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Cognitive impairment in chronic migraine compared to pseudotumor cerebri

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ABSTRACT

Introduction. We aimed to define the prevalence of objective cognitive impairment in a group of chronic migraineurs, and to define how migraineurs with cognitive impairment differed from those without impairment, and in doing so to compare cognitive impairment in chronic migraine to another chronic headache-related disorder already associated with cognitive impairment (i.e. pseudotumor cerebri syndrome).

Objectives. Cognitive impairment in migraine, especially chronic migraine, has been too little studied. Only a few studies have been done, demonstrating that cognitive impairment exists in chronic migraineurs. It is not known how this compares to other headache-related conditions.

Material and methods. We administered a cognitive battery consisting of the National Adult Reading Test, Mini-Mental Status Examination, Digit Span, Boston Naming Test, Rey Auditory Verbal Learning Test, Trail Making Test, Controlled Oral Word Association, and Category Fluency. Cognitive impairment was defined as mild single-domain with one test score, and mild multi-domain with two scores more than two standard deviations below the mean for age-, gender-, and education-adjusted norms. The data from this study was compared to our previously published population of patients with pseudotumor cerebri syndrome.

Results. One hundred prospectively recruited patients with chronic migraine were enrolled. Fifty-seven patients had normal cognitive profiles. Forty-three patients demonstrated mild cognitive impairment, and more than half (n = 24) showed impairment in multiple cognitive domains. Migraineurs with multi-domain impairment had higher pain intensity, shorter duration of disease, were taking narcotics, had more impaired vision-related mental health scores, and worse social health scores. We found an association between objective cognitive impairment and subjective perception of impairment only when controlling for pain. We found no associations with depression and topiramate use. The mean composite cognitive Z score was no different in chronic migraineurs and patients with pseudotumor cerebri.

Conclusions and clinical implications. Most chronic migraineurs have normal cognitive profiles, but a large proportion of them do experience mild cognitive impairment, especially in multiple domains. The impairment seen in migraine is similar to that in pseudotumor cerebri syndrome, which has already been associated with mild cognitive impairment. Cognitively impaired migraineurs are different from non-impaired/less impaired migraineurs in several ways, which may be an important factor in influencing their migraine treatment.

Key words: migraine, cognition, impairment, pseudotumor cerebri syndrome

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Introduction

The experience of chronic pain has multiple biopsychosocial implications, only one of which is cognitive impairment. The negative effects of chronic pain on general cognition, learning and memory, attention, information processing, and executive function have been well studied [1]. Cognitive dysfunction has also been implicated in migraine. Migraineurs perceive cognitive dysfunction during all phases of the complex migraine cycle [2]. Multiple studies have confirmed the presence of reversible, objective cognitive impairment during a migraine (pain) attack, with negative effects on executive function, processing speed, working memory, visuospatial processing, attention, and/or verbal learning similar to the impairments seen in chronic (non-headache) pain [3, 4]. Worse cognitive performance on some tasks has been linked to increasing migraine frequency, so it is not surprising that chronic migraineurs, who have more attacks, have been found to have greater cognitive impairment compared to episodic migraineurs [5, 6].

Most patients with pseudotumor cerebri syndrome (PTCS) experience headache. The headache phenotype is varied, but most often it resembles migraine or probable migraine [7], Similar to patients with migraine, patients with PTCS report subjective cognitive dysfunction, and have demonstrated objective impairment in multiple cognitive domains including learning and memory, attention, processing speed, reaction time, visuospatial memory, and executive functioning [8–14]. Objective cognitive impairment has been found in our previous large sample of patients with PTCS to correlate with headache severity and headache-related disability but not with measures intrinsic to intracranial pressure (i.e. opening pressure, papilloedema grade, and visual function) [14].

This introduces the idea that the cognitive impairment seen in PTCS may be similar to impairment experienced in any other headache or chronic pain disorder including chronic migraine. This relationship has not previously been explored.

The aims of our study were therefore to: 1) define the prevalence of objective cognitive impairment in a group of chronic migraineurs and define associated factors; and 2) compare the cognitive profiles of patients with chronic migraine to our previously reported sample of patients with PTCS [14].

Clinical rationale for study

Cognitive impairment in migraine, especially chronic migraine, is understudied. Only a few studies have been done, demonstrating that cognitive impairment exists in chronic migraine [6, 15]. It is not known how cognitive impairment in chronic migraine compares to other headache-related conditions.

Material and methods

Patient selection

One hundred patients with chronic migraine were recruited prospectively during new or existing appointments at The Johns Hopkins Headache Centre (n = 96) or from elective inpatient admission to the hospital affiliated with the headache centre, for the treatment of chronic migraine (n = 4) between November 2014 and May 2015. Chronic migraine was diagnosed by the neurologists or nurse practitioner of the Headache Centre according to the criteria set out by the International Classification of Headache Disorders, 3rd edition, beta version (i.e. headache occurring on 15 or more days per month for more than three months, and which on at least eight days per month has the features of migraine) [16]. Sample size was determined by the number of consecutive patients meeting the inclusion criteria, who consented to cognitive testing during the recruitment period. Patients with mental health conditions under treatment, e.g. depression, were included and the depression was examined in our linear regression model for the following reasons.

Depression and mood have been shown to have no impact on objective cognitive impairment in migraine [6, 17]. Furthermore, mental health conditions are extremely common in chronic migraine. The incidence of depression in migraineurs ranges from c.9% to almost 50% especially in chronic migraineurs, and anxiety affects more than half of migraineurs [18]. Keeping in mind this high incidence, excluding these conditions would have drastically reduced our sample size, something which we felt would have compromised our study in the light of previously demonstrated null relationships. Study patients had no neurological disorders aside from chronic migraine.

Patients with the following conditions were excluded: episodic migraine (< 14 headache days per month), pseudotumor cerebri syndrome, previously diagnosed cognitive impairment, non-native English speakers, patients with language impairment, and patients with hearing impairment.

History

Patients were asked to self-report the following information: age, gender, education, headache characteristics, and duration of headache disorder. Medical records were reviewed by the author (OF) for history of sleep apnoea, and the current use of narcotics, acetazolamide, and topiramate. Our historical search was tailored to factors common between chronic migraine and pseudotumor cerebri management.

Examination

A single physician (OF) tested visual acuity using a retro illuminated Early Treatment Diabetic Retinopathy Study chart and corresponding LogMAR values were recorded. Colour vision was tested using Hardy-Rand-Rittler plates.

Participant-completed questionnaires

All participants were asked to complete self-administered questionnaires including: the Headache Impact Test (HIT-6), a six item scale to assess headache-related disability which yields a range from 36 (no disability) to 78, where

a score of 60 or more is considered severe headache-related disability [19]; the Numerical Rating Pain Scale (NRS) where 0 indicates the absence of pain and 10 represents the most intense pain possible; the STOP-Bang screening tool for sleep apnoea, in which the presence of three or more characteristics indicates a high risk for the condition [20]; the Prospective and Retrospective Memory Questionnaire (PRMQ) to assess for subjective memory failures in everyday situations, where scores range from 16 to a maximum impairment of 80, with the mean in normal adults being 39 [21]; the National Eye Institute Visual Function Questionnaire (VFQ 39) to assess vision-related disability [22]; and two scales measuring quality of life in neurological disorders, the Neuro-QOL v1.0 Ability to participate in social roles and activities-Short Form and the Neuro-QOL v1.0 Depression-Short Form [23]. The Ability to participate in social roles and activities-Short Form is an 8-item scale yielding raw scores in the range 8 to 40, with higher scores indicating better (desirable) self-reported social health. The Depression-Short Form is an 8-item scale yielding raw scores in the range 8 to 40 with higher scores indicating worse (undesirable) self-reported emotional health. For scoring, raw scores from both scales are converted to T-scores according to published tables [23]. All questionnaires were scored by a single physician (OF).

Data from the HIT-6, NRS, STOP-Bang, and PRMQ was missing in three patients, from the VFQ 39 in four patients, from the Ability to participate in social roles and activities-Short Form in 18 patients, and from the Depression-Short form in 17 patients. The PRMQ was self-completed by the patients prior to initiation of the objective cognitive testing.

Cognitive testing

All participants were assessed using a battery of cognitive tests administered in a private room of the clinic or hospital by the same physician (OF) and the same test instructions were used during all sessions. The tests included: 1) National Adult Reading Test in English (NART) to estimate premorbid intelligence [24]; 2) Mini Mental Status Examination (MMSE); 3) Digit Span repetition, forward to test attention and backward to test working memory and executive function [25]; 4) Boston Naming Test (BNT) for confrontational naming [26]; 5) Rey Auditory Verbal Learning Test (RAVLT), a test of verbal memory, learning and retrieval [27]; 6) Trail Making Test (TMT), part A for psychomotor speed and part B for executive function [28]; 7) Controlled Oral Word Association task for letters CFL (COWA) to assess phonemic fluency and executive function [29]; and 8) Category fluency (animals) to test semantic fluency and memory [30].

Raw test scores were converted to standardised Z scores based on published norms for healthy adults and were adjusted for age, gender, and education. Impairment was defined as a Z score below two standard deviations (SD). Mild cognitive impairment (MCI) single-domain was defined as an impaired score in any one cognitive domain (not restricted to the memory domain), compared to age-, gender-, and education-adjusted norms. MCI multi-domain was defined as impaired performance in two or more domains. We also determined a composite cognitive Z score from the mean of tests 2 to 8 inclusive [31]. The rationale for our definition of MCI was previously detailed in our earlier work defining cognitive impairment in pseudotumor cerebri syndrome [14].

Patients with pseudotumor cerebri syndrome

A very similar research protocol was used to recruit patients with PTCS at the Centre for Cerebrospinal Fluid Disorders at Johns Hopkins Hospital between August 2009 and May 2015. This protocol and results were published previously [14]. The data pertaining to the patients with chronic migraine was collected separately, but the two groups were compared for the purpose of this study.

Statistical analysis

To compare the characteristics between chronic migraineurs without objective cognitive impairment, with MCI single-domain and with MCI multi-domain, one-way ANOVA tests or Kruskal-Wallis tests were used for continuous variables, and chi-square tests or Fisher's exact tests were used for categorical variables. For post-hoc pairwise comparisons, Tukey's HSD tests and Dunn's tests were used for continuous variables and chi-square tests or Fisher's exact tests with Bonferroni correction were used for categorical variables. Simple linear regression models with robust standard error estimates were carried out respectively to evaluate the association between the composite cognitive Z score and the baseline factors that could predict cognitive dysfunction. A multiple linear regression model was generated using backward-stepwise selection with candidate predictors selected based on $p < 0.2$ from the simple linear regression models. We forced NRS to be included as a term in the multiple linear regression model to control for the impact of active severe headache on cognition.

To compare the characteristics between patients with chronic migraine and patients with PTCS, two sample t-tests or U Mann-Whitney test were used for continuous variables, and chi-square tests or Fisher's exact tests were used for categorical variables. Statistical analysis was performed using Stata 17.0 software (StataCorp LLC). A p value of 0.05 or less was considered statistically significant.

Institutional review board approval

This study was approved by the Johns Hopkins Medical Institutions' Institutional Review Board. All patients gave written informed consent for participation. This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki. No formal prospective protocol was registered.

Results

Demographics

One hundred patients with chronic migraine were enrolled. Baseline characteristics of the sample, divided into groups without, with MCI single-domain, and with MCI multi-domain, are set out in Table 1. Chronic migraineurs with MCI multi-domain had fewer years of education than migraineurs without impairment, but otherwise there were no demographic differences.

The chronic migraine sample was compared to our previously published sample of 101 patients with pseudotumor cerebri syndrome [14]. Given the inherent risk factors common to most patients with pseudotumor cerebri syndrome (i.e. younger reproductive-age women with elevated body mass index), there were multiple baseline differences between the two groups. These are set out in Table 2.

Objective cognitive impairment in chronic migraine and clinical characteristics

All one hundred enrolled patients with chronic migraine completed the full cognitive battery. Nearly 60% (n = 57) of the patients had normal cognitive performance when compared to published age-, gender-, and education-adjusted norms. Forty-three per cent demonstrated MCI, specifically 19% (n = 19) in a single domain, and 24% (n = 24) in multiple domains (Tab. 1).

There were no differences in the self-perception of cognitive impairment, with PRMQ scores not differing between any of the groups. Interestingly, the mean PRMQ score in migraineurs with the highest level of impairment (MCI multi-domain) was 39.8, which is consistent with the mean in normal healthy adults (Tab. 1) [21].

Migraineurs with MCI multi-domain had higher headache intensity as measured by NRS at the time of testing compared to migraineurs with no MCI (p = 0.044), though all had severe headache-related disability as measured by the HIT-6 scale (p = 0.55). Migraineurs with MCI multi-domain had significantly shorter duration of disease compared to the patients without impairment (p = 0.004) (Tab. 1).

We investigated these counterintuitive results further using linear regression models, and we found a trend of decreasing headache intensity with longer duration of disease, presented in Figure 1. With each increasing year of disease, we saw a 0.07 drop in NRS (headache intensity) (95% CI:

Table 1. Demographics and clinical characteristics of chronic migraineurs with and without cognitive impairment

	N	Without objective cognitive impairment	With MCI single-domain	With MCI multi-domain	P- value
		N = 57	N = 19	N = 24	
Demographics					
Age (mean ± SD)		42.1 ± 11.6	40.1 ± 14.9	36.5 ± 13.8	0.21
Female (%)		51 (89.5%)	13 (68.4%)	21 (87.5%)	0.11
Education, yrs (mean ± SD)		16.1 ± 2.1*	15.2 ± 2.5	13.8 ± 1.7*	< 0.001
Clinical characteristics					
BMI kg/m^2 (mean ± SD)		28.6 ± 7.5	27.1 ± 4.8	28.6 ± 5.6	0.68
Sleep apnoea (% yes)		10 (17.5%)	1 (5.3%)	3 (12.5%)	0.45
STOP BANG (mean ± SD)	2:1	2.13 ± 1.54	1.89 ± 0.83	2.13 ± 1.60	0.82
Headache intensity, NRS (mean ± SD)	2:1:0	3.72 ± 2.79*	3.50 ± 3.19	5.46 ± 3.02*	0.036
HIT-6 Score (mean ± SD)	2:1:0	64.3 ± 6.0	63.8 ± 5.0	65.8 ± 9.0	0.55
Duration of disease, yrs (median, IQR)		21.0 (5.0, 30.0)*	6.0 (3.0, 27.0)	4.5 (1.0, 15.0)*	0.003
VA (mean ± SD)	1:0:0	0.02 ± 0.09	0.05 ± 0.12	0.02 ± 0.12	0.64
CV (median, IQR)	1:0:0	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	0.83
Total VFQ39 (median, IQR)	2:1:1	92.0 (83.7, 96.8)	95.2 (87.1, 96.2)	89.8 (73.7, 93.7)	0.095
VFQ Mental Health (median, IQR)	2:1:1	95 (85, 100)*	100 (85, 100)	90 (50, 95)*	0.036
VFQ Ocular Pain (mean ± SD)	2:1:1	75 (50, 100)	81.3 (62.5, 100)	75 (37.5, 87.5)	0.26
Depression SF T-Score (mean ± SD)	6:4:7	49.1 ± 7.0	46.6 ± 8.5	49.9 ± 7.9	0.41
Social Health SF T-Score (mean ± SD)	7:4:7	43.9 ± 6.2*	43.6 ± 8.2	39.4 ± 5.4*	0.050
PRMQ (mean ± SD)	2:1:0	37.0 ± 10.1	35.6 ± 13.3	39.8 ± 14.3	0.50
Narcotics use (% yes)		14 (24.6%)	0 (0%)*	8 (33.3%)*	0.010
Acetazolamide use (% yes)		1 (1.8%)	0 (0%)	1 (4.2%)	0.68
Topiramate use (% yes)		14 (24.6%)	7 (36.8%)	10 (41.7%)	0.11

BMI — body mass index; CV — colour vision; HIT-6 — Headache Impact Test 6 score; MCI — mild cognitive impairment; NRS — Numerical Rating Pain Scale; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; SF — short form; VA — visual acuity; VFQ39 — Visual Function Questionnaire score
*Pairwise difference statistically significant for p < 0.05

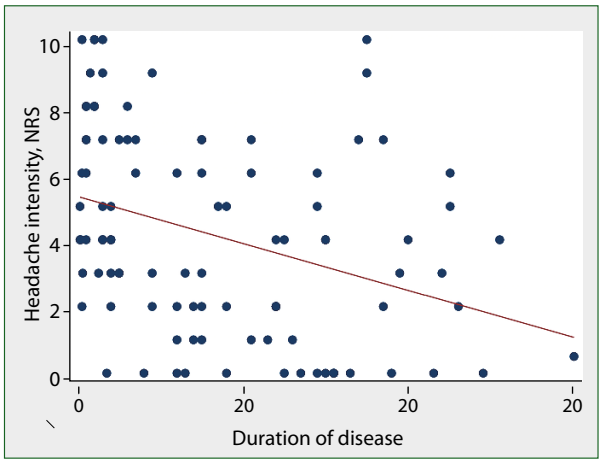

Figure 1. Relationship between duration of chronic migraine and headache severity at time of testing as measured by numerical rating scale (NRS)

–0.107, –0.034, p < 0.001). However, controlling for NRS and analysing the regression of composite Z score on duration, we found that duration of disease was still statistically significant (beta coefficient = 0.016, p < 0.001) meaning that factors other than improving pain intensity must be at play.

Eight of the 24 patients (33.3%) with MCI multi-domain were taking narcotics compared to none of the patients with MCI single-domain (p = 0.017). Topiramate use did not differ significantly among the groups (p = 0.11) (Tab. 1).

The average Depression-Short Form T-score for all three groups, i.e. no MCI, MCI single-domain, and MCI multi-domain, was 46.6–49.9 (p = 0.41), indicating that the self-reporting of depression symptoms was similar to that of the general adult population. Migraineurs with MCI multi-domain experienced the greatest vision-related mental health impairment, as indicated by the lowest median VFQ39 Mental Health subscale (p = 0.036). This was despite no statistical differences in the mean visual acuity, colour vision, or ocular pain among the three groups. Finally, migraineurs with MCI multi-domain had the lowest (worst) mean T-score when grading social health as measured by the Ability to participate in social roles and activities-Short Form (p = 0.050) (Tab. 1).

Simple regression models agreed with the above findings. We found a negative association between composite cognitive score and NRS (beta coefficient = –0.069, p = 0.022). We found positive associations between composite cognitive Z score and duration of education, duration of disease, vision-related quality of life, and social health (beta coefficients = 0.136, 0.018, 0.016, 0.036, p = < 0.001, p = < 0.001, p = < 0.001, p = 0.002, respectively). These relationships remained statistically significant in our multiple linear regression model controlling for NRS. There was no relationship between composite cognitive Z score and narcotics use. PRMQ was negatively associated with composite cognitive score only when controlling for NRS in the multiple linear regression model (see Supplementary materials).

Objective cognitive impairment in chronic migraine compared to pseudotumor cerebri

The 100 patients with chronic migraine were compared to our previously studied sample of 101 patients with pseudotumor cerebri syndrome. Overall, there was no difference in the mean composite cognitive Z score between these two separate populations. Patients with pseudotumor syndrome had worse performance on the BNT, RAVLT recognition portion, and Trails B compared to patients with chronic migraine. Chronic migraineurs performed worse on RAVLT i.e. total recall. Performances did not differ on the MMSE, digit span, retention, and delayed recall portions of RAVLT, Trials A, COWA and Category fluency between the two groups. This is set out in Table 2.

Discussion

This is one of few studies to have measured objective cognitive impairment in a group of chronic migraineurs, and this is the first study to compare cognition in chronic migraine to a different chronic headache-related condition (PTCS) and vice versa. Only patients with chronic migraine (> 15 headache days per month) were included, and fortunately the majority had normal cognitive profiles. When MCI occurred in chronic migraine, it tended to be in multiple domains. The patients with MCI multi-domain had higher levels of pain at the time of testing, the shortest duration of disease, and had the highest proportion of narcotics use compared to patients with MCI-single domain or patients with no impairment at all. Patients with MCI multi-domain had worse vision-related mental health and social health scores compared to the cognitively normal group of migraineurs. We found a relationship between subjectively reported cognitive impairment and objectively tested impairment, but only when controlling for headache intensity. We also found no relationship between cognitive impairment and self-reported symptoms of depression.

Our results agree with several other studies that have found cognitive impairment in chronic migraine. Ferreira et al. studied 30 chronic migraineurs compared to 30 controls without migraine, finding they had worse performance on tests of general cognitive ability (Montreal Cognitive Assessment), language (verbal fluency), visuospatial skills (clock drawing) and attention (Stroop test) [15]. Latysheva et al. studied 144 chronic migraineurs alongside 44 episodic migraineurs, finding significantly worse performance in multi-domain cognitive function as measured by the Digital Symbol Substitution Test, and verbal memory as measured by the RAVLT total recall. We also found our chronic migraineurs had the most impairment in the total recall subsection of the RAVLT, and notably more than the group with PTCS. Unlike our study, they found no correlation between self-reported subjective cognitive impairment and objective cognitive impairment [6]. It is possible that migraineurs in higher levels of pain perceive themselves as more cognitively impaired, because we only

Table 2. Comparison of chronic migraine cohort to pseudotumor cerebri cohort: demographics, clinical characteristics, and results of cognitive battery

	PTCS	Chronic migraine	P-value
	N = 101	N = 100	
Demographics			
Age (mean ± SD)	34.0 ± 8.9	40.4 ± 12.9	< 0.001
Female (% yes)	92 (91.1%)	85 (85.0%)	0.18
Education, yrs (mean ± SD)	14.3 ± 2.4	15.4 ± 2.3	0.001
Clinical characteristics			
BMI kg/m^2 (mean ± SD)	36.2 ± 8.4	28.4 ± 6.6	< 0.001
Sleep apnoea (% yes)	18 (17.8%)	14 (14.0%)	0.46
STOP BANG (mean ± SD)	2.47 ± 1.46	2.08 ± 1.44	0.064
Headache intensity, NRS (mean ± SD)	6.91 ± 2.39	4.11 ± 2.99	< 0.001
HIT-6 Score (mean ± SD)	61.5 ± 10.8	64.6 ± 6.7	0.018
Duration of disease, yrs (median, IQR)	1.00 (0.25, 2.00)	13.0 (3.0, 28.0)	< 0.001
VA (mean ± SD)	0.00 ± 0.14	0.03 ± 0.10	0.15
CV (median, IQR)	10.0 (9.75, 10.0)	10.0 (10.0, 10.0)	0.007
Total VFQ39 (median, IQR)	80.4 (71.0, 90.6)	92.0 (82.3, 96.1)	< 0.001
General Health VFQ (mean ± SD)	59.0 ± 18.5	62.2 ± 22.0	0.28
General Vision VFQ (median, IQR)	80.0 (70.0, 85.0)	85.0 (72.5, 95.0)	< 0.001
VFQ Ocular Pain (median, IQR)	62.5 (37.5, 75.0)	75.0 (50.0, 100.0)	< 0.001
VFQ Near Activities (median, IQR)	86.3 (70.8, 95.8)	91.7 (79.2, 100.0)	0.047
VFQ Distance Activities (median, IQR)	83.3 (66.7, 91.7)	95.8 (83.3, 100.0)	< 0.001
VFQ Social Functioning (median, IQR)	100.0 (83.3, 100.0)	100.0 (100.0, 100.0)	0.002
VFQ Mental Health (median, IQR)	75.0 (50.0, 90.0)	95.0 (82.5, 100.0)	< 0.001
VFQ Role Difficulties (median, IQR)	87.5 (62.5, 100.0)	100.0 (81.3, 100.0)	0.001
VFQ Driving (median, IQR)	83.3 (66.7, 91.7)	83.3 (66.7, 100.0)	0.54
VFQ Colour Vision (median, IQR)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.31
VFQ Peripheral Vision (median, IQR)	75.0 (50.0, 100.0)	100.0 (75.0, 100.0)	< 0.001
PRMQ (mean ± SD)	39.4 ± 13.6	37.4 ± 11.8	0.29
Narcotics use (% yes)	10 (9.9%)	22 (22.0%)	0.019
Acetazolamide use (% yes)	50 (49.5%)	2 (2.0%)	< 0.001
Topiramate use (% yes)	9 (8.9%)	31 (31.0%)	< 0.001
Cognitive testing			
Composite cognitive Z score (mean ± SD)	–0.25 ± 0.80	–0.24 ± 0.85	0.93
MMSE (mean ± SD)	–0.51 ± 1.46	–0.63 ± 1.26	0.52
Forward Digit Span (mean ± SD)	0.82 ± 1.38	1.15 ± 1.32	0.084
Backward Digit Span (mean ± SD)	–0.28 ± 1.09	–0.30 ± 1.09	0.91
BNT (median, IQR)	–0.68 (–2.82, 0.12)	–0.33 (–1.41, 0.64)	0.008
RAVLT — Total Recall (median, IQR)	–0.20 (–1.10, 0.60)	–0.80 (–1.50, 0.27)	0.015
RAVLT Retention (mean ± SD)	–0.31 ± 1.26	–0.38 ± 1.18	0.71
RAVLT Delayed Recall (mean ± SD)	–0.25 ± 1.24	–0.35 ± 1.23	0.56
RAVLT Recognition (median, IQR)	0.52 (0.21, 0.90)	0.21 (–0.30, 0.81)	0.032
Trails A (median, IQR)	0.28 (–0.24, 0.73)	0.48 (–0.30, 0.95)	0.19
Trails B (median, IQR)	–0.78 (–2.29, 0.22)	–0.28 (–1.32, 0.86)	0.007
COWA (mean ± SD)	–0.16 ± 1.17	–0.26 ± 1.07	0.55
Category Fluency — Animals (mean ± SD)	–0.23 ± 1.08	–0.29 ± 1.01	0.67

BMI — body mass index; BNT — Boston Naming Test; COWA — Controlled Oral Word Association task; CV — colour vision; HIT-6 — Headache Impact Test 6 score; MMSE — Mini Mental Status Examination; NRS — Numerical Rating Pain Scale; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; PTCS — pseudotumor cerebri syndrome; RAVLT — Rey Auditory Verbal Learning Test; VA — visual acuity; VFQ39 — Visual Function Questionnaire score

found this relationship in a multiple linear regression model controlling for headache intensity.

We found that chronic migraineurs with higher levels of headache pain at the time of testing exhibited greater levels of cognitive impairment. The two studies mentioned above did not assess headache intensity, so a direct comparison cannot be made. However, cognitive impairment in episodic migraine has been related to attack severity in the past [4].

Earlier works found no relationship between mood, depression, and objective cognitive performance in migraineurs [6, 17] despite the high association of psychiatric comorbidities with migraine [18].

The relationship that we identified between cognitive impairment and shorter duration of disease is counterintuitive, but is not new as Rist and Kurth also demonstrated [32]. The effect of duration is especially curious because the migraine brain is different in many ways, including in structural and functional areas related to cognition (hippocampus, parahippocampal gyrus, and orbitofrontal cortex) [33]; migraineurs with a higher frequency of headaches have been found to have smaller hippocampal volumes compared to those with lower frequency headaches [34] and migraineurs to have a higher degree of white matter lesion burden over time [35].

One would think that the cumulative effect of recurrent attacks over time would cause greater cognitive impairment, and greater negative neuroplasticity, but in our study the longer duration of disorder had a positive outcome. We did find that migraineurs with longer duration of chronic migraine had lower pain scores, but duration of disease still had an independent positive correlation with cognition, after adjusting for pain scores. The reason for this is not known. It is possible that migraineurs with longer disease duration have learned better coping skills over the years, although the similar severe headache-related disability scores among cognitively normal as opposed to cognitively impaired groups would argue against this. It is also possible that migraineurs with longer duration of disease have had higher healthcare use over the years, and thus have had more frequent opportunities for intervention on modifiable risk factors for cognitive impairment (e.g. hypertension, a sedentary lifestyle, and smoking). We can only hypothesise this because these factors were not studied.

A very interesting and novel finding was our association of cognitive impairment with vision-related mental health, especially considering normal visual activity and colour vision. Migraineurs have already been reported to have significant reductions in visual quality of life, especially in chronic migraine, with similar impairment to neuro-ophthalmic disorders such as optic neuritis and myasthenia gravis [36]. This impairment is predominantly related to dry eye, but also to photophobia [37].

Finally, we demonstrated, for the first time, that chronic migraineurs have a similar level of cognitive impairment to patients with PTCS, a condition already known to cause cognitive impairment in young women otherwise not at risk for cognitive decline. Our previous study reported that cognitive impairment in PTCS was related to headache intensity and headache-related disability, which is similar to what we found in our latest study, though headache-related disability did not yield any associations for the chronic migraine group. Many patients with PTCS meet the diagnostic criteria for chronic migraine. Our results support the notion that the similar cognitive impairments seen in both conditions are, at least in part, migraine-related.

Our study has several limitations. Firstly, the patients were recruited from a tertiary referral headache centre, so it is very likely that our sample was more significantly disabled compared to chronic migraineurs seeking care from primary care or general neurology clinics. Secondly, we did not perform any follow up cognitive testing to investigate the reversibility of impairment after making positive changes (i.e. withdrawing opiates, controlling acute pain). A longitudinal study is needed to determine if these deficits are reversible with improvement in migraines, but is beyond the scope of our current study. Thirdly, our migraineurs differed in many baseline characteristics compared to our earlier sample of patients with PTCS.

Conclusions, clinical implications and future directions

While most chronic migraineurs have normal cognitive profiles, multi-domain mild cognitive impairment is indeed present in a large proportion of patients, supporting the notion that migraine is an "invisible" disability. This should be recognised when chronic migraineurs need extra help, for example at work or school. We have identified several modifiable factors comorbid with cognitive impairment in chronic migraineurs — pain intensity, narcotics use, worse vision-related quality of life, and worse social health. Improved acute headache relief, avoidance of narcotics, special measures to help with visual disability (e.g. lubricating drops for dry eye, and tinted lenses for photosensitivity), and functional restoration programmes aimed at helping migraineurs to be more active in the community may be particularly important in migraineurs who experience cognitive impairment. Improved headache prevention, e.g. with the initiation of onabotulinumtoxinA or monoclonal antibodies directed against calcitonin gene related peptide or its receptor, could be used to both reduce acute headache severity and reduce the need for analgesics such as narcotics [38, 39]. In our clinical experience, patients with chronic migraine often worry that they are developing a neurodegenerative disease when they experience migraine-related cognitive impairment.

Our study serves to validate their symptoms, and provides information on the scope of disability caused by migraine, as well as pointing to several, highly modifiable, risk factors for improvement.

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