of life (HRQoL). The aim of our study was to assess HRQoL differences in migraineurs and in patients with MOH and to examine how headache characteristics such as years with headache, aura symptoms, triptan use, headache pain severity and headache frequency are related to HRQoL.
Methods – In this cross-sectional study 334 participants were examined (248 were recruited from a tertiary

Háttér és célkitűzés – Általános és betegségspecifikus életminőség-kérdőívet használó vizsgálatok eredményei alapján mind migrénben, mind fájdalomcsillapító-túlfogyasztáshoz társuló fejfájásban (FTTF) szenvedő betegek esetében alacsonyabb életminőség-értékeket mértek a kontrollrésztvevőkhöz hasonlítva. Vizsgálatunk célja egyrészt a migrénben és FTTF-ben szenvedő betegek életminőségének, valamint a fejfájás-karakterisztika (fejfájós évek száma, auratünetek, triptánhasználat, fejfájássúlyosság és fejfájás-gyakoriság) életminőségre gyakorolt hatásának vizsgálata volt.

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headache centre and 86 via advertisements). The Comprehensive Headache-related Quality of life Questionnaire (CHQQ) was used to measure the participants' HRQoL. Data showed normal distribution, therefore beside Chi-squared test parametric tests (e.g. independent samples t-test) were used with a two-tailed $p<0.05$ threshold. Linear regression models were used to determine the independent effects of sex, age, recruitment method, headache type (migraine vs. MOH) and headache characteristics (presence of aura symptoms, years with headache, headache pain severity, headache frequency and triptan use) separately for each domain and for the total score of CHQQ. Significance threshold was adopted to $p \leq 0.0125$ (0.05/4) to correct for multiple testing and avoid Type I error.
Results – Independent samples t-tests showed that patients with MOH had significantly lower scores on all CHQQ domains than migraineurs, except on the social subscale. Results of a series of regression analyses showed that triptan use was inversely related to all the domains of HRQoL after correction for multiple testing ($p<0.0125$). In addition, headache pain severity was associated with lower physical ($p=0.001$) and total scores ($p=0.002$) on CHQQ subscales.
Conclusion – Based on the results, different headache characteristics (but not the headache type, namely migraine or MOH) were associated with lower levels of HRQoL in patients with headache. Determining which factors play significant role in the deterioration of HRQoL is important to adequately manage different patient populations and to guide public health policies regarding health service utilization and health-care costs.

Keywords: *headache characteristics, health-related quality of life, medication overuse headache, migraine, triptan use*

Módszerek – Keresztmetszeti vizsgálatunkban 334 beteg vett részt (248 beteg fejfájás-ambulanciánkról, valamint 86 beteg hirdetés útján). A résztvevők életminőségének értékeléséhez az Átfogó Fejfájással Kapcsolatos Életminőség kérdőívet (CHQQ) használtuk. Adataink normáleloszlást mutattak, így χ^2-próba mellett parametrikus teszteket alkalmaztunk (például független mintás t-próba), a szignifikanciaszintet $p < 0,05$-ban határoztuk meg. A nem, életkor, beválogatási kritériumok, fejfájástípus, valamint fejfájás-karakterisztika (auratünetek megléte, fejfájós évek száma, fejfájás súlyossága, fejfájás gyakorisága, triptánhasználat) életminőségre gyakorolt hatásának vizsgálatához lineáris regressziós modelleket használtunk mind a három CHQQ-alskála és az összpontszám tekintetében is. Az utóbbi esetében az I. típusú hiba elkerülésének érdekében a szignifikanciaszintet $p \leq 0,0125$ (0,05/4) értékben határoztuk meg.
Eredmények – A fejfájástípust önmagában vizsgálva az FTTF-ben szenvedő betegek a szociális alskála kivételével szignifikánsan alacsonyabb CHQQ-értékeket értek el, mint a migrénes betegek. A többi változó bevonásával elvégzett regressziós elemzések alapján a triptánhasználat mutatott fordított összefüggést az összes CHQQ-alskála-értékkel ($p < 0,0125$). A vizsgált fejfájás-karakterisztikák közül a fejfájás súlyossága mutatott szignifikáns kapcsolatot az alacsonyabb fizikaialskála-értékekkel ($p = 0,001$), valamint az alacsonyabb CHQQ-összpontszámmal ($p = 0,002$).
Következtetés – Eredményeink azt mutatják, hogy a fejfájás-karakterisztika (és nem a fejfájás típusa önmagában) összefüggést mutat a fejfájós betegek alacsonyabb életminőségével. Az életminőség-változást előidéző faktorok meghatározása fontos a különböző betegpopulációk adekvát kezelésének, valamint az egészségügyi szolgáltatások igénybevételével és az egészségügyi költségekkel kapcsolatos népegészségügyi intézkedéseknek a megtervezése érdekében.

Kulcsszavak: *egészséggel összefüggő életminőség, fájdalomcsillapító-túlfogyasztáshoz társuló fejfájás, fejfájás-karakterisztika, migrén, triptánhasználat*

Objective and subjective indicators are available to study the impact of headache disorders. Assessing the quality of life (QoL), as a subjective indicator, is an established tool for measuring the burden of headache from a patient's perspective. For instance, generic QoL instruments, such as Medical Outcome Survey 36-item Short-Form Health Survey (SF-36)[1], and disease-specific ones, such as the Migraine-specific Quality of Life Questionnaire (MSQ2.1)[2] were successfully used in headache trials. It has been demonstrated that migraineurs report lower health-related quality of life (HRQoL), measured by SF-36[3, 4] and Short Form (SF)-12[5], compared to the general non-migraineur population. Similarly, patients with medication overuse headache (MOH) have shown decreased scores in all health-related domains of SF-36 compared to healthy individuals, with the highest differences for bodily pain and physical activity[6]. In addition, significantly impaired QoL was found in patients with MOH in the fields of role–physical functioning (problems with work or other daily activities as a result of physical health), bodily pain (interference of normal activities because of pain), general health (personal evaluation of health including current health, health out-

look, and resistance of illness), and social functioning (impact of physical health or emotional problems on social activities) compared to patients with episodic migraine, but there was no significant difference between chronic migraine and MOH groups in QoL measured by SF-36[7]. In a previous study analgesic overuse caused significantly lower values on the physical functioning and bodily pain subscales of SF-36 in a mixed group of chronic migraine, chronic tension-type headache, and new daily persistent headache patients[8]. It is possible that headache sufferers with the highest functional impact are those who tend to automedicate[8] which could explain the impairment of QoL in patients with analgesic overuse. Alternatively, analgesic overuse may worsen primary headaches and thereby explaining the decrease in QoL[8].

However, only a small number of studies have investigated the association between HRQoL and headache characteristics. These studies reported that increased migraine severity (indexed by the combination of migraine frequency and pain intensity)[3], lower patient age[9], longer disease duration[9], higher headache frequency[9, 10] and female gender[11] were related to decreased HRQoL in migraineurs. Thus, it would be important to further investigate which aspect of headache characteristics, such as the above mentioned headache frequency and severity, extended by the presence of aura symptoms, years with headache, or painkiller, especially triptan use, have significant effect on HRQoL in migraine and MOH. Regarding migraine aura symptoms, we did not find any studies investigating the association of migraine aura and HRQoL – which is surprising as patients usually indicate that the aura symptoms cause significant distress in daily functioning[12]. In a real-world analysis, patients with insufficient response to triptans reported significantly greater HRQoL burden, with lower MSQ scores (after controlling for age, sex, migraine frequency, comorbidities, duration of illness, preventive medication use and presence of aura) than triptan responders (pain freedom within 2 h in 4/5 attacks)[13], but more studies are needed to understand the association between triptan use and QoL in migraineurs or in patients with MOH.

Regarding the instruments measuring QoL in patients with headache, most of them were specifically developed for migraineurs, thus leaving patients with other headache types without a suitable tool. This limitation was addressed by the development of the Comprehensive Headache-related Quality of life Questionnaire (CHQQ) which is intended for use in all headache types[14]. The CHQQ is a validated tool in Hungarian[14] and Serbian[15] patients and is being validated in ongoing studies among English patients with episodic and chronic migraine and tension-type headache. In addition, in a pilot study, significant improvements were detected in QoL after successful treatment of MOH, which indicates that CHQQ may be an adequate tool for assessing QoL in headache treatment trials[16]. It should be also noted that the headache-specific CHQQ better reflected the decrease of QoL than the generic SF-36 instrument in patients with cluster headache during the active phase[17].

Therefore, in the present study our aim was to use CHQQ in patients with migraine and in patients with MOH to examine the relationship between inter-individual differences in headache characteristics and HRQoL. We hypothesized that poorer HRQoL would be related to the headache type (migraine or MOH), the presence of aura symptoms, years with headache, headache pain severity, headache frequency, and triptan usage.

Material and methods

SUBJECTS

The present study was part of a research program conducted in the Headache Center of the Semmelweis University. The participants were recruited between 2015 and 2019 from the headache clinic and by advertisements (university advertisements, and newspapers). In the headache clinic population (later referred to as *clinical group*) no exclusion criteria were applied. In the population recruited through advertisement (later referred to as *research group*) exclusion criteria were the following: current or past history of serious medical, major psychiatric or neurologic disorders, use of daily medication (except contraceptives and acute headache medication in MOH patients), and the use of preventive headache medications. In both subgroups, episodic migraine and MOH patients were diagnosed by neurologists. Migraine and MOH patients were eligible if they fulfilled the diagnostic criteria of ICHD-3[18] of migraine and MOH, with or without aura symptoms in both groups. Altogether 334 subjects were recruited and completed all study assessments (in the clinical group, migraine: 198, MOH: 50; in the research group, migraine: 71, research MOH: 15). Among patients with MOH 34 patients had migraine, 9 patients had tension-type headache and 22 patients had mixed (migraine and tension-type) headache before the development of MOH. The demographic characteristics of the investigated populations are

displayed in **Table 1**. The study was approved by the local ethics committees (ethical permission numbers: 23421/2015/EKU, 014946/2016/OTIG, OGYÉI/49553/2017, 204/2011) and the ethics committee of Semmelweis University, and was carried out in accordance with the Declaration of Helsinki.

QUESTIONNAIRES

Demographic data (e.g., sex, age), and the following headache-related variables were collected during the clinical assessment: years with headache, migraine frequency (average number of migraine days per month), presence of aura symptoms (yes/no), painkiller usage (patients reported drug names, which were clustered to three groups based on the ingredients, namely NSAID [Non-Steroidal Anti-Inflammatory Drug], combined analgesics, and triptan, and if the patient has not used painkiller drug, we coded as "no") and migraine severity (assessed by a visual analogue scale [VAS]). We used the simplest VAS, a straight horizontal line of 100 mm. The ends were defined as the extreme limits of the headache, orientated from the left (pain free) to the right (worst pain).

CHQQ was used to measure the headache-related QoL of the subjects. The CHQQ is a 23-item headache-specific QoL questionnaire developed and validated by the Headache Research Group, Department of Neurology, Semmelweis University[12, 14]. The questionnaire measures patients' QoL in detail covering the last four weeks. A 5-point Likert scale was used to answer the questions (for example: *How much did you bother with the headache in your free time (reading, listening to music, hobby, etc.)?* or *How much did the headache interfere with your work activity?*) ranging from the absolute absence of restriction (*not bother at all*) to maximal restriction (*made it impossible*), then the values are transformed to a 0-100-point scale, on which the absence of restriction is equal to 100 points and the full restriction to 0 point. Three dimensions (Physical, Mental, and Social) and the Total score were calculated without weighting the item scores. All CHQQ domain scores were scaled from 0%=worst to 100%=best health/function/ability in accordance with the original scoring of the CHQQ[14]. In our study, the questionnaire demonstrated excellent internal consistency on the total score (Cronbach's alpha: 0.913) and good internal consistency on physical (Cronbach's alpha: 0.807), mental (Cronbach's alpha: 0.828), and social scales (Cronbach's alpha: 0.802).

STATISTICAL ANALYSIS

All analyses were performed using the statistical software package IBM SPSS 21.0 for Windows (IBM). Based on Skewness and Kurtosis, the data showed normal distribution, therefore we used parametric tests. Independent samples t-test was applied to calculate the differences of age, years with headache, headache frequency, headache pain severity, and each domain of CHQQ between migraine and MOH patients. Chi-squared test was used to determine differences in sex, the presence of aura and triptan medication across groups. All statistical testing above adopted a two-tailed $p<0.05$ threshold. To determine the independent effects of sex, age, recruitment method, headache type (migraine vs. MOH) and headache characteristics (presence of aura symptoms, years with headache, headache pain severity/VAS, headache frequency and triptan use) we tested them in linear regression models (all factors were included to the model in one step with enter method) separately for each domain and for the total score of CHQQ. Taking into account the 4 multiple regression models we set the significance threshold to $p\leq0.0125$ (0.05/4) to correct for multiple testing and avoid Type I error.

Results

DESCRIPTIVE STATISTICS

The demographic characteristics of the investigated populations and the statistical comparison of the migraine and MOH subgroups are displayed in **Table 1**.

Patients with MOH were significantly older than patients with migraine and reported significantly higher headache frequency in the last month. The pain severity of the headaches measured by VAS was approximately the same in migraine and MOH groups and no significant difference was found in years with headache between migraine and MOH patients. The proportion of patients with or without aura, with or without triptan use, and belonging to clinical or research group in the migraine and MOH subgroups showed no significant differences. 97.8% of the migraineurs used at least one type of painkiller, while all the patients with MOH used painkiller (as expected). In the whole sample, 71.3% used NSAID, 23.7% combined analgesics and 18% triptan, and 13.5% used at least two types of painkillers. Thus, because of the widespread application of non-triptan painkillers we only included triptan use to the further analysis to inves-

Table 1. *Demographic and clinical characteristics of migraine and medication overuse headache groups*

	Whole sample (N=334)	Migraine (N=269)	MOH (N=65)	Test statistic (t/χ^2)	Effect size (Cohen's d)
Female (n, %)	288 (86.2%)	235 (87.4%)	53 (81.5%)	χ^2: 1.494	–
Age (mean, SD)	35.57 (11.89)	34.03 (10.85)	41.98 (13.81)	t: 4.334**	0.69
Headache years (mean, SD)	13.77 (11.20)	13.23 (10.16)	16.00 (14.62)	t: 1.452	0.25
Headache frequency (mean, SD)	9.90 (9.66)	6.56 (6.85)	23.71 (7.01)	t: 17.773**	2.49
Headache pain severity (VAS, mean, SD)	53.87 (28.29)	54.25 (28.19)	52.29 (28.90)	t: 0.492	0.07
Aura (n, %)	yes: 44 (13.2%)	yes: 37 (13.8%)	yes: 7 (10.8%)	χ^2: 0.408	–
Painkillers	yes: 328 (98.2%)	yes: 263 (97.8%)	yes: 65 (100%)	χ^2: 1.476	–
Triptan medication (n, %)	yes: 60 (18%)	yes: 46 (17.1%)	yes: 14 (21.5%)	χ^2: 0.700	–
Recruitment method	clinical: 248 (74.3%) research: 86 (25.7%)	clinical: 198 (73.6%) research: 71 (26.4%)	clinical: 50 (76.9%) research: 15 (23.1%)	χ^2: 0.301	–
CHQQ Physical (mean, SD)	41.19 (17.88)	42.05 (18.44)	37.59 (14.93)	t: 2.085*	0.25
CHQQ Mental (mean, SD)	47.65 (16.72)	48.72 (16.83)	43.23 (15.59)	t: 2.505*	0.33
CHQQ Social (mean, SD)	48.14 (21.60)	49.11 (22.03)	44.15 (19.36)	t: 1.801	0.23
CHQQ Total (mean, SD)	45.51 (16.09)	46.48 (16.39)	41.47 (14.20)	t: 2.475*	0.31

MOH: medication overuse headache, SD: standard deviation, CHQQ: Comprehensive Headache-related Quality of life Questionnaire, VAS: visual analogue scale
*p<0.05, **p<0.001

tigate predictors of QoL. Patients with MOH reported lower physical, mental, social, and total CHQQ scores compared to migraine, the differences were significant on all dimensions except the social subscale using pairwise comparisons without covariates **(Table 1)**.

RELATIONSHIP BETWEEN QUALITY OF LIFE AND HEADACHE-RELATED VARIABLES

The following explanatory variables were used to explain physical, mental, social and total CHQQ scores in the total population: sex, age, recruitment method (belonging to the clinical or research subgroup), headache type (migraine/MOH), years with headache, aura symptoms, triptan use, headache pain severity and headache frequency. Results are presented in **Table 2**. The regression models explained 22.0% of the total variance of CHQQ social, 20.3% of the total variance of CHQQ physical, and 19.6% of the variance of the CHQQ total score, while only 11.1% variance was explained of the CHQQ mental subscale.

After correction for multiple testing, better physical QoL was associated with research subsample status, younger age, no triptan use, and less severe headache pain. Higher scores on the mental subscale were associated with no triptan use. Better social QoL was related to research subsample status and no triptan use. Regarding the total score, significant association was found with recruitment method, triptan use and headache pain severity.

Notably, headache type was not a significant explanatory variable on any of the CHQQ subscales after controlling for demographic and other headache characteristics. The most consistently associated variables with higher CHQQ scores were no triptan use and less severe headache pain.

POST HOC TEST: THE RELATIONSHIP BETWEEN TRIPTAN USE AND OTHER HEADACHE-RELATED VARIABLES

Taking into account that triptan use was consistently associated with all CHQQ subscales, for exploratory purposes we tested how triptan use was related to other headache-related variables. Our results demonstrated that triptan users reported significantly more years of headache, but headache frequency and headache pain severity were independent of triptan use **(Table 3)**. In addition, we compared the two groups on CHQQ subscales, and the results were in accordance with the results of regression analyses. Namely, those who use triptans reported worse QoL **(Table 3)**.

Table 2. *Standardized regression weights between headache-related quality of life and demographic and headache-related variables*

	Physical headache related QoL		Mental headache related QoL		Social headache related QoL		CHQQ total	
	stand. beta	p value	stand. beta	p value	stand. beta	p value	stand. beta	p value.
Sex (male/female)	*–0.114*	*0.023*	–0.091	0.086	–0.054	0.27	*–0.101*	*0.045*
Age	–0.182	0.005	–0.100	0.15	–0.085	0.19	–0.140	0.032
Clinical/research subsample	0.286	<0.001	0.082	0.17	0.322	0.001	0.241	0.001
Headache type (migraine/MOH)	–0.051	0.48	0.006	0.94	–0.016	0.83	–0.022	0.77
Headache years	0.056	0.34	0.088	0.16	–0.060	0.30	0.044	0.46
Aura (yes/no)	0.054	0.30	0.074	0.18	*0.125*	*0.016*	0.091	0.085
Triptan use (yes/no)	0.163	0.002	0.171	0.002	0.160	0.002	0.187	0.001
Headache pain severity (VAS)	–0.166	0.001	*–0.128*	*0.017*	*–0.122*	*0.015*	–0.158	0.002
Headache frequency	–0.004	0.95	*–0.171*	*0.041*	–0.059	0.46	–0.096	0.23
R^2/Adjusted R^2	0.203/0.180		0.111/0.086		0.220/0.198		0.196/0.174	

QoL: quality of life, MOH: medication overuse headache, CHQQ: Comprehensive Headache-related Quality of life Questionnaire, VAS: visual analogue scale, stand. beta: standardized beta coefficient, normal: significant results after correction for multiple testing, italic: nominally significant results

Discussion

In this study, we examined the quality of life in migraine and MOH patients. Based on group comparison, MOH patients reported worse HRQoL on all CHQQ subscales and on total scores compared to migraine patients, although the differences were small in magnitude. Notably, our further analyses revealed that not the headache-type but other headache characteristics were important in explaining interindividual differences in quality of life. Our results demonstrated that triptan use and headache pain severity assessed with VAS were most consistently associated with HRQoL measured by CHQQ after controlling for sex, age, recruitment method and other headache-related variables, such as headache type, aura symptoms, years with headache and headache frequency. Interestingly, headache type, namely migraine or MOH, was not significantly associated with any CHQQ subscales in our study after controlling for other headache characteristics.

MOST CONSISTENTLY ASSOCIATED FACTORS WITH ALL HRQOL DOMAINS

Triptan use was associated with lower scores on all CHQQ subscales, while headache pain severity was associated with lower scores on physical and total CHQQ subscales.

Triptans, i.e. serotonin (5-hydroxytryptamine [5-HT]) agonists with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors, are commonly prescribed agents for the acute treatment of migraine[19]. Our knowledge about the link between triptan use and HRQoL is quite scarce. In a recent study, HRQoL and work productivity were significantly impacted in triptan non-responders compared to triptan responders[13], which observation might be explained by the ongoing severe headaches. However, according to our findings, triptan use was associated with poor HRQoL even though headache frequency and headache pain severity (VAS) were not significantly different between triptan users and non-users. Thus, one possible explanation for the association between triptan use and impaired HRQoL in our study could be that patients with higher burden of headache and lower HRQoL prefer to use triptans. Indeed, triptan users reported significantly more years with headache than non-users in our study, supporting that triptan use might be a surrogate marker of patients with longer disease duration, as it was suggested also by previous studies[1, 20]. In addition, 21.5% of MOH patients used triptans while only 17.1% of migraine patients; although this difference was not significant but the overrepresentation of MOH patients might partially contribute to the lower HRQoL in triptan users. Another potential explanation for our results could be that well-known side effects of triptans (sleepiness/tiredness, difficulty in thinking, dizziness, nausea, racing heartbeat, muscle weakness, warm sensation, chest pressure) are also important factors in migraine management and significantly affect patient compliance and satisfaction[21]. Therefore, it would be important to investigate the HRQoL in users of calcitonin gene-related peptide (CGRP) receptor antagonist second generation gepants, a

Table 3. *Differences in headache frequency, headache years, headache pain severity, and quality of life scores between triptan users (N=60) and non-users (N=274)*

		Mean (SD)	Test statistics (t)	Effect size (Cohen's d)
Headache frequency	Triptan users	9.33 (7.54)	0.602	0.07
	Triptan non-users	10.03 (10.08)		
Headache years	Triptan users	18.03 (13.18)	2.862*	0.41
	Non-triptan users	12.83 (10.52)		
Headache pain severity (VAS)	Triptan users	50.35 (33.52)	0.927	0.15
	Non-triptan users	54.64 (27.02)		
CHQQ Physical	Triptan users	35.10 (15.63)	3.230*	0.42
	Non-triptan users	42.52 (18.09)		
CHQQ Mental	Triptan users	42.17 (15.07)	3.044*	0.40
	Non-triptan users	48.85 (16.85)		
CHQQ Social	Triptan users	40.92 (20.18)	3.023*	0.41
	Non-triptan users	49.73 (21.61)		
CHQQ Total	Triptan users	39.44 (13.45)	3.704**	0.46
	Non-triptan users	46.84 (16.34)		

SD: standard deviation, CHQQ: Comprehensive Headache-related Quality of life Questionnaire
*p<0.01, **p<0.001

novel group of acute migraine drugs, where side effects and rebound headaches are much less prevalent[22, 23].

Headache pain severity, measured by pain intensity on a VAS, was associated with physical domain and total HRQoL scores after controlling for multiple testing, and at nominal level with mental and social domains as well, even after controlling for other headache-related variables. To the best of our knowledge, only one study investigated the effect of migraine severity on HRQoL reporting a negative relationship between HRQoL and migraine severity (indexed by the combination of migraine frequency and pain intensity)[3] and our result is in line with this observation. In addition, pain severity in other pain-related conditions, such as multiple myeloma[24], fibromyalgia[25], or chronic low back pain[26] also has a major impact on HRQoL.

HRQOL AND OTHER HEADACHE-RELATED FACTORS

Contrary to previous studies[9, 10], headache frequency was not consistently associated with HRQoL domains. However, headache frequency showed negative relationship with mental health domain of CHQQ, although only at nominal level, which is in line with a previous study that found an association between higher migraine frequency (either with or without aura) and depression and anxiety symptoms (measured by Beck Depression Inventory and Hospital Anxiety and Depression Subscales)[27]. Indeed, this relationship between migraine and depression is also supported by genetic findings[28]. It is also worth mentioning that our regression model with demographic and headache-related variables explained the lowest total variance in the mental health domain of CHQQ supporting that different domains of HRQoL are not equally affected by headache-related variables.

In our sample, aura symptoms were nominally associated with worse social HRQoL. Regarding migraine aura symptoms, we did not find any studies investigating the association with HRQoL. Important to note that other disorders with transient neurological symptoms, for example Ménière's disease[29], benign paroxysmal positional vertigo[30] were also associated with significantly worse HRQoL. These findings may support our observation that besides migraine severity and triptan use, additional transient aura symptoms might contribute to further impairment in HRQoL by limiting social activities.

HEADACHE TYPE AND HRQOL

Importantly, although all CHQQ domains (except for the social subscale) differed significantly between migraine and MOH patients, the headache type did not remain significantly associated with any CHQQ subscales or the total score after controlling for other variables

In a cross-sectional study from the Medication Overuse Treatment Strategy trial EuroQol EQ-5D-5L questionnaire was used to measure QoL in patients with MOH according to the ICHD-3 beta

criteria. Similarly to our results quality of life scores were lower in patients with higher headache frequency for all EQ-5D-5L measures except for self-care scale[31]. In line with the previous study an increase in the number of headache free days in migraineurs with equal or more than 4 headache days in a month was associated with improved HRQoL measured by the EuroQol-5D questionnaire[32]. However, we could not replicate these findings in our study after controlling for other headache-related factors. Headache chronicity had both indirect and direct effects on QoL, measured by MSQ2.1 questionnaire in episodic and chronic migraine patients[11]. Interestingly in this study one of the directly contributing factors in determining lower QoL was female gender, but the pathophysiology is still unclear[11]. In our study we found similar trends for the CHQQ total score and the physical subscale even after correction of other headache-related factors suggesting that HRQoL in females is more affected by migraine than in males. In another study, both episodic and chronic migraineurs had significantly lower mental composite scores (MCS) and physical composite scores (PCS) on SF-36 (MCS and PCS are norm-based scores, with higher scores reflecting better HRQoL) compared to non-migraine controls, but the HRQoL of episodic and chronic migraineurs was not compared[33]. *Matilde Leonardi* et al. observed a lower SF-36 MCS and PCS in patients with increased migraine severity (according to frequency and pain intensity), but only MCS showed significant change[3]. These studies above, using SF-36 to measure patients HRQoL used only MCS and PCS, but not each subscale separately. In an older study significantly lower values on the physical functioning and bodily pain subscales of SF-36 were detected in a mixed group of chronic migraine, chronic tension-type headache, new daily persistent headache with analgesic overuse[8]. Therefore, based on previous studies and our results, it is important to take headache-related factors into account in future studies focusing on the effect of migraine and analgesic overuse on HRQoL.

In addition, the use of preventive headache medication, which is taken on a daily basis in order to reduce the frequency, severity and duration of headaches, may also interfere with HRQoL. Based on previous studies, different types of preventive medications can lead to QoL improvement both in episodic and in chronic migraine patients[34–37] and also in patients with MOH[38, 39]. As we will discuss in the limitation section, migraine preventive medication was an exclusion criterion in the research subsample, but not in the clinical subsample, however we have not recorded the exact type and dose of the preventive medications. Therefore, in further studies it would be valuable to evaluate the interaction between different types of preventive medications, headache-related variables and variance of HRQoL in a bigger sample size.

Limitations

While comorbidity was an exclusion criterion in the research subsample, in our clinical subsample psychiatric and somatic comorbidities were not systematically explored which might have influenced our results. Another limitation is the difference in preventive medication use: in the research subsample neither migraine nor MOH patients received headache preventive medication, but in the clinical group, preventive headache medication was not an exclusion criterion. In addition, we did not record the exact dose and frequency of the preventive medications in the clinical sample. The evaluation of the difference of HRQoL among patients with and without preventive medication would also be valuable. Finally, MOH develops in patients with a pre-existing primary headache, in most of the cases in patients with migraine[40], but in a lesser extent in patients with history of tension-type headache[40] or cluster headache alone[41]. This was the case in our study: 52% of the MOH patients had migraine, 34% had both migraine and tension-type headache, and 14% had pure tension-type headache before MOH developed. Therefore, it is possible that pre-existing primary headache disorders may influence HRQoL in MOH patients that should be further investigated in future studies.

Conclusion

Despite the significant difference in HRQoL between migraine and MOH patients, the variance of HRQoL was not explained by the headache type itself, but rather by other headache-related variables, among which the most consistent factors were triptan use and headache pain severity. Our results support that investigating the relationship of different headache-related variables with HRQoL is important to determine the key factors in the deterioration in HRQoL, to adequately manage different patient populations and to guide public health policies regarding health service utilization and health-care costs.

CONFLICT OF INTEREST

AEE is an employee of Gedeon Richter Plc. Medical Division, but the company did not provide any funding, or have any further role in the preparation of the article. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions: MM: substantial contributions to the conception; interpretation of data; have drafted the work or substantively revised it; GyK: substantial contributions to the conception; the acquisition, analysis; interpretation of data; have drafted the work and substantively revised it; DB: acquisition of data; substantively revised the work; AG: acquisition of data; substantively revised the work; AEÉ: acquisition of data; substantively revised the work ; ES: acquisition of data; substantively revised the work; KG: acquisition of data; substantively revised the work, DD: acquisition of data; substantively revised the work, NK: acquisition of data; substantively revised the work; TGy: acquisition of data; substantively revised the work ; GJ: substantial contributions to the conception; design of the work; the acquisition, analysis; interpretation of data; have drafted the work and substantively revised it; CsE: substantial contributions to the conception; the acquisition, analysis; have drafted the work and substantively revised it.

All authors have approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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ETHICS STATEMENT

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional (Semmelweis University Ethics Committee) and national research committee (Medical Research Council, Hungary) and with the Helsinki Declaration. Informed consent was obtained from all individual participants involved in the study.

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