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Cognitive Complaints and Cognitive Impairment in Patients with Chronic Daily Headache

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Comorbidities in chronic daily headache (CDH) include emotional disorders (depression, anxiety), insomnia, and musculoskeletal pain at other sites. In CDH, the most common type is a subjective (reported by patients themselves) and/or objective (based on the results of cognitive tests) reduction in cognitive functions, which can be caused by emotional disorders, insomnia and/or brain diseases, and a negative effect of chronic pain on cognitive functions.

Study objective: *to analyze cognitive complaints and their changes in patients with CDH.*

Patients and methods. *Subjective complaints and cognitive functions were evaluated in 90 patients (76 women and 14 men) aged 23 to 78 years old (mean age, 46.7±12.0 years old) with primary forms of CDH according to the Montreal Cognitive Assessment (MoCA) for 12 months. The majority (68.9%) of patients with CDH complained of diminished memory; however, mild memory disorders (25-26 MoCA scores) were found in only a small portion of patients (23.3%). All individuals with subjective memory impairment were found to have neurotic disorders (depression, anxiety disorder) and/or insomnia or a concurrence of a mental disorder and insomnia.*

Results and discussion. *All the patients received treatment options, including optimal pharmacotherapy for headache and concomitant diseases, an educational conversation, cognitive-behavioral therapy, and therapeutic exercises. In cognitive impairment (CI), cognitive training was used and Ginkgo biloba extract (EGb 761®) prescribed; in sleep disorders, sleep hygiene rules were explained.*

The therapy decreased the mean number of days with headache per month from 29.1±2.03 (at baseline) to 9.3±9.35 (at 12-month follow-up) (p=0.002); while subjective complaints regressed in the majority of patients; mild MoCA changes persisted only in 6.7% of the patients.

Management tactics for CDH patients having mild CI and cardiovascular risk factors and the use of EGb 761® to improve cognitive functions were evaluated.

Conclusion*. It has been ascertained that in many cases CI is associated with emotional disorders and insomnia, as well as with pathophysiological mechanisms of chronic pain itself; CI in some patients has a vascular origin. The use of combined treatment programs can promptly and effectively reduce the frequency of headache and improve cognitive functions. EGb 761® (Tanakan®) has a beneficial effect on subjective CI and mild CI.*

Keywords: *cognitive impairment; subjective cognitive impairment; mild cognitive impairment; chronic pain; chronic daily headache; treatment; prevention; Ginkgo biloba extract (EGb 761®).*

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In Russia, the prevalence of chronic daily headache (CDH) is the highest – 10.5% [1], which may be associated with insufficient level of diagnosis and administration of ineffective treatments [2, 3]. Most patients with CDH have a drug-induced headache (DIH) and comorbidities (musculoskeletal pain of a different location, insomnia, mental disorders) [4, 5]. In addition to CDH, patients often complain of memory impairment, fatigue, reduced working capacity, irritability, tearfulness [6–8]. In this connection, a number of studies point to the comorbidity of CDH and cognitive impairment (CI) and discuss the causes of reduction in cognitive functions in patients with chronic pain syndromes [7]. The most common causes of CI in patients with chronic non-cancer pain are neurotic mental disorders (anxiety, depression), primary (vascular, degenerative) factors, long-term use of sedative drugs [7, 9]. Some authors have described negative effect of chronic pain itself on cognitive functions due to suppression of neuroplasticity, reduction of gray matter volume in the dorsolateral and medial prefrontal cortex, anterior cingulate cortex and insula – structures that are responsible for cognitive and emotional modulation of pain [10–12]. It is believed that impairment of cognitive functions due to the influence of chronic pain is characterized by deterioration of executive functioning, episodic memory, attention, speed of mental processes [10, 13].

The Clinic of Nervous System Diseases at I.M. Sechenov First Moscow State Medical University conducted a study, which included 90 patients with CDH, in whom the prevalence of comorbid diseases was evaluated, and treatment optimization was performed. The results of treatment were published earlier [14–17]. Many patients complained of memory impairment and reduced working capacity.

The **objective** of this study is to analyze cognitive complaints and their changes in patients with CDH.

Patients and methods. 90 patients (76 females and 14 males) aged 23 to 78 years old (mean age 46.71±12.0 years old) with primary forms of CDH were included in the study.

Inclusion criteria: 1) males or females aged ⩾18 years old; 2) presence of a primary form of CDH; 3) satisfactory health status as assessed by the investigator; 4) the patient's willingness and ability to follow treatment recommendations in this study.

Exclusion criteria (at least one of the following): 1) severe physical disease; 2) exacerbation or decompensation of a chronic physical disease; 3) severe mental illness requiring treatment in an inpatient psychiatric facility; 4) headache associated with a mental illness according to the criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3) [18]; 5) severe neurological disease; 6) concurrent severe pain syndrome of another location; 7) chronic or severe infectious disease; 8) oncological disease; 9) pregnancy.

The diagnosis of headache was established in accordance with ICHD-3 criteria [18].

All patients were examined for insomnia – a common comorbid disease affecting cognitive functions; underwent assessment of emotional status using Spielberger-Hanin's State-Trait Anxiety Inventory, Beck Depression Scale, and a psychiatric consultation. In patients with complaints of memory impairment, cognitive functions were examined using the Montreal Cognitive Assessment (MoCA).

All patients were assessed for the presence of cardiovascular risk factors: hyperlipidemia (blood chemistry), arterial atherosclerosis (duplex scan of the neck vessels), arterial hypertension – AH (triplicate measurement of blood pressure [BP] during a day, prior therapists' reports), atrial fibrillation (electrocardiography, prior therapists' reports). We reviewed a hereditary history of cardiovascular diseases, memory impairment, and mental disorders.

All patients underwent treatment, including optimal pharmacotherapy for headache and concomitant diseases, an educational conversation, cognitive-behavioral therapy, and therapeutic exercises. In cognitive impairment (CI), cognitive training was used and EGb 761® (Tanakan®) prescribed; in sleep disorders, sleep hygiene rules were explained.

Patients received consultations for 2 months (8 weeks): 2 weeks – daily at the inpatient stage; 6 weeks – once a week at the outpatient stage. Neuropsychological examination was performed before the treatment and 3, 6 and 12 months after the start of the treatment.

Statistical analysis. Data on the clinical and neuropsychological parameters before the treatment, after 3, 6 and 12 months of follow-up were processed using descriptive and comparative statistics. Descriptive statistics were used for all analyzed parameters depending on a variable: in the analysis of quantitative variables the arithmetic mean, standard deviation and root-mean-square deviation, minimum and maximum values were calculated, and in the analysis of qualitative variables the incidence and percentage (%) of the total number were used. Some of the data obtained were presented as M ± m, where M is the arithmetic mean, m is the root-mean-square deviation, which describes the characteristic range for a parameter. The statistical analysis was performed depending on the distribution of the sample set using the parametric Student's test, Fisher's test, χ^2, or non-parametric Kolmogorov-Smirnov test using the statistical software package SPSS v11.5 for Windows. Also, SPSS package was used to calculate the exact values of the respective confidence probability (p), and significant differences between the arithmetic means.

Results. In 30 (33.3%) of 90 patients, chronic migraine was diagnosed, 37 (41.1%) patients had chronic tension headache (CTH), 23 (25.6%) had CTH in combination with episodic migraine. The duration of CDH varied from 4 months to 10 years (mean 3.51 ± 1.95 years). 73 patients (81.1%) suffered from DIH. For the previous 3 months the patients had experienced headache daily or at least 20 days per month (mean number of days with headache per month 29.1 ± 2.03).

Most patients (n = 52, or 57.8%) had concurrent musculoskeletal pain in the neck or back. Fibromyalgia was diagnosed in 8 (8.9%) cases. 43 patients (47.8%) suffered from insomnia.

According to the psychiatrist's opinion, 47 (52.2%) patients had mental illnesses, among which neurotic disorders prevailed. A depressive episode was diagnosed in 18 (20%) patients, dysthymia – in 3 (3.3%) patients, panic disorder – in 18 (20%), generalized anxiety – in 3 (3.3%), cluster A personality disorder (schizoid, schizotypal, such as "verschroben"-phenomenon) – in 10 (11.2%), a combination of cluster A personality disorder and cluster B hysterical personality disorder – in 6 (6.7%), a combination of cluster A personality disorder and cluster C anxiety (avoidant, obsessive-compulsive) disorder – in 4 (4.4%) patients.

62 (68.9%) patients with CDH complained of diminished memory. When using MoCA scale, only 21 (23.3%) patients were found to have mild CI (MCI); 41 (45.6%) patients had subjective complaints of diminished memory (Figure 1). All patients with subjective memory impairment were diagnosed with neurotic disorders (depression, anxiety disorder) or insomnia, or a concurrence of a mental disorder and insomnia. 8 (8.9%) patients had non-amnestic MCI of a vascular origin in the absence of insomnia and mental disorder. In 7 (7.8%) patients, non-amnestic MCI of a vascular origin were detected in the presence of mental neurotic disorders and/or insomnia. In 6 (6.7%) patients, MCI was diagnosed in the absence of cardiovascular risk factors, aggravated hereditary CI history, while the profile of impairments (decreased attention, motivation, speed of task completion, variability of CI severity during task completion) and the presence of a mental disorder confirmed the secondary nature of CI in relation to emotional disorders (depression, anxiety).

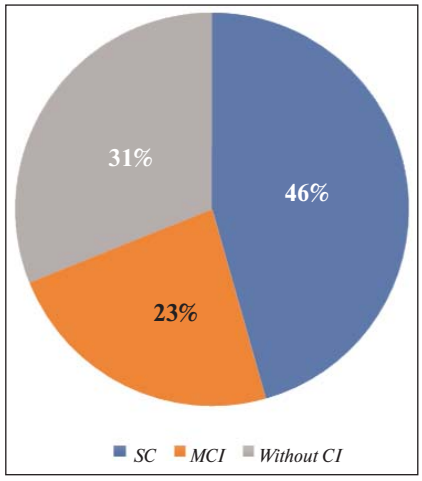

Figure 1. *Prevalence of subjective cognitive complaints (SC) and MCI in 90 patients with CDH*

As a result of treatment, the mean number of days with headache per month decreased from 29.1 ± 2.03 before the treatment to 12.1 ± 8.2 after 3 months (p = 0.004), 9.9 ± 9.44 after 6 months (p = 0.002) and 9.3 ± 9.35 after 12 months (p = 0.002). At month 3 after the start of treatment, most of the

Changes in cognitive functions in 90 patients with CDH during the treatment (based on MoCA), n (%)

Scores	Pre-treatment	Month 3 Follow-up	Month 6 Follow-up	Month 12 Follow-up
24–25 (MCI)	21 (23,3)	10 (11,1)	6 (6,7)	6 (6,7)
26–30 (normal)	69 (76,7)	80 (88,9)	84 (93,3)	84 (93,3)

patients (62.2%) had a clinical effect maintained for 12 months. At months 6 and 12 after the start of treatment, the number of patients who achieved a clinical effect increased to 70% and 72.2%, respectively.

According to MoCA, at month 3 of follow-up cognitive functions normalized in 11 (12%) patients, at month 6 - in 4 (4.4%) additional patients; at month 12, only 6 (6.7%) patients had MCI (see Table).

As a result of treatment, in most of the patients complaints not only of CDH, but also of comorbid disorders disappeared (Figure 2). Among the comorbidities, depressive disorders were the most resistant to treatment. In all the cases, in which the treatment of headache was effective, there was a significant improvement in the emotional status according to the questionnaires (Beck Depression Scale, Spielberger–Hanin's State-Trait Anxiety Inventory), regression of pre-existing depressive and anxiety disorders, insomnia, memory disorders, MCI (based on the MoCA results). In patients who failed to achieve significant reduction in the incidence of headache, there was no significant improvement in cognitive functions, emotional status, or sleep.

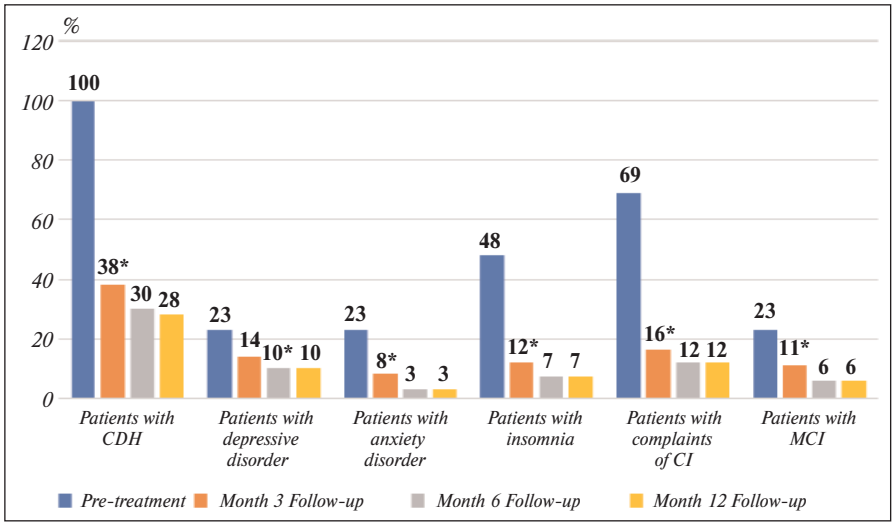

Figure 2. *Decrease in the number of patients with CDH and comorbid disorders during the treatment. * – p <0.001 when comparing this parameter with its previous value.*

Discussion. The study results show a high prevalence of memory impairment complaints (68.9%) in patients with CDH, while only one-third had MCI, and the remaining complaints were subjective. In most cases, subjective memory impairment, MCI were combined with emotional disorders (depression, anxiety disorder) and insomnia, that is consistent with data from other studies showing the negative effect of such disorders on cognitive functions [8, 9, 19, 20].

In recent years, the role of chronic pain in the development of CI has been actively discussed [12, 13]. Chronic pain is considered as a factor that can induce neurodegenerative changes in the brain, reduce neuroplasticity and worsen cognitive functions [10, 11, 21]. In our study, which included 90 patients with CDH, the effective headache treatment was associated with regression of complaints of memory impairment and MCI. In patients with the lack of efficacy during headache treatment, cognitive functions did not improve. The findings confirm the role of chronic pain in the development of subjective CI and MCI in our patients. However, the prevalence of emotional disorders and insomnia in patients with CDH, combined improvement in emotional status, sleep quality, cognitive functions and pain relief during the treatment indicate a complex origin of CI in most cases.

The present study has demonstrated the efficacy of combining optimal pharmacotherapy for headache and comorbid disorders with non-drug methods (cognitive-behavioral therapy, educational conversations about headache, sleep hygiene, cognitive training), and such therapy ensured positive results also in CI (subjective and MCI). In 16.7% of patients, cardiovascular risk factors and vascular origin of CI (in combination with or without emotional disorders, insomnia) were detected.

In CI of a vascular origin, control of cardiovascular risk factors is needed, and medications improving cognitive functions may be efficient: among these Ginkgo biloba extract – EGb 761® (Tanakan®) – is the most studied [22]. Efficacy and safety of EGb 761® were evaluated in more than 400 international and Russian clinical studies. Meta-analysis data from clinical studies confirm the drug efficacy in patients with CI [23]. The authors of the systematic review published in 2016 concluded that treatment with EGb 761® ensured positive results in moderate CI [24].

Tanakan® is widely used in France to improve cognitive functions in elderly people [22]. In 2013, the results of a prospective observational study lasting for 20 years were presented; the study included 3,612 elderly patients, 589 of whom periodically received EGb 761®, 149 – piracetam, and 2,874 patients did not use these drugs [25]. Patients taking EGb 761® had a significant slowing down of CI as compared with patients who took piracetam or did not use any memory improving agents. According to the meta-analysis published in 2014, EGb 761® has no effect on blood pressure when used either as monotherapy or as an adjunct to antihypertensive treatment [22], and can therefore be recommended even for patients with vascular risk factors such as AH.

EGb 761® is indicated for middle-aged patients with complaints of diminished memory and for those having minimal impairment based on neuropsychological examination. This is confirmed by a clinical study involving 300 patients aged 45–65

years old, in whom EGb 761® treatment for 12 weeks resulted in a significant improvement in cognitive functions compared with placebo [26].

The efficacy of EGb 761® was demonstrated in the combined therapy of mild cognitive impairment in younger patients with complaints of difficulties in learning new information, memory impairment, fatigue and decreased activity, diagnosed with tension-type headache. Such patients have CI of a mild neurodynamic nature, they may often have no objective memory impairment. Tanakan® has a positive effect on neurodynamic CI: it improves short-term auditory and visual memory (compared to baseline), alertness, reduces lability and exhaustion, thus leading to decreased fatigue and increased working capacity in younger patients [25].

Conclusion. Patients with CDH have a high incidence of complaints of diminished memory and MCI. Most of such patients have CI of a complex origin. In many cases, CI is associated with the presence of emotional disorders (depression, anxiety disorder), insomnia, as well as with pathophysiological mechanisms of chronic pain. Some patients have CI of a vascular origin. The use of combined treatment programs (optimal pharmacotherapy, behavioral therapy, educational conversations about sleep hygiene, cognitive training) can relatively promptly and effectively reduce the frequency of headache and improve cognitive functions. In patients of various ages with subjective CI and MCI, EGb 761® (Tanakan®) can be effectively used to improve cognitive functions, and it may be taken even in the presence of concomitant hypertension.

It is reasonable to conduct further studies that will investigate the causes of CI in patients with CDH with or without complaints of diminished memory, and explore the effect of age, duration of chronic pain and comorbid disorders on cognitive functions.

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