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Когнитивная дисфункция, боль и аффективные расстройства у пациентов с мальформацией Киари 1-го типа в контексте реципрокных взаимоотношений

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АННОТАЦИЯ

Обоснование. Мальформация Киари 1-го типа (МК1) представляет собой многокомпонентную патологию. Симптомокомплекс МК1 имеет вариабельную структуру в пределах ликвородинамических, мозжечковых, стволовых и спинальных нарушений. Новым компонентом является когнитивная дисфункция. Обсуждаются различные гипотезы её формирования. Наряду с самостоятельной ролью МК1 в развитии когнитивной дисфункции, большое значение придается болевому синдрому и аффективным расстройствам.

Цель. Выявить особенности когнитивного статуса у пациентов с мальформацией Киари 1-го типа и оценить взаимосвязь с болевым синдромом и аффективными нарушениями.

Материал и методы. В исследование были включены 110 взрослых пациентов с МК1 в возрасте 25,61±6,9 года. Контрольную группу составили 50 человек в возрасте 26,36±5,0 лет. Оценка нейровизуальных показателей проводилась на МР-томографе с индукцией магнитного поля 1,5 Т. Для оценки когнитивного статуса были использованы MMSE, MoCA и тест прокладывания пути. Оценка болевого синдрома проводилась при помощи опросника SF-MPQ-2-RU и визуальной аналоговой шкалы, оценка аффективных нарушений — с использованием HADS и DASS-21.

Результаты. Пациенты с МК1 имели достоверно более низкие когнитивные показатели. Дефицит установлен в доменах исполнительного функционирования, зрительно-пространственных навыков, внимания, отсроченного воспроизведения и речи. Ассоциация когнитивного снижения и патогномоничной для МК1 головной боли может свидетельствовать о наличии общих патогенетических механизмов. Решающее значение, вероятно, принадлежит мозжечковой дисрегуляции — дисфункции универсального процесса мозжечкового преобразования. Предполагается, что эмоциональные расстройства совокупно влияют на структуру когнитивного статуса, не являясь основным звеном патогенеза.

Выводы. Пациенты с МК1 демонстрируют значимое когнитивное снижение. Мозжечковая дисрегуляция может быть общим механизмом, лежащим в основе когнитивной дисфункции и патогномоничной для МК1 головной боли. Эмоциональные расстройства совокупно влияют на структуру когнитивного статуса, не являясь основным звеном патогенеза.

Ключевые слова: *мальформация Киари 1-го типа, МК1, когнитивная дисфункция, болевой синдром, аффективные расстройства.*

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Cognitive dysfunction, pain and affective disorders in patients with Chiari malformation type 1 in the context of reciprocal relationships

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ABSTRACT

BACKGROUND. Chiari malformation type 1 (CM1) is a multicomponent pathology. The CM1 symptom complex has a variable structure within the limits of cerebrospinal fluid, cerebellar, brainstem and spinal disorders. A new component is cognitive dysfunction. Various hypotheses of its formation are discussed. Along with the independent role of CM1 in the development of cognitive dysfunction, great importance is attached to pain and affective disorders.

AIM. To identify the features of cognitive status in patients with CM1 and to assess the relationship with pain and affective disorders.

MATERIAL AND METHODS. The study included 110 adult patients with CM1 aged 25.61±6.9 years. The control group consisted of 50 people aged 26.36±5.0 years. The assessment of neuroimaging parameters was carried out on an MR tomograph with an induction of a magnetic field of 1.5 T. MMSE, MoCA, and the Trail Making Test were used to assess cognitive status. The pain syndrome was assessed using the SF-MPQ-2-RU questionnaire and the visual analogue scale, assessment of affective disorders — HADS and DASS-21.

RESULTS. Patients with CM1 had significantly lower cognitive indicators. Deficits are found in the domains of executive functioning, visual-spatial skills, attention, delayed recall and speech. The association of cognitive decline and pathognomonic headache for CM1 may indicate the presence of common pathogenic mechanisms. The decisive importance probably belongs to cerebellar dysregulation — dysfunction of the universal process of cerebellar transformation. It is assumed that emotional disorders collectively affect the structure of cognitive status, not being the main link in pathogenesis.

CONCLUSIONS. Patients with CM1 show significant cognitive decline. Cerebellar dysregulation may be a common mechanism underlying cognitive dysfunction and pathognomonic for CM1 headache. Emotional disorders collectively affect the structure of cognitive status, not being the main link in pathogenesis.

Keywords: *Chiari malformation type 1, CM1, cognitive dysfunction, pain, affective disorders.*

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Chiari malformation type 1 (CM1) is a multicomponent pathology whose main radiological sign is the descent of the cerebellar tonsils into the spinal subarachnoid space by more than 3–5 mm [1–4].

The CM1 symptom complex has a very variable structure within the known set of cerebrospinal fluid circulation, cerebellar, brainstem, and spinal disorders [3–5].

Cognitive dysfunction is a new component of the CM1 symptom complex, which has recently become the subject of numerous discussions [6–8].

According to the results of recent studies, despite the lack of consensus regarding the characteristics of the cognitive status in CM1 patients and the degree of involvement of individual neuropsychological domains, the authors note that CM1 patients demonstrate generally lower cognitive performance, in particular, the deficit was established in executive functioning, visual-spatial thinking, verbal memory, attention, and speech processing [7–11].

Various hypotheses for the formation of cognitive dysfunction are discussed. Along with the independent role of CM1 in its development [12, 14], pain syndrome [13, 15–18] and affective disorders [8, 19] are of great importance in the formation of a neuropsychological defect.

Pain syndrome, being one of the most common components of the clinical presentation in CM1, in the vast majority of cases, is caused by headaches, the incidence of which, according to various sources, reaches 90% [4, 5]. At the same time, about 50% of CM1 patients report the presence of anxiety-depressive disorders [15].

Statistical control of pain and affect in several studies allowed leveling manifestations of cognitive dysfunction in CM1 patients [8]. However, according to other data, the cognitive deficit remained the same, even after controlling for the effects of pain and anxiety-depressive manifestations [11, 15].

Thus, the issue of cognitive dysfunction and the relationship of cognitive status aspects with pain syndrome and affective disorders in CM1 patients remains open to date and requires a comprehensive study.

The work aimed to identify characteristics of the cognitive status in CM1 patients and assess the relationship between pain and affective disorders.

MATERIALS AND METHODS

The study included 110 adult patients with CM1 (78 (71%) men, 32 (29%) women) aged 25.61 ± 6.9 years. The control group consisted of 50 patients (31 (62%) men, 19 (38%) women) aged 26.36 ± 5.0 years without signs of CM1 or other organic pathology of the brain.

The neuroimaging parameters were assessed on an MRI scanner with a magnetic field induction of 1.5 T. Cognitive status was assessed using the Mini-Mental State Examination (MMSE) scale, the Montreal Cognitive Assessment (MoCA) scale, and the Trail-Making Test (TMT). All subjects underwent a detailed assessment of their neurological status. The SF-MPQ-2-RU questionnaire and a visual analog scale were used to assess the pain syndrome. Affective disorders were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Depression Anxiety Stress Scale – 21 (DASS-21).

Statistical data analysis was performed on IBM SPSS Statistics 28.0 using the nonparametric Mann–Whitney test, Student's *t*-test for quantitative data, and χ^2 test for frequency analysis. The strength and direction of the relationship between quantitative characteristics were assessed using the Spearman correlation coefficient, and the critical significance level was $p < 0.05$.

RESULTS

Subjective assessment of cognitive status by CM1 patients showed complaints of impaired memory/attention in 19.1% of patients. Only 4% of the subjects in the control group complained of cognitive disorders ($p = 0.012$).

An objective assessment of the cognitive status in the comparison groups showed minimal significant differences according to MMSE data, namely 28.91 ± 1.27 points in the CM1 group versus 29.26 ± 1.16 points in the control group ($p = 0.049$). At the same time, a significant difference was established according to the MoCA test. Thus, the total MoCA score in the group of CM1 patients was 27.06 ± 1.38 points versus 28.58 ± 1.46 points in the control group ($p < 0.001$). A statistically significant difference was registered in executive functioning, visual-spatial skills, attention, delayed recall, and speech (Table 1).

Analysis of patients' performance of TMT showed similar differences. TMTA in the group of CM1

Table 1. MoCA and MMSE survey results, scores

Scales	CM1 (n = 110)	Control (n = 50)	p
MMSE	28.91±1.27	29.26±1.16	0.049
MoCA, general	27.06±1.38	28.58±1.46	<0.001
Visual-constructive/executive skills	1.77±0.42	1.92±0.27	0.012
Clock drawing test	2.55±0.57	2.88±0.33	<0.001
Naming	3.0±0	3.0±0	1.0
Attention	4.95±0.67	5.58±0.83	<0.001
Speech	2.55±0.50	2.86±0.41	<0.001
Abstraction	1.94±0.25	1.90±0.30	0.211
Delayed recall	4.35±0.66	4.58±0.73	0.027
Orientation	5.95±0.21	5.84±0.42	0.876

Note: MoCA — Montreal Cognitive Assessment; MMSE — Mini-Mental State Examination; CM1 — Chiari malformation type 1.

Table 2. Trail-Making Test (TMT) results, s

TMT	CM1 (n = 110)	Control (n = 50)	p
A	39.15±3.37	38.0±2.51	0.016
B	92.73±12.05	78.4±4.57	<0.001

Note: CM1 — Chiari malformation type 1.

patients was 39.15 ± 3.37 s versus 38.0 ± 2.51 s in the control group (p = 0.016), TMTB was 92.73 ± 12.05 s versus 78.4 ± 4.57 s, respectively (p < 0.001), which also demonstrated a deficit in the structure of executive functioning, visual-spatial skills, and attention in CM1 patients compared with the control group (Table 2).

The incidence of headaches in CM1 patients in our study was 83.6%.

The study of the structure of headaches in CM1 patients enabled us to distinguish three main subgroups, namely headaches pathognomonic for CM1 (CM1HA; n = 53), headaches of a nature different from CM1HA (non-CM1HA; n = 39), and absence of headaches (no HA, n = 18).

The CM1HA subgroup (48.2%) included patients whose headaches met the criteria for pathognomonic headaches for CM1, according to the International Classification of Headache Disorders – 3 (ICHD-3). This type of headache was associated with CM1, provocation by coughing or other Valsalva-like maneuvers, occipital or suboccipital location, often of short duration, and other clinical signs of CM1 in the patient.

All other CM1 patients with headaches different from CM1HA were assigned to the non-CM1HA subgroup (35.5%). Non-CM1HA in most cases was represented by tension headaches (84.6%), migraine was registered in 20.5% of CM1 patients, and trigeminal autonomic cephalalgias were noted in 2.5% of cases. Subgroup 3 included CM1 patients who did not complain of headaches (without HA) (16.3%).

The chronic and frequent episodic nature of CM1HA was presented in 60.4% of headache cases, and episodic nature was noted in 39.6% of cases. In the non-CM1HA subgroup, the chronic and frequent episodic headache was registered in 43.6% of headache cases, while episodic headache was noted in 56.4% of cases.

In the control group, the chronic and frequent episodic headache was registered in 9.7% of cases, while episodic headache was noted in 90.3% of cases. 29 (93.5%) of the study subjects had tension headaches, 2 (6.4%) patients had migraine, and 19 (38%) study subjects had no complaints of headaches (Table 3).

An analysis of the relationship between cognitive dysfunction and the type of headache in CM1 patients showed the following (Table 4).

CM1HA patients did not have a significant difference according to MMSE data compared with non-CM1HA patients. At the same time, the total MoCA score was significantly lower in the subgroup of CM1HA patients, with 26.2 ± 1.24 points versus 27.48 ± 0.79 points in the subgroup of non-CM1HA

Table 3. Characteristics of headaches in CM1 patients, n (%)

Indicators	CM1 (*n* = 110)	Control (*n* = 50)	p
CM1HA including: – chronic – intermittent	53 (48.2) 32 (60.4) 21 (39.6)	0	<0.001
non-CM1HA including: – chronic – intermittent	39 (35.5) 17 (43.6) 22 (56.4)	31 (62) 3 (9.7) 28 (90.3)	0.002 0.002 0.002
Tension headache	33 (84.6)	29 (93.5)	0.243
Migraine	8 (20.5)	2 (6.4)	0.324
Trigeminal autonomic cephalalgias	1 (2.5)	0	0.369
No headaches	18 (16.3)	19 (38)	0.003

Note: CM1 — Chiari malformation type 1; CM1HA — headaches pathognomonic for CM1; non-CM1HA — headaches of a nature different from CM1HA.

Table 4. Indicators of cognitive functioning according to MMSE and MoCA in patients with different types of headaches, scores.

Indicators	CM1HA (*n* = 53)	non-CM1HA (*n* = 39)	No headache (*n* = 18)	Control (*n* = 50)
	1	2	3	4
MMSE	28.54±1.51$^{¥\#}$	29.05±0.94$^{£}$	29.66±0.48$^{\#£}$	29.26±1.16
MoCA, general	26.2±1.24$^{¥*\#}$	27.48±0.79$^{¥*£}$	28.66±0.76$^{\#£}$	28.58±1.46
Visual-constructive/executive skills	1.60±0.49$^{¥*\#}$	1.89±0.30*	2.0±0*$^{\#}$	1.92±0.27
Clock drawing test	2.32±0.58$^{¥*\#}$	2.69±0.52*	2.88±0.32$^{\#}$	2.88±0.33
Naming	3.0±0	3.0±0	3.0±0	3.00±0
Attention	4.67±0.58$^{¥*\#}$	5.02±0.66$^{¥*£}$	5.55±0.51$^{\#£}$	5.58±0.83
Speech	2.54±0.50$^{¥}$	2.48±0.50$^{¥}$	2.72±0.46	2.86±0.41
Abstraction	1.90±0.29	1.97±0.16	1.94±0.23	1.9±0.30
Delayed recall	4.18±0.70$^{¥*}$	4.48±0.60*	4.55±0.51	4.58±0.73
Orientation	5.96±0.19	5.92±0.26	6.0±0	5.84±0.42

Note: $^{¥}$significant differences from the control group ($p \leq 0.05$); *significant differences between groups 1 and 2 ($p \leq 0.05$); $^{\#}$significant differences between groups 1 and 3 ($p \leq 0.05$); $^{£}$significant differences between groups 2 and 3 ($p \leq 0.05$); MMSE — Mini-Mental State Examination; MoCA — Montreal Cognitive Assessment scale.

patients ($p \leq 0.05$). Based on the results of the MoCA subtests in CM1HA patients, compared with the subgroup of non-CM1HA patients, a significant decrease was noted in executive functioning, visual-spatial skills, attention, and delayed recall.

All CM1 patients who complained of headaches had significantly lower cognitive performance compared with CM1 patients without headaches. Thus, patients with headaches pathognomonic for CM1 had lower total scores for MMSE and MoCA, as well as a decrease in the domains of executive functioning, visual-spatial skills, attention, and delayed recall according to MoCA compared with CM1 patients without headaches. Non-CM1HA patients also had significantly lower total scores for MMSE and MoCA compared with CM1 patients who did not complain of headaches. However, according to the results of MoCA subtests in non-CM1HA patients, a significant difference in the scores of 5.02 ± 0.66 points (CM1 with non-CM1HA) versus 5.55 ± 0.51 points (CM1 without HA) was revealed only in the domain of attention ($p \leq 0.05$).

Comparison of cognitive functioning parameters according to MMSE and MoCA in CM1 patients without HA and the parameters of patients from the control group did not reveal significant differences (Table 4).

Thus, a relationship was revealed between impaired cognitive functioning in CM1 and specific headache (CM1HA) associated with the pathological

Table 5. TMT scores by headache type, s

Indicators	CM1HA (n = 53)	non-CM1HA (n = 39)	No headache (n = 18)	Control (n = 50)
	1	2	3	4
TMT A	48.58±3.54¥*#	38.20±2.74*	37.0±2.08#	38.0±2.51
TMT B	96.81±13.60¥*#	90.17±9.51¥*	86.26±6.86¥#	78.4±4.57

Note: ¥significant differences from the control group ($p \leq 0.05$); *significant differences between groups 1 and 2 ($p \leq 0.05$); #significant differences between groups 1 and 3 ($p \leq 0.05$); £significant differences between groups 2 and 3 ($p \leq 0.05$).

Table 6. Characteristics of the severity of affective disorders in the comparison groups according to HADS and DASS-21, n (%)

Severity of affective disorders	CM1 (n = 110)	Control (n = 50)	p
Within normal limits	44 (40%)	33 (66%)	0.002
Moderate	46 (42%)	7 (14%)	0.002
Severe	20 (18%)	10 (20%)	0.785

Note: HADS — Hospital Anxiety and Depression Scale; DASS-21 — Depression Anxiety Stress Scale – 21.

mechanisms of the malformation. Based on this, it can be assumed that the formation of cognitive dysfunction in CM1 is associated not so much with the influence of the cephalgic syndrome in general but may have common pathogenetic mechanisms that underlie the cognitive deficit and the headache pathognomonic for CM1.

Nevertheless, the fact of the probable influence of the cephalgic syndrome on the cognitive status of CM1 patients should also be taken into account, which is reflected in a significant decrease in the total MMSE and MoCA scores in both subgroups of CM1 patients with headaches compared with CM1 patients without headaches, and in the absence of significant differences in the cognitive status of CM1 patients without HA and those from the control group.

In turn, a significant deficit in the attention domain in patients with headaches other than pathognomonic for CM1, compared with CM1 patients who did not have headaches, confirms the currently known mechanisms of the distracting effect of pain on the processes of cognitive modulation (Table 4).

According to TMT data, all CM1 patients had significant differences in cognitive status compared with the control group, regardless of the type of headache. CM1HA patients required the longest time to complete tasks for two subtests (A and B). Non-CM1HA patients and CM1 patients without headaches required significantly more time to complete the subtest B task than the control group (Table 5).

The data obtained confirm the hypothesis of a probable commonality of the pathogenetic mechanisms underlying cognitive dysfunction and headache pathognomonic for CM1. The vulnerability of two subtests (A and B) in CM1HA patients indicates an apparent deficit in the structure of executive functioning in these patients compared with non-CM1HA patients and CM1 patients without headaches (Table 5).

To study the effect of anxiety-depressive disorders on the structure of cognitive functioning in CM1 patients, we analyzed the results of the HADS and DASS-21 questionnaires, which enabled us to identify a greater representation of emotional disorders in the group of CM1 patients compared with the control group (Table 6).

The results of testing CM1 patients according to MMSE, MoCA, and TMT (A and B) were analyzed in the context of three subgroups, namely those with severe emotional disorders, with moderate anxiety-depressive disorders, and with normal values according to the reference data of the HADS and DASS-21 questionnaires. For comparison, patients with emotional disorders were excluded from the control group (Table 7).

Analysis of the test results in the comparison groups showed that CM1 patients with normal HADS and DASS-21 scores, nevertheless, demonstrated a significant decrease in the total MoCA score and deficits in the attention and speech domains compared with the control group patients. Compared with the control group, patients with severe emotional disorders had the lowest indicators, demonstrating a significant decrease in total scores for MMSE and MoCA, as well as deficits in functioning, visual-spatial skills, attention, delayed recall, and speech.

Table 7. Parameters of cognitive functioning according to MMSE and MoCA in patients with Chiari malformation type 1, depending on the severity of affective disorders, scores.

Indicators	Affective disorders			Control (n = 33)
	Within normal limits (n = 44)	Moderate (n = 46)	Severe (n = 20)	
	1	2	3	4
MMSE	29.43±0.84*#	28.93±1.08¥*£	26.70±1.62¥#£	29.33±0.95
MoCA, general	28.13±0.85¥*#	26.63±1.16¥*£	25.75±0.97¥#£	29.23 ±0.98
Visual-constructive/executive skills	1.98±0.15*#	1.71±0.45¥*£	1.45±0.51¥#£	1.93±0.24
Clock drawing test	2.81±0.39*#	2.47±0.54¥*£	2.15±0.59¥#£	2.90±0.29
Naming	3.0±0	3.0±0	3.0±0	3.00±0
Attention	5.29±0.55¥*#	4.80±0.65¥*	4.55±0.60¥#	5.78±0.54
Speech	2.63±0.49¥	2.47±0.50¥	2.55±0.51¥	3.00±0
Abstraction	1.95±0.21	1.91±0.28	1.95±0.22	1.93±0.24
Delayed recall	4.50±0.59	4.28±0.65¥	4.15±0.81¥	4.69±0.63
Orientation	5.95±0.21	5.96±0.21	5.95±0.22	6.0±0

Note: ¥significant differences from the control group ($p \le 0.05$); *significant differences between groups 1 and 2 ($p \le 0.05$); #significant differences between groups 1 and 3 ($p \le 0.05$); £significant differences between groups 2 and 3 ($p \le 0.05$); MMSE — Mini-Mental State Examination; MoCA — Montreal Cognitive Assessment scale.

Table 8. TMT scores by the severity of affective disorders, s

Indicators	Affective disorders			Control (n = 33)
	Within normal limits (n = 44)	Moderate (n = 46)	Severe (n = 20)	
	1	2	3	4
TMT A, s	37.13±2.00*#	39.93±3.56¥*£	41.80±2.84¥#£	37.72±2.36
TMT B, s	87.79±7.73¥*#	96.06±14.17¥*	95.95±11.52¥#	77.75±4.46

Note: ¥significant differences from the control group ($p \le 0.05$); *significant differences between groups 1 and 2 ($p \le 0.05$); #significant differences between groups 1 and 3 ($p \le 0.05$); £significant differences between groups 2 and 3 ($p \le 0.05$).

According to the TMT data, CM1 patients with normal HADS and DASS-21 scores required more time to complete the subtest B task than the control group. At the same time, there were no significant differences in the time to complete the task of subtest A. Patients with severe anxiety-depressive disorders, on average, required the longest time to complete both subtest A and subtest B (Table 8).

The data obtained enable us to conclude that there is a relationship between cognitive dysfunction in CM1 patients and the severity of affective disorders. The high prevalence of anxiety-depressive disorders and the trend toward an increase in cognitive deficit in patients with severe emotional disorders are probably consistent with the presence of concomitant headaches and neurological symptoms in these CM1 patients, which jointly affects the cognitive status structure. A significant decrease in the total MoCA score and deficits in the attention and speech domains confirm an independent role of malformation in the occurrence of cognitive deficit in CM1 patients along with difficulties in performing TMTB in patients with normal HADS and DASS-21 scores compared with the control group,.

DISCUSSION

The results of the study results demonstrate the presence of cognitive dysfunction in CM1 patients.

Subjective cognitive impairments were noted by 19.1% of CM1 patients, complaining of difficulties in remembering information, and impaired concentration of attention. Our data indicate a lower prevalence of subjective cognitive impairment compared with

the literature data indicating the presence of memory impairment in 44% of CM1 respondents, which is probably due to the average age of the respondents (25.61 ± 6.9 years in our study and 35.0 ± 14.8 years according to a comparative study) [20].

An objective assessment of the cognitive status of CM1 patients revealed significantly lower rates compared with the control group. Thus, the total MoCA score in the group of CM1 patients was 27.06 ± 1.38 points versus 28.58 ± 1.46 points in the control group ($p < 0.001$). CM1 patients, on average, required more time to complete tasks for two TMT subtests, namely TMTA in the group of CM1 patients was 39.15 ± 3.37 s versus 38.0 ± 2.51 s in the control group ($p = 0.016$), and TMTB was 92.73 ± 12.05 s versus 78.4 ± 4.57 s, respectively ($p < 0.001$).

A hallmark of cognitive dysfunction in CM1 was the presence of pathology in executive functioning, visual-spatial skills, attention, delayed recall, and speech.

This specificity of cognitive decline, revealed in our study, is consistent with the data of several recent studies [7–11].

The incidence of headaches in CM1 patients in our study was 83.6%. The highest percentage of headaches (48.2%) was presented by CM1HA. This type of headache met the criteria of headaches pathognomonic for CM1, according to the International Classification of Headache, 3rd revision (ICHD-3).

In 60.4% of cases, CM1HA was chronic and frequently episodic (more than 10–15 days per month). Patients with CM1HA showed the most pronounced cognitive decline according to MMSE, MoCA, and TMT (A and B).

We established a relationship between impaired cognitive functioning in CM1 and specific headache (CM1HA) associated with the pathological mechanisms of malformation, which suggests the presence of common pathogenetic mechanisms underlying both cognitive deficit and headache pathognomonic for CM1.

The results of numerous studies of the influence of chronic pain syndrome on the structure and activity of brain processes indicate a direct interaction between the nociception mechanisms and the modulation nature of cognitive functions. In particular, it is assumed that chronic pain syndrome requires an increase in inhibitory control, distracting and influencing the efficiency of cognitive processes [13, 16, 17].

Along with the independent role of the cephalgic syndrome in the formation of cognitive impairment in CM1 patients, which is demonstrated as a significant decrease in cognitive performance in both subgroups of CM1 patients with headaches compared with CM1 patients without headaches, the decisive role probably belongs to the cerebellar dysregulation which is dysfunction of the universal process of cerebellar transformation. Disruption of regulation of interrelated cognitive processes and pain modulation processes can lead to the formation of cognitive dysfunction in CM1 patients and contribute to chronic pain syndrome, thereby creating a vicious circle. In turn, the pathology of cerebrospinal fluid circulation as a fundamental mechanism for the development of CM1-specific headaches should probably be considered as one of the vicious circle links exacerbating the dysfunction of cerebro-cerebellar bonds.

Affective disorders, which can be associated with both the long-term chronic pain syndrome and the severity of neurological symptoms, and also have an independent nature, being frequently associated with CM1, according to research data, can have a direct negative impact on cognitive processes. However, despite the close interaction of cognitive and affective processes, the authors of the studies failed to establish a direct relationship between cognitive deficits and emotional disorders in CM1 patients [6, 8, 11].

The results of our study indicate a greater representation of anxiety-depressive disorders in the group of CM1 patients compared with the control group. Thus, 42% of CM1 patients had moderate emotional disorders, and 18% had severe emotional disorders.

The lowest indicators, demonstrating deficits in executive functioning, visual-spatial skills, attention, delayed recall, and speech compared with the control group, were in patients with severe emotional disorders, probably due to concomitant headaches and neurological symptoms in these CM1 patients. At the same time, the moderate cognitive deficit in patients with normal HADS and DASS-21 scores confirmed an independent role of malformation in cognitive deficit.

CONCLUSIONS

1. According to our results, patients with Chiari malformation type 1 have significantly lower cognitive performance. Specifically, deficits have been revealed in executive functioning, visual-spatial

skills, attention, delayed recall, and speech.

2. Patients with headache pathognomonic for Chiari malformation type 1, according to the criteria for the International Classification of Headache, 3rd revision, demonstrated the most significant cognitive dysfunction.

3. This scientific fact, on the one hand, suggests an independent role of the cephalgic syndrome in the formation of cognitive impairment in patients with Chiari malformation type 1. On the other hand, it may indicate the presence of common pathogenetic mechanisms of cognitive decline and headache pathognomonic for Chiari malformation type 1. Cerebellar dysregulation is probably of decisive importance, a dysfunction of the universal process of cerebellar transformation. Disruption of regulation of interrelated cognitive processes and pain modulation processes can result in the formation of cognitive dysfunction in patients with Chiari malformation type 1, and contribute to chronic pain syndrome, thereby creating a vicious circle. In turn, the pathology of cerebrospinal fluid circulation as a fundamental mechanism for the development of headaches specific to Chiari malformation type 1 should be considered as one of the links in a vicious circle that exacerbates the dysfunction of cerebro-cerebellar bonds.

4. A large representation of anxiety-depressive disorders in patients with Chiari malformation type 1, along with a tendency to an increase in cognitive deficit in patients with severe emotional disorders, is probably consistent with the presence of pain and neurological symptoms in these patients, which jointly affects the structure of cognitive status. In turn, the cognitive deficit in patients with Chiari malformation type 1 without signs of emotional disorders indicates an independent role of Chiari malformation type 1 in forming cognitive dysfunction.

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СПИСОК ИСТОЧНИКОВ

1. Milhorat T.H., Chou M.W., Trinidad E.M. et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients // Neurosurgery. 1999. Vol. 44. N. 5. P. 1005–1017. DOI: 10.1097/00006123-199905000-00042.

2. Tetik B., Mert Doğan G., Paşahan R. et al. Multi-parameter-based radiological diagnosis of Chiari malformation using machine learning technology // International journal of clinical practice. 2021. Vol. 75. N. 11. P. 14746. DOI: 10.1111/ijcp.14746.

3. Крупина Н.Е. Развитие представлений о мальформации Киари (обзор литературы) // Вестник Уральского государственного медицинского университета. 2016. №1–2. С. 87–92.

4. Файзутдинова А.Т., Богданов Э.И. Клинико-радиологическое обоснование выделения подтипов первичной мальформации Киари 1-го типа // Журнал неврологии и психиатрии им. С.С. Корсакова. 2020. Т. 120. №8. С. 64–69. DOI: 10.17116/jnevro202012008164.

5. Сурженко И.Л., Менделевич Е.Г. Симптоматика изолированной мальформации Киари 1 и сочетанной с сирингомиелией // Казанский медицинский журнал. 2009. Т. 90. №1. С. 23–26.

6. García M., Lázaro E., López-Paz J.F. et al. Cognitive functioning in Chiari malformation type I without posterior fossa surgery // Cerebellum. 2018. Vol. 17. N. 5. P. 564–574. DOI: 10.1007/s12311-018-0940-7.

7. Rogers J.M., Savage G., Stoodley M.A. A systematic review of cognition in Chiari I malformation // Neuropsychology review. 2018. Vol. 28. N. 2. P. 176–187. DOI: 10.1007/s11065-018-9368-6.

8. Allen P.A., Houston J.R., Pollock J.W. et al. Task-specific and general cognitive effects in Chiari malformation type I // PloS ONE. 2014. Vol. 9. N. 4. P. e94844. DOI: 10.1371/journal.pone.0094844.

9. García M., Lázaro E., Amayra I. et al. Analysis of visuospatial abilities in Chiari malformation type I // Cerebellum. 2020. Vol. 19. N. 1. P. 6–15. DOI: 10.1007/s12311-019-01056-y.

10. Besteiro González J.L., Torres Campa-Santamarina J.M. Anomalies in the cognitive-executive functions in patients with Chiari malformation type I // Psicothema. 2018. Vol. 30. N. 3. P. 316–321. DOI: 10.7334/psicothema2017.401.

11. Houston J.R., Allen P.A., Rogers J.M. et al. Type I Chiari malformation, RBANS performance, and brain morphology: Connecting the dots on cognition and macrolevel brain structure // Neuropsychology. 2019. Vol. 33. N. 5. P. 725–738. DOI: 10.1037/neu0000547.

12. Rastogi A., Cash R., Dunlop K. et al. Modulation of cognitive cerebello-cerebral functional connectivity by lateral cerebellar continuous theta burst stimulation // Neuroimage. 2017. Vol. 158. P. 48–57. DOI: 10.1016/j.neuroimage.2017.06.048.

13. Houston J.R., Hughes M.L., Lien M.C. et al. An electrophysiological study of cognitive and emotion processing in type I Chiari malformation // Cerebellum. 2018. Vol. 17. N. 4. P. 404–418. DOI: 10.1007/s12311-018-0923-8.
14. Guell X., Hoche F., Schmahmann J.D. Metalinguistic deficits in patients with cerebellar dysfunction: empirical support for the dysmetria of thought theory // Journal of Neuropsychiatry and Clinical Neurosciences. 2004. Vol. 16. N. 3. P. 367–378. DOI: 10.1007/s12311-014-0630-z.
15. Garcia M.A., Allen P.A., Li X. et al. An examination of pain, disability, and the psychological correlates of Chiari Malformation pre- and post-surgical correction // Disability and Health Journal. 2019. Vol. 12. N. 4. P. 649–656. DOI: 10.1016/j.dhjo.2019.05.004.
16. Baliki M.N., Geha P.Y., Apkarian A.V., Chialvo D.R. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics // The Journal of Neuroscience. 2008. Vol. 28. N. 6. P. 1398–1403. DOI: 10.1523/JNEUROSCI.4123-07.2008.
17. Allen P.A., Delahanty D., Kaut K.P. et al. Chiari 1000 Registry Project: assessment of surgical outcome on self-focused attention, pain, and delayed recall // Psychological Medicine. 2018. Vol. 48. N. 10. P. 1634–1643. DOI: 10.1017/S0033291717003117.
18. Moriarty O., McGuire B.E., Finn D.P. The effect of pain on cognitive function: a review of clinical and preclinical research // Progress in Neurobiology. 2011. Vol. 93. N. 3. P. 385–404. DOI: 10.1016/j.pneurobio.2011.01.002.
19. Ma Q., Zeng L.L., Shen H. et al. Altered cerebellar-cerebral resting-state functional connectivity reliably identifies major depressive disorder // Brain Research. 2013. Vol. 1495. P. 86–94. DOI: 10.1016/j.brainres.2012.12.002.
20. Fischbein R., Saling J.R., Marty P. et al. Patient-reported Chiari malformation type I symptoms and diagnostic experiences: a report from the national Conquer Chiari Patient Registry database // Neurological Sciences. 2015. Vol. 36. N. 9. P. 1617–1624. DOI: 10.1007/s10072-015-2219-9.

REFERENCES

1. Milhorat TH, Chou MW, Trinidad EM et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery*. 1999;44(5):1005–1017. DOI: 10.1097/00006123-199905000-00042/
2. Tetik B, Mert Doğan G, Paşahan R et al. Multi-parameter-based radiological diagnosis of Chiari malformation using machine learning technology. *Int J Clin Pract*. 2021;75(11):e14746. DOI: 10.1111/ijcp.14746.
3. Krupina NE. The development of ideas about Chiari malformation (literature review). *Vestnik Uralskogo gosudarstvennogo meditsinskogo universiteta*. 2016;1–2:87–92. (In Russ.)
4. Faizutdinova AT, Bogdanov EI. Clinical and radiological rationale for distinguishing subtypes of primary Chiari I malformation. *Zhurnal nevrologii i psikhiatrii imeni SS Korsakova*. 2020;120(8):64–69. (In Russ.) DOI: 10.17116/jnevro202012008164
5. Surzhenko IL, Mendelevich EG. Symptoms of isolated Chiari malformation 1 and combined with syringomyelia. *Kazanskiy meditsinskiy zhurnal*. 2009;90(1):23–26. (In Russ.)
6. García M, Lázaro E, López-Paz JF et al. Cognitive functioning in Chiari malformation type I without posterior fossa surgery. *Cerebellum*. 2018;17(5):564–574. DOI: 10.1007/s12311-018-0940-
7. Rogers JM, Savage G, Stoodley MA. A systematic review of cognition in Chiari I malformation. *Neuropsychol Rev*. 2018;28(2):176–187. DOI: 10.1007/s11065-018-9368-6.
8. Allen PA, Houston JR, Pollock JW et al. Task-specific and general cognitive effects in Chiari malformation type I. *PLoS ONE*. 2014;9(4):e94844. DOI: 10.1371/journal.pone.0094844.
9. García M, Lázaro E, Amayra I et al. Analysis of visuospatial abilities in Chiari malformation type I. *Cerebellum*. 2020;19(1):6–15. DOI: 10.1007/s12311-019-01056-y.
10. Besteiro González JL, Torres Campa-Santamarina JM. Anomalies in the cognitive-executive functions in patients with Chiari malformation type I. *Psicothema*. 2018;30(3):316–321. DOI: 10.7334/psicothema2017.401.
11. Houston JR, Allen PA, Rogers JM et al. Type I Chiari malformation, RBANS performance, and brain morphology: Connecting the dots on cognition and macrolevel brain structure. *Neuropsychology*. 2019;33(5):725–738. DOI: 10.1037/neu0000547.
12. Rastogi A, Cash R, Dunlop K et al. Modulation of cognitive cerebello-cerebral functional connectivity by lateral cerebellar continuous theta burst stimulation. *Neuroimage*. 2017;158:48–57. DOI: 10.1016/j.neuroimage.2017.06.048.
13. Houston JR, Hughes ML, Lien MC et al. An electrophysiological study of cognitive and emotion processing in type I Chiari malformation. *Cerebellum*. 2018;17(4):404–418. DOI: 10.1007/s12311-018-0923-8.
14. Guell X, Hoche F, Schmahmann JD. Metalinguistic deficits in patients with cerebellar dysfunction: empirical support for the dysmetria of thought theory. *Cerebellum*. 2015;14(1):50–58. DOI: 10.1007/s12311-014-0630-z.
15. Garcia MA, Allen PA, Li X et al. An examination of pain, disability, and the psychological correlates of Chiari Malformation pre- and post-surgical correction. *Disabil Health J*. 2019;12(4):649–656. DOI: 10.1016/j.dhjo.2019.05.004.
16. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci*. 2008;28(6):1398–1403. DOI: 10.1523/JNEUROSCI.4123-07.2008.
17. Allen PA, Delahanty D, Kaut KP et al. Chiari 1000 Registry Project: assessment of surgical outcome on self-focused attention, pain, and delayed recall. *Psychol Med*. 2018;48(10):1634–1643. DOI: 10.1017/S0033291717003117.
18. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol*. 2011;93(3):385–404. DOI: 10.1016/j.pneurobio.2011.01.002.
19. Ma Q, Zeng LL, Shen H et al. Altered cerebellar-cerebral resting-state functional connectivity reliably identifies major depressive disorder. *Brain Res*. 2013;1495:86–94. DOI: 10.1016/j.brainres.2012.12.002.
20. Fischbein R, Saling JR, Marty P et al. Patient-reported Chiari malformation type I symptoms and diagnostic experiences: a report from the national Conquer Chiari Patient Registry database. *Neurol Sci*. 2015;36(9):1617–1624. DOI: 10.1007/s10072-015-2219-9.

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