# Cognitive impairment in chronic migraine: a cross-sectional study in a clinic-based sample

Comprometimento cognitivo na enxaqueca crônica: um estudo transversal em uma amostra clínica

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**ABSTRACT**

Cognitive impairment has been described in all phases of a migraine attack and interictally. However, the prevalence and phenotype of such impairment in chronic migraine (CM) have not yet been studied. **Objectives:** The aim of this study was to evaluate both the prevalence of the objective cognitive deficit in patients with CM and the factors underlying its etiology. **Methods:** 144 patients with CM and 44 age-matched patients with low-frequency episodic migraine (EM) (a maximum of 4 headache days per month) participated in this study. Neuropsychiatric characteristics were measured with the HADS Hospital Anxiety and Depression Scale. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA), Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), and the Perceived Deficits Questionnaire (PDQ-20). **Results:** Compared to EM, CM subjects demonstrated higher subjective and objective cognitive impairment across all tests. CM patients had 4 times higher odds of achieving a RAVLT score in the lower quartile range compared to EM (*Odds Ratio* [OR] 3.8; 95% confidence interval [95%CI] 1.5–9.6; p=0.005). In the MoCA, CM patients demonstrated the most striking impairment in memory/delayed recall (65.3%), attention (46.5%), abstraction (30.6%), and language (27.1%). Chronic headache and level of education, but not gender, depression or anxiety, were independent predictors of cognitive impairment. **Conclusions:** Cognitive impairment is prevalent in the CM population during their mildest possible pain and may be caused by a central sensitization. Timely preventive treatment of EM is warranted.

**Keywords:** migraine; chronic migraine; cognition; memory; depression.

**RESUMO**

O comprometimento cognitivo foi descrito em todas as fases de um ataque de enxaqueca, de maneira intermitente. Entretanto, a prevalência e o fenótipo desse comprometimento na enxaqueca crônica (EC) não foram estudados. **Objetivos:** O objetivo deste estudo foi avaliar a prevalência do déficit cognitivo objetivo em pacientes com EC e fatores subjacentes à sua etiologia. **Métodos:** 144 pacientes com CM e 44 pacientes pareados por idade com enxaqueca episódica (EE) de baixa frequência (máximo de 4 dias de dor de cabeça por mês) foram incluídos. As características neuropsiquiátricas foram medidas pela Hospital Anxiety and Depression Scale (HADS). A função cognitiva foi avaliada por meio da Montreal Cognitive Assessment (MoCA), o Digit Symbol Substitution Test (DSST), o Rey Auditory Verbal Learning Test (RAVLT) e o Perceived Deficits Questionnaire (PDQ-20). **Resultados:** Em comparação com a EE, os indivíduos com EC demonstraram um comprometimento cognitivo subjetivo e objetivo maior em todos os testes. Os pacientes com CM tiveram 4 vezes mais chances de alcançar um escore RAVLT na faixa quartil inferior, em comparação com EE (*Odds Ratio* [OR] 3,8; intervalo de confiança de 95% [IC95%] 1,5–9,6; p=0,005). No MoCA, os pacientes com EC demonstraram o maior prejuízo na memória/atraso na recordação (65,3%), atenção (46,5%), abstração (30,6%) e linguagem (27,1%). Dor de cabeça crônica e nível de escolaridade, mas não o sexo, depressão ou ansiedade, foram preditores independentes de comprometimento cognitivo. **Conclusões:** O comprometimento cognitivo é prevalente na população com enxaqueca crônica mesmo durante uma dor muito leve e pode ser causado pela sensibilização central. O tratamento preventivo oportuno da enxaqueca episódica se faz necessário.

**Palavras-chave:** transtornos de enxaqueca; enxaqueca crônica; cognição; memória; depressão.

Migraine is one of the most common pain disorders, and its prevalence affects up to 25% of young women[1]. Chronic migraine (CM) is a disabling condition with a prevalence of up to 5.1% and possibly even higher in Russia[2,3]. In two large epidemiological studies — CaMEO and AMPP — MIDAS-assessed disability reached as high as 38-45 points (severe disability)[4]. In CM, the rate of severe disability reached 79-82%. Disability in CM has traditionally been associated with continuous pain and regular pain exacerbations, and insufficient response to acute treatments.

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However, data on the poorer cognitive performance of migraineurs during both interictal[5,6,7] or ictal[8,9] phases are present when compared to healthy controls. Patients with migraine are suggested to show selective defects in executive/attention and visuospatial domains[6,10]. Such cognitive symptoms have significant impact on patient disability[9]. Most often, patients experience reversible difficulties with various aspects of cognition, including attention, executive function, psychomotor speed, language, and memory. These deficits may persist even after their headache resolution, with roughly 60% of patients reporting asthenia, tiredness, depression and concentration difficulties[11,12]. These findings were corroborated by a systematic review of Gil-Gouveia et al.[13], in which authors concluded that cognitive symptoms are described in all phases of the migraine attack phenomenology.

Subjective and objective cognitive impairment is relatively well studied in major depression[14]. Depression is highly comorbid with migraine and especially CM. When compared to healthy controls, CM patients have a 3.8 increased risk of being depressed[15], and up to 85% of CM patients have some level of depression[16]. This means that depression may be a major cause of cognitive decline in migraine.

However, some authors show no link between subjective cognitive symptoms and depression in episodic migraine (EM) and fibromyalgia[7,17]. In the prospective study on EM subjects, Gil-Gouveia et al. demonstrated that the differences found were unrelated to age, gender, literacy, anxiety, pain intensity or duration of the attack, and that they were fully reversible[8]. A more recent study by Santangelo et al. has also shown no correlation between depression and cognitive performance in migraine[18]. Cognitive issues may be linked to a reversible brain dysfunction during a migraine attack.

Studies on the cognitive performance in CM still lack. However, some authors demonstrate decreasing cognitive skills with increasing headache frequency[19,20]. CM patients may experience continuous headache or frequent migraine attacks with almost overlapping prodromal or post-dromal symptoms. Based on such data, we hypothesize that CM patients may experience significant cognitive decline, which might contribute greatly to their disability.

Cognitive performance is understudied in migraine. Studies included subjects with EM — whether ictally or interictally. Based on the afore mentioned considerations, the present study aimed at investigating the cognitive profile in a clinic-based sample of CM patients, using the widely available and easy-to-use Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (DSST) tools, along with other cognitive instruments. Moreover, we compared their cognitive performance with subjects with low-frequency EM and investigated the possible relations between cognitive impairment and psychological symptoms, such as depression and anxiety.

## METHODS

144 patients with CM and 44 age-matched patients with low-frequency EM (a maximum of 4 headache days per month) were studied. All subjects were recruited at the Alexander Vein Headache Clinic. Inclusion criteria were a) age 18-59 years old; b) history of CM or EM as defined by the International Classification of Headache Disorders – III beta. The diagnosis was made by a specialist headache neurologist during patient consultation; c) written informed consent. CM patients were included if they presented themselves at the consultation during their mildest headaches or headache-free (the pain intensity range was 0–4 cm on the 10-cm visual analogue scale (VAS), with a mean intensity of 2.1 cm). Patients who first presented during a headache exacerbation could be included during their next consultation at the time of no/mild headache. EM patients had to be headache-free for at least 48 hours to minimize the chance of post-dromal cognitive dysfunction. Patient demographics and history were recorded, and a complete neurological examination was performed to exclude secondary headaches. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS)[21]. HADS defines depression/anxiety as absent at 0-7 points, subclinical at 8-10 points, and clinical at over 11 points.

The exclusion criteria for all groups were major psychiatric disorders (except for mild or moderate depression and anxiety), the use of benzodiazepines, antidepressants and anticonvulsants (these drugs had to be discontinued at least two weeks prior to the study) or intake of 'rescue' medications within six hours before commencing the examination. The study was approved by the Sechenov University Ethics Committee.

The demographic and clinical aspects, such as disease duration, number of headache days per month, and pain intensity at the time of examination were recorded. Cognitive function was assessed using the Perceived Deficits Questionnaire (PDQ-20), Montreal Cognitive Assessment (MoCA), Digit Symbol Substitution Test (DSST) and Rey Auditory Verbal Learning Test (RAVLT).

The PDQ-20 was developed to provide a self-report measure of cognitive dysfunction[22]. This instrument consists of 20 questions and provides an assessment of several domains of cognitive functioning: attention/concentration, retrospective memory, prospective memory, and planning/organization.

The MoCA aims to evaluate global cognitive status and several cognitive domains: memory, attention, language, orientation, visuospatial and executive functions. The MoCA total score ranges from 0 (worst performance) to 30 (best performance), with 26 points taken as the cutoff value for mild cognitive impairment[23].

The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper, that requires a subject to match

symbols to numbers according to a key located on the top of the page. The subject copies the symbol into spaces below a row of numbers. The number of correct symbols within 90 seconds constitutes the score. The DSST is a valid and sensitive measure of cognitive dysfunction impacted by many domains[24]. Performance on the DSST correlates with real-world functional outcomes.

The RAVLT evaluates a wide diversity of functions: short-term auditory-verbal memory, learning rate, retrieval rate, learning strategies and more[25]. Participants are given a list of 15 unrelated words and are asked to repeat them over five different trials (trials 1-5). Another list of 15 unrelated words is then given and the patient must again repeat the original list of 15 words, and again after 20 minutes (trial 6). We assessed three parameters: total learning (a sum of all correctly recalled words in five trials), learning rate (number of words recalled in trial 5 minus the number of words recalled in trial 1) and delayed recall (number of words recalled in trial 5 minus the number of words recalled in trial 6 after 20 minutes).

The Shapiro-Wilk normality test was performed to evaluate the distribution of demographic, cognitive and behavioral variables. The comparison between EM and CM patients on demographic, neuropsychiatric and cognitive aspects was performed with the Mann-Whitney test and chi-square (or Fisher's exact test), as appropriate. The performance of patients on the MoCA was also compared to the published normative data to identify how many individuals had clinically relevant cognitive impairment[23]. Within the sample of CM patients, the association between clinical, neuropsychiatric and cognitive variables was carried out by means of Spearman's rank correlation coefficient. Nominal variables are presented in relative (%) frequencies, whereas continuous variables are presented by median and interquartile range (Q1, Q3). A significant difference was set at a two-tailed p-value of <.05. All analyses were performed using Statistica, version 12 (Statsoft Inc., Palo Alto, CA, USA).

## RESULTS

One hundred forty-four consecutive patients with a diagnosis of CM (132 women and 12 men) were enrolled. Also, 44 patients with low-frequency EM were included (40 women and 4 men) (see Table 1 for a summary of demographic and clinical characteristics). A total of 67.4% of patients had concomitant medication-overuse headache (MOH). Over 90% of these patients were using triptans, whereas the rest were overusing caffeine-containing analgesics or triptans plus combination analgesics.

CM patients had a higher level of depression and anxiety when compared to EM patients. However, because subjects with clinically relevant depression/anxiety were excluded from the study, both of our groups demonstrated

HADS-defined absence of depression. Anxiety reached subclinical levels in the CM population.

Compared to EM, CM subjects demonstrated higher subjective cognitive impairment as measured by the PDQ-20 (for all cognitive test scores see Table 2). Interestingly, PDQ-20

**Table 1.** Clinical and demographic characteristics of the patient population.

|  | EM | CM | p-value |
|---|---|---|---|
| n | 44 | 144 | - |
| Gender, female/male | 40/4 | 132/12 | 0.5 |
| Age, years | 37.0 (30, 42) | 42.5 (31, 50) | 0.06 |
| Education, years | 14.5 (10, 15) | 14.0 (12, 15) | 0.3 |
| Headache frequency, days/month | 3.0 (2, 4) | 20.0 (15, 23.5) | 0.00 |
| Frequency of analgesic intake, days/month | 2.0 (2, 4) | 17.0 (10, 22) | 0.00 |
| Headache history, years | 17.5 (13, 27) | 22.5 (15, 32) | 0.25 |
| Chronic headache history, years | - | 3,0 (1, 5) | - |
| Age of CM onset, years | - | 36 (25, 46) | - |
| MOH, % | - | 67.4 | - |
| Anxiety, HADS points | 5.0 (4, 6) | 9.0 (6, 12) | 0.00 |
| Depression, HADS points | 4.5 (2, 8) | 6.0 (4, 9) | 0.002 |

EM: episodic migraine; CM: chronic migraine; HADS: Hospital Anxiety and Depression Scale; MOH: medication overuse headache. Results are presented as median (Q1, Q3).

**Table 2.** Cognitive profile of the chronic migraine and episodic migraine populations.

|  | EM | CM | p-value |
|---|---|---|---|
| PDQ-20, points | 19.0 (12, 27) | 22.0 (16, 34) | 0.04 |
| PDQ-20, attention/concentration | 8.0 (5, 11) | 7.0 (5, 11) | 0.98 |
| PDQ-20, retrospective memory | 4.0 (1, 8) | 4.5 (3, 7) | 0.17 |
| PDQ-20, prospective memory | 4.0 (3, 7) | 4.5 (2.5, 7) | 0.94 |
| PDQ-20, planning/organization | 6.0 (3, 9) | 6.0 (2.5, 8) | 0.21 |
| DSST, correct symbols | 49.5 (46, 55) | 42.0 (36, 49) | 0.000 |
| RAVLT total learning, words | 35.0 (31, 41) | 31.0 (26, 37) | 0.001 |
| RAVLT leaning rate | 0.0 (-1, 1) | 0.0 (-2, 1) | 0.26 |
| RAVLT delayed recall | 1.0 (0, 1) | 1.0 (0, 2) | 0.18 |
| MoCA, points | 28.0±3.0 | 27.5 (26.5, 29) | 0.08 |

EM: episodic migraine; CM: chronic migraine; PDQ-20: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitution Test; RAVLT: Rey Auditory Verbal Learning Test; MoCA: Montreal Cognitive Assessment. Results are presented as median (Q1, Q3).

performance did not correlate with any of the objective cognitive tests (DSST, RAVLT or MoCA) but correlated positively with the level of depression and anxiety (Spearman rho=0.38 and 0.24, respectively).

CM subjects had a significantly lower DSST performance. Moreover, 28.5% of patients with CM and only 13.6% of patients in the control group had the DSST score in the lower quartile range (p=0.04).

In CM subjects the RAVLT total learning score was also significantly lower when compared to low-frequency EM controls. Also, the total learning score did not reach the previously published cut-off values for the respective age group[25] in both groups (p=0.0001 for both groups). Patients with CM had 4 times higher odds of achieving a RAVLT total learning score in the lower quartile range when compared to the EM cohort (*Odds Ratio* [OR] 3.8; 95% confidence interval [95%CI] 1.5-9.6; p=0.005).

The MoCA results were lower in CM subjects when compared to EM ones, but within the normal range in both groups. Nonetheless, 18% of CM subjects and 6.8% of controls scored lower than the cut-off point for mild cognitive impairment (26 points) even when pain-free or almost pain-free (p=0.09). CM patients demonstrated the most striking impairment in memory/delayed recall (65.3%), attention (46.5%), abstraction (30.6%), and language (27.1%).

No differences in cognitive performance were observed between patients with and without MOH. Pain intensity at the time of testing did not correlate with cognitive performance.

We did not observe any clinically significant correlations between neuropsychiatric parameters and performance on objective cognitive tests (Table 3). Interestingly, anxiety correlated positively with RAVLT and MoCA scores, suggesting that mild anxiety may be even helpful in improving cognitive performance.

Seeking to further study the effect of neuropsychiatric and other parameters on the cognitive status in CM patients, the DSST performance (as a general measure of several cognitive functions) was analyzed with the multiple linear regression (Table 4). Years of education and chronic headache were found to influence the DSST score (p=0.02 and p=0.04, respectively). Depression and anxiety had no influence on cognitive performance.

## DISCUSSION

This study aimed to investigate the cognitive profile in CM. During the last decade, data on pronounced cognitive deficit in patients with migraine without aura have emerged[5,6,7,8,10,11,12,18,19,20,26], both ictally and interictally. During the migraine attack, cognitive impairment has been demonstrated at every stage, including the non-painful phases of pro and post-drome. Moreover, the severity of interictal cognitive deficit has been shown to correlate with headache frequency[19,20]. This study shows that patients with CM are characterized by significant cognitive impairment even during their mildest possible headache or when headache-free.

PDQ-20 results show that a significant number of CM patients have subjective cognitive decline. However, these reports correlate with depression rather than with the objective tests, meaning that patients who do not complain of cognitive problems at work and at home may in fact be still significantly impaired.

CM patients were proved to have significant deficits in different aspects of cognition, including 'complex attention', which was measured with the DSST[24], memory, with the RAVLT, and other domains, including language and abstraction, as evidenced by the MoCA. These differences were found in comparison with subjects with low-frequency EM. CM may phenotypically run as very frequent migraine attacks,

Table 3. Correlation between clinical parameters, cognitive scores and behavioral scores in patients with chronic migraine.

| | HADS, depression | HADS, anxiety |
|---|---|---|
| Age | -0.05 | -0.12 |
| HA frequency | 0.24 | **0.27** |
| Frequency of analgesic intake | -0.04 | -0.02 |
| HA history | 0.001 | -0.17 |
| CM history | -0,19 | -0,03 |
| PDQ-20 | **0.38** | **0.24** |
| DSST | -0.08 | -0.05 |
| RAVLT, total learning | 0.07 | **0.21** |
| MoCA | -0.07 | **0.33** |

HADS: Hospital Anxiety and Depression Scale; HA: headache; CM: chronic migraine; PDQ-20: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitution Test; RAVLT: Rey Auditory Verbal Learning Test; MoCA: Montreal Cognitive Assessment. Significant correlations with p<0.05 are shown in bold.

Table 4. Factors influencing cognitive impairment in chronic migraine.

| Parameter | b* | p-value |
|---|---|---|
| Age | -0.16 | 0.46 |
| Gender | -0.08 | 0.39 |
| Education | 0.21 | 0.02 |
| HA duration | -0.33 | 0.14 |
| Frequency of analgesic intake | -0.05 | 0.7 |
| HADS, depression | -0.02 | 0.8 |
| HADS, anxiety | -0.01 | 0.9 |
| Chronic headache | -0.27 | 0.04 |

b*: standardized regression coefficient; HA: headache; HADS: Hospital Anxiety and Depression Scale.

in which post-drome of the previous attack is very close in time to the prodrome of the next one; they may even overlap. CM may also run as a mixture of classic migraine pain with less severe pain in-between. In both situations, attack-related cognitive dysfunction may linger and be detected interictally. Cognitive changes during the migraine attack have been postulated to be caused by a reversible brain dysfunction[13]. Our findings seem to corroborate this hypothesis. This may explain why CM patients face continuous cognitive impairment, even when they are pain-free.

It is noteworthy, however, that patients with low-frequency EM also have a certain level of cognitive impairment. For instance, in the RAVLT, these patients scored below the accepted cut-off value for subjects aged 30-39 (55.9 words)[25], meaning that brain dysfunction during migraine attacks may not be fully reversible and may become very stable during headache chronification.

Similar cognitive changes are described in major depression and are even listed as diagnostic criteria of major depression in DSM-5[27]. Since depression is highly comorbid with migraine and other types of chronic pain, it is natural to assume that cognitive impairment in these patient population is, at least in part, caused by depression.

In this study, we enrolled CM patients with mild, moderate or no depression to investigate the etiological role of other factors. No correlation was found between the levels of depression and anxiety, and any objective measures of cognitive performance. Moreover, the presence of CM in the study, rather than depression, was an independent risk factor for worse performance in the DSST. These findings corroborate the study by Ferreira et al. in patients with various types of chronic pain[28]. The present study shows that neuropsychiatric parameters may not be the exclusive cause of cognitive dysfunction in chronic pain.

In our findings, only the level of education and the presence of chronic pain predicted a worse cognitive performance, whereas gender, disease duration, depression and anxiety did not. Interestingly, acute therapy overuse and MOH did not influence cognitive function in our population. Recently, this has also been shown in a small CM population[29]. Whereas lower education levels are an established detrimental factor for cognitive performance[25,30], the impact of chronic pain itself, rather than the associated depression, is a new finding.

Migraine chronification is closely associated to central sensitization (CS), which is developed during every attack and gradually becomes continuous with pain chronification. Maladaptive neuroplasticity has been described in the brain of chronic pain and CM sufferers, including periaqueductal gray, globus pallidus, and striatum, strengthening their connectivity with other areas responsible for nociception and cognition (prefrontal cortex, anterior cingulate gyrus, amygdala and insular cortex),

increasing excitability and eventually causing grey matter atrophy[31,32,33]. This may explain why cognitive deficits also become chronic and can be detected after pain resolution and the end of post-drome. Moreover, it is yet unknown when this maladaptive process becomes irreversible, causing a proportion of CM patients to experience sustained cognitive impairment and become refractory to headache treatment. It was shown previously that similar cognitive changes in depression persist in about half of the patients even in remission[34].

In light of these findings, timely initiation of preventive treatment in EM is warranted to prevent CS, headache chronification and sustained cognitive impairment.

Strengths: to our knowledge, this is the second study on the cognitive performance in patients with CM; the previous one included a small sample size and was published very recently[29]. In our study, cognitive performance was tested across various domains, using different tools. The DSST and MoCA are easy-to-use and require about 10 minutes to be completed, making them easily applicable in routine clinical practice.

This study has several limitations. Firstly, the sample size is rather small. Secondly, although we tried to control for depression by excluding patients with severe depression, this disease and anxiety levels were still higher in the CM group. This is due to high comorbidity between CM and depression and respective difficulties in enrolling only patients without depression. Furthermore, the observed cognitive decline in CM patients could be, in part, caused by other confounding variables, such as sleep disorders, not evaluated in the study.

In summary, CM patients present significantly impaired performance in several cognitive domains, including memory and attention, during their mildest pain and when pain-free. The cognitive deficit is sustained and unrelated to migraine exacerbations. Chronic pain (and level of education) rather than clinical parameters or depression are independent predictors of cognitive decline in CM subjects. Cognitive impairment in CM may be caused by CS and maladaptive neuroplasticity in the brain, areas responsible for nociception, antinociception and cognition. These findings corroborate the importance of timely preventive treatment of EM. The DSST and MoCA are easy-to-use and widely available tools for time-intensive cognitive testing in migraine patients. Further studies with larger sample sizes to assess the changes in cognitive performance with disease progression and after treatment are warranted.

## ACKNOWLEDGMENTS

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