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Evaluation of structural variations in the pituitary gland, hormonal status and laboratory markers of the central nervous system functioning in patients with chronic disorders of consciousness

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BACKGROUND: Consciousness is the state of being awake and aware of oneself and the environment. The disorders of consciousness result from pathologies that impair awareness. The development of effective comprehensive personalized interventions contributing to the recovery of consciousness in patients with chronic disorders of consciousness is one of the most pressing and challenging tasks in modern rehabilitation.

AIM: The aim of this study was to understand structural problems of the pituitary gland, blood levels of gonadotropins and melatonin as well as brain damage markers in the blood and cerebrospinal fluid in patients with chronic disorders of consciousness and to analyze the levels of the above markers among different groups of patients depending on the level of impaired consciousness.

MATERIALS AND METHODS: We examined 61 chronic disorders of consciousness patients and identified three groups depending on the level of consciousness including 24 patients with unresponsive wakefulness syndrome, 24 patients with a minus minimally conscious state, and 13 patients with minimally conscious state plus. We performed magnetic resonance imaging of chiasmatic-sellar region and determined blood serum levels of follicle-stimulating and luteinizing hormones and melatonin, as well as urinary level of 6-sulfatoxymelatonin and the content of brain derived neurotrophic factor (BDNF), apoptosis antigen (APO-1), FasL, glutamate, and S100 protein in the blood serum and cerebrospinal fluid.

RESULTS: The patients were examined in the age ranging from 15 to 61 years old. Patient groups were homogeneous by the level of consciousness in terms of age and duration of chronic disorders of consciousness by the time of examination. The patients did not differ in the pituitary volume regardless of the level of consciousness. No significant differences were found between the groups with different levels of consciousness when studying the levels of melatonin in the blood serum and its metabolite in the urine. A peak in melatonin secretion was detected at 3 a.m. in 54.5% of the patients, which can be considered as a favorable prognostic marker for further recovery of consciousness. Hypogonadotropic ovarian failure was found in 34% of the patients, with normogonadotropic ovarian failure in the remaining patients. Serum APO-1 and BDNF levels were significantly higher in patients with minimally conscious state relative to those with unresponsive wakefulness syndrome. Significantly lower levels of glutamate in the cerebrospinal fluid were detected in women with unresponsive wakefulness syndrome compared to patients with minimally conscious state.

CONCLUSIONS: Further in-depth examination and accumulation of data on patients with chronic disorders of consciousness may provide an opportunity to identify highly informative markers for predicting outcomes and to develop new effective approaches to rehabilitation of consciousness in this category of patients.

Keywords: chronic disorders of consciousness; minimally conscious state; gonadotropic function; ovarian failure; magnetic resonance imaging of chiasmatic-sellar region; brain-derived neurotrophic factor; apoptosis antigen APO-1; FasL; glutamate; S100 protein.

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Оценка структурных изменений гипофиза, особенностей гормонального статуса и лабораторных маркеров функционального состояния центральной нервной системы у пациенток с хроническим нарушением сознания

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Обоснование. Сознание — это состояние бодрствования и осознания себя и окружающей среды. Расстройства сознания возникают в результате патологий, нарушающих осознание. Разработка эффективных комплексных персонифицированных мероприятий, способствующих восстановлению сознания у пациентов с хроническим нарушением сознания, — одна из самых актуальных и сложных задач в современной реабилитации.

Цель — изучить структурные изменения гипофиза, уровень гонадотропинов и мелатонина в крови, а также маркеров повреждения головного мозга в крови и спинномозговой жидкости у пациентов с хроническим нарушением сознания и проанализировать уровни вышеуказанных маркеров среди разных групп пациентов в зависимости от уровня нарушения сознания.

Материалы и методы. Обследована 61 пациентка, выделены три группы в зависимости от уровня сознания: в вегетативном состоянии с синдромом ареактивного бодрствования — 24 пациентки, в состоянии минимального сознания «минус» — 24 пациентки, в состоянии минимального сознания «плюс» — 13 пациенток. Выполнена магнитно-резонансная томография хиазмально-селлярной области; определены уровни фолликулостимулирующего, лютеинизирующего гормонов и мелатонина в сыворотке крови и 6-сульфатоксимелатонина в моче; нейротрофического фактора мозга (BDNF), антигена апоптоза (APO-1), FasL, глутамата, S100 в сыворотке крови и спинномозговой жидкости.

Результаты. Обследованы пациентки в возрастном диапазоне от 15 до 61 года. Группы пациенток по уровню сознания были однородны по возрасту и по продолжительности хронического нарушения сознания к моменту обследования. У пациенток вне зависимости от уровня сознания отличия в объеме гипофиза отсутствовали. Значимых различий между группами с разным уровнем сознания при исследовании уровня мелатонина в сыворотке крови и его метаболита в моче не обнаружено. Выявлен пик секреции мелатонина в 03:00 у 54,5 % пациенток, что можно рассматривать как благоприятный прогностический маркер для дальнейшего восстановления сознания. У 34 % пациенток обнаружена гипогонадотропная недостаточность яичников, у остальных пациенток — нормогонадотропная недостаточность яичников. Уровни APO-1 и BDNF в сыворотке крови были значительно выше у пациенток в состоянии минимального сознания, чем у пациенток в вегетативном состоянии / с синдромом ареактивного бодрствования. Был достоверно снижен уровень глутамата в спинномозговой жидкости у женщин в вегетативном состоянии / с синдромом ареактивного бодрствования по сравнению с пациентками в состоянии минимального сознания.

Заключение. Дальнейшее углубленное обследование и накопление данных о пациентках с хроническим нарушением сознания может позволить определить высокоинформативные маркеры для прогнозирования исходов, а также разработки новых эффективных подходов к реабилитации сознания у данной категории больных.

Ключевые слова: хроническое нарушение сознания; состояние минимального сознания; овариальная недостаточность; магнитно-резонансная томография хиазмально-селлярной области; нейтротрофический фактор мозга (BDNF); антиген апоптоза (APO-1); FasL; глутамат; белок S100.

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BACKGROUND

Consciousness is a state of wakefulness and awareness of oneself and the environment [1]. Consciousness disorders arise due to pathologies that impair awareness. The development of effective complex personalized measures that contribute to the restoration of consciousness in patients with chronic disorders of consciousness (CDC) after acute craniocerebral injury (CCI) and hypoxia is one of the most urgent and difficult tasks in modern rehabilitation. CDC is a state that develops after a coma and is accompanied by restored wakefulness without complete conscious activity restoration within a period of >28 days after the brain damage [1]. The prevalence of CDC is rather difficult to determine since such patients are widely distributed among different types of institutions and medical specialties, and some live at home. According to statistics, the number of patients with CDC in the United States of America averages as 46 patients per 1 million population, and 14 people per 1 million population in the United Kingdom [2]. Statistical data of the Russian Federation on the number of patients with CDC are currently not presented [3].

This study aimed to analyze the structural changes in the pituitary gland and the level of gonadotropins and melatonin in the blood, as well as markers of brain damage in the blood and cerebrospinal fluid in patients with CDC; and analyze the levels of the above-mentioned markers among different groups of patients based on the level of impaired consciousness, namely in a minimally conscious state (MCS) "plus," MCS "minus," and vegetative state/with the syndrome of reactive wakefulness (VS/SAW).

MATERIALS AND METHODS

The study was conducted at the Professor A.L. Polenov Russian Research Institute of Neurosurgery, a branch of the V.A. Almazov National Medical Research Center. The study included 61 female patients with CDC, who were distributed into three groups based on the level of consciousness, namely 24 patients for VS/SAW, 24 patients for MCS "minus," and 13 patients for MCS "plus."

The clinical and laboratory data and functional research methods were analyzed. Impaired consciousness was diagnosed after a five-fold assessment of each patient on the Coma Recovery Scale [4, 5].

Magnetic resonance imaging (MRI) of the chiasmosellar region was performed on a Signa Exite 1.5T (GE) magnetic resonance imager with a magnetic field induction of 1.5 Tesla. Modes T1 and T2 were used in the sagittal and coronary planes. Research result interpretation assessed the size and volume of the pituitary gland and special attention were paid to the type and degree of structural changes.

Hormonal research was conducted in oligomenorrhea or amenorrhea, wherein hormonal levels in the blood were determined, namely luteinizing hormone (LH) and follicle-stimulating hormone (FSH), on an Immulite 1000 immunochemiluminescence analyzer (DPC, Germany), manufacturer of reagents Siemens. Internal quality control was performed using Lyphochek Immunoassay Plus Control, Levels 1, 2, and 3 manufactured by Bio-Rad.

Collected was 24-hour urine with a division of portions into daytime (from 08:00 to 12:00) and nighttime (from 12:00 to 08:00) to determine the concentration of 6-sulfatoxymelatonin and was assessed by enzyme-linked immunosorbent assay (ELISA) using a 6-Sulfatoxymelatonin ELISA reagent kit (Buhlmann Laboratories AG, Switzerland). Blood sampling was performed 6 times a day to determine the level of melatonin, namely at 08:00, 15:00, 18:00, 21:00, 24:00, and 3:00 in test tubes with a coagulation activator. The melatonin concentration in the blood serum was assessed by solid-phase ELISA using the Melatonin ELISA reagent kit (IBL INTERNATIONAL GMBH, Germany). Chromatographic columns that were supplied as part of the kit (C18 RP 1 cm^3/100 mg) were used for extraction. ELISA was performed in microplates following the instructions. Reference values for serum melatonin were 18.5–180 pg/ml at 03:00 and 3.8–80.4 pg/ml at 08:00. Reference values for 6-sulfatoxymelatonin in urine were >8 μg for the night, >3 μg for the daytime, and >20 μg for 24 hours. 6-Sulfatoxymelatonin in the night urine should be 2–3 times higher than in the daytime urine.

The level of brain-derived neurotrophic factor (BDNF), apoptosis antigen (APO-1), apoptosis receptor ligand (Fas-L), glutamate, and S100 in serum and cerebrospinal fluid was studied by ELISA using an automatic immunoassay analyzer Personal Lab (Adalt, Italy). The S100 protein concentration was determined by ELISA using a CanAg S100 reagent kit (S100 total — $\alpha\beta + \beta\beta$ isoforms) (Fujirebio Diagnostics AB, Sweden). Glutamate concentration was assessed using the Glutamate ELISA reagent kit (IBL America, USA), the BDNF using the Human Free BDNF reagent kit (R&D Systems, USA), the apoptosis receptor sAPO-1/Fas using the Human sAPO-1/Fas ELISA reagent kit (Invitrogen, Austria), and the Fas-L concentration using the Human sFas Ligand ELISA reagent kit (Invitrogen, Austria).

Statistical methods. Data were statistically processed using the Statistica 10 software. The distribution parameters of the sample were assessed using the Kolmogorov–Smirnov test. The Kruskal–Wallis test was used to calculate the statistical significance of differences between quantitative parameters for nonparametric data distribution. The hypothesis of equality of mean values in the study groups was rejected at a significance level of p-values of <0.05.

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RESULTS

Patients aged from 15 to 61 years old with an average age of 28.8 ± 9.5 years were examined. The group of patients in the level of consciousness were homogeneous in age (the average age was 29 ± 10.8, 29.9 ± 8.8, and 26.3 ± 7.9 years in groups 1, 2, and 3, respectively [$p = 0.43$]) and by the duration of CDC by the time of examination (the duration was 5.2 ± 4.6, 4.5 ± 4.5, and 3.5 ± 3.4 months in groups 1, 2, and 3, respectively [$p = 0.42$]).

Based on the MRI data, the size of the pituitary gland was determined using the equation $V = 1/2\ abc$, where a is the vertical size, b is the horizontal size, and c is the sagittal size of the pituitary gland. Calculations results revealed no difference in the volume of the pituitary gland in patients of all groups, which accounted for 0.36 ± 0.12, 0.39 ± 0.16, and 0.37 ± 0.1 cm^3 in group 1, 2, and 3, respectively, regardless of the consciousness level ($p = 0.85$).

A group of 11 patients determined the level of melatonin in the blood serum and the melatonin metabolite in the daytime and nighttime urine. Patients aged 17–43 years, with a mean age of 26.5 ± 9 years and duration of disorder of consciousness from 1 to 15 months on average 3 months were examined, wherein 7 had VS/SAW at the time of examination and 4 had MCS. Patients were distributed into two subgroups according to the consciousness level, wherein subgroup 1 included patients with MCS having a mean age of 28.3 ± 9.1 years (24 to 41 years), duration of consciousness disorder of 5.8 ± 5.4 months (1 to 15 months), FSH level of 3.9 ± 0.9 IU/L (minimum value 3.1 IU/L and maximum value 4.8 IU/L), LH level of 2.2 ± 1.8 IU/L (minimum value 0.26 IU/L and maximum value 5 IU/L); whereas the subgroup 2 included patients with VS/SAW with the mean age of 25.4 ± 9.5 years (17 to 43 years), duration of consciousness disorder of 1.6 ± 1.5 months (1 to 2 months), FSH level of 3.6 ± 3 IU/L (minimum value 0.33 IU/L and maximum value 8.46 IU/L), and LH level of 2.8 ± 2.2 IU/L (minimum value 0.2 IU/L and maximum value 7.3 IU/L).

The blood serum level of melatonin was studied (Table 1) and a comparative analysis was performed among the patients with VS/SAW and MCS.

The level of the melatonin metabolite in daytime urine was 3.8 ± 1.2 and 13.1 ± 12.8 ng/mL in groups 1 and 2 ($p = 0.8$); that in the night urine was 5.1 ± 0.1 and

Table 1. The level of melatonin in the blood serum of patients with chronic disorders of consciousness

Time of measurement	Melatonin level in patients with VS/SAW, pg/ml	Melatonin level in patients with MCS, pg/ml	*p* (intergroup difference)
15:00	8.3	4.2	0.38
18:00	8.4	2.1	0.7
21:00	7.4	1.6	0.37
24:00	35.6	1.1	0.36
03:00	71.6	1.5	0.9
06:00	17.4	21.2	0.2

Note. MCS: minimally conscious state; VS/SAW: vegetative state/syndrome of reactive wakefulness.

Table 2. The blood serum level of melatonin in patients with chronic disorders of consciousness, ng/mL

Patient number	Measurement time					
	15:00	18:00	21:00	24:00	03:00	06:00
1	5.23	7.67	7.19	4.97	**19.1**	1.5
2	9.22	3.86	9.17	6.03	56.3	**254**
3	0.5	0.74	1.88	9.72	**148**	3.64
4	67.7	69	11.1	7.32	36.4	**88.7**
5	19.2	16.7	13.3	**92.1**	47.8	47.1
6	21.5	29.4	22.5	58.4	**803**	403
7	–	4.04	12	15	10.1	22.5
8	4.17	2.1	1.6	1.08	1.52	**21.2**
9	–	2.03	–	102	**120**	27.1
10	6.64	11.1	5.63	112	67.6	**124**
11	13.7	36.1	25.5	**29.7**	14.2	4.47

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16.7 ± 9.2 ng/mL in groups 1 and 2 (p = 0.49). No significant differences were revealed between the groups with different levels of consciousness in the level of melatonin in blood serum and urine (the Mann–Whitney test was used for statistical processing). The peak of melatonin secretion was recorded at 03:00 in 6 patients, wherein 3 had VS/SAW and 3 had MCS (Table 2).

MCS was found in 11 of the 26 examined patients aged 17–43 years (mean age 26.5 ± 9 years), whereas 15 had VS/SAW. Hypogonadotropic ovarian failure was revealed in 9 (34.6%) patients, with the FSH level of 1.3 ± 0.4 IU/L (0.3–1.7 IU/L) and LH of 0.5 ± 0.4 IU/L (0.1–2.0 IU/L), and the rest of the patients had normogonadotropic ovarian failure, with the FSH level of 5.1 ± 2 IU/L (2.7–9.7 IU/L) and LH of 2.3 ± 2.2 IU/L (0.26–7.3 IU/L). Hypergonadotropic ovarian failure was not identified among this group of patients. No differences were found between the groups in the level of consciousness based on the FSH and LH level comparisons, namely the FSH level was 4.6 ± 3 IU/L (0.33–9.67) and the LH level was 2.5 ± 2.5 IU/L (0.16–7.3) in patients with VS/SAW, whereas in female patients with MCS, the FSH level was 3.1 ± 1.7 IU/L (1.18–7.06) and the LH level was 1.05 ± 1.2 IU/L (0.1–5) (Mann–Whitney test, p = 0.2; p = 0.14).

The level of APO-1 (also known as the apoptosis receptor CD95) in the blood serum was determined in 9 patients aged 17–41 years (mean age 26 ± 8 years), wherein 4 had VS/SAW and 5 had MCS. The APO-1 level was lower than the reference values indicated by the manufacturer of the test systems (1334–2411 pg/mL), namely from 363.6 to 887 pg/mL in 55.6% of patients (mean value 689.5 ± 199.6 pg/mL), whereas, in 33.3% of female patients, the level of APO-1 was within the reference values, on average 1776.7 ± 346.3 pg/mL and in 1 patient this marker was 80 times higher than the norm (194755 pg/mL). Significant differences were revealed between the groups with different levels of consciousness (VS/SAW and MCS) with the APO-1 levels of 640 ± 191.9 and 40194.5 ± 86403.2 pg/mL, respectively (p = 0.037).

The level of BDNF in the blood serum was studied in 10 patients aged 17–41 years (mean age 26 ± 8 years), wherein 5 had VS/SAW and another 5 had MCS. The BDNF level ranged from 8540 to 49820 pg/mL (mean value 22742 ± 12423.1 pg/mL). In all patients, the BDNF level was higher than the reference values indicated by the manufacturer of the test systems (42.58–6186 pg/mL). Significant differences were revealed between groups with different levels of consciousness (VS/SAW and MCS) with the BDNF level of 15832 ± 6443.5 and 29652 ± 13651.4 pg/mL, respectively (p = 0.025).

Thus, the blood levels of APO-1 and BDNF were significantly higher in patients with MCS than those with VS/SAW.

The levels of APO-1 and BDNF in the cerebrospinal fluid of all examined patients were below the determined limit.

The serum Fas-L level was determined in 9 patients aged 17–41 years (mean age 26 ± 8 years), wherein 4 VS/SAW and 5 had MCS. The reference values indicated by the manufacturer of the test systems did not detect Fas-L in the peripheral blood. The Fas-L level ranged from 0.02 to 0.36 ng/mL (mean value 0.21 ± 0.1 ng/mL). No significant differences in the Fas-L level were found between the groups with different levels of consciousness (VS/SAW and MCS), which amounted to 0.2 ± 0.1 and 0.236 ± 0.1 ng/mL, respectively (p = 0.39).

The Fas-L level in the cerebrospinal fluid was assessed in 8 patients aged 17–43 years (mean age 26 ± 10 years), wherein 4 had VS/SAW and another 4 had MCS. The Fas-L level ranged from 0.032 to 0.176 ng/mL (mean value 0.08 ± 0.06 ng/mL). No significant differences were found in the Fas-L levels between the groups with different levels of consciousness (VS/SAW and MCS), namely 0.07 ± 0.06 and 0.09 ± 0.06 ng/mL, respectively (p = 0.56).

The serum glutamate level was determined in 10 women aged 17–41 years (mean age 26 ± 8 years), wherein 5 had VS/SAW and another 5 had MCS. The glutamate level was higher than the reference values in 50% of patients and ranged from 30.2 to 44.3 μg/mL (mean value 36.7 ± 6.4 μg/mL). No significant differences were found in the glutamate levels between the groups with different levels of consciousness (VS/SAW and MCS), namely 25 ± 10.8 and 31.7 ± 9.6 μg/mL, respectively (p = 0.59).

The level of glutamate in the cerebrospinal fluid was determined in 9 patients aged 17–43 years (mean age 28 ± 10 years), wherein 5 had VS/SAW and 4 had MCS. Glutamate levels ranged from 1.6 to 17.2 μg/mL (mean value 3.8 ± 5 μg/mL). Significant differences were revealed between the groups with different levels of consciousness, namely the level of glutamate in the cerebrospinal fluid in patients with VS/SAW was 1.9 ± 0.2 μg/mL and was significantly lower than patients with MCS (6.2 ± 7.3 μg/mL) (p = 0.019).

The level of S100 protein in the blood serum was determined in 1 patient with VS/SAW aged 31 years and in the cerebrospinal fluid in 3 patients, wherein 2 had VS/SAW and 1 had MCS, aged 28, 31, and 45 years, respectively). The level of S100 protein in the blood serum was 22.7 ng/L and on average of 434.3 ng/L in the cerebrospinal fluid.

DISCUSSION

Hormonal examination of patients with CDC

The scientific literature presents a small number of works focused on the study of the hormonal status of patients with CDC. The work of the researchers from Japan in

1989 presented the data of hormonal examination (LH, FSH, thyroid-stimulating hormone, cortisol, and prolactin) after the stimulation with releasing factors of 33 patients with VS/SAW. Significant deviations from the norm were revealed, namely, the LH level was changed in 67% of patients, FSH in 45%, cortisol in 39%, thyroid-stimulating hormone in 36%, and prolactin in 15% of cases. The hormonal secretion from the anterior pituitary gland was impaired in all female patients, and the most pronounced changes were registered in 52% of patients. A direct relationship was established between the incidence of disorders and the duration of VS/SAW. The authors suggested that the function of the anterior pituitary gland is impaired in patients with VS/SAW and worsens progressively later [6].

A large number of publications are focused on the hormonal examination of patients in the acute period after CCI. M. Klose et al. obtained the values of gonadotropins that correlate with the age of women, who have no hypogonadotropic ovarian failure [7]. Z. Olivecrona et al. determined the level of gonadotropins on days 1–4 after injury. However, data on the menstrual cycle and the intake of hormonal drugs by the women examined were not provided. LH, FSH, and estradiol levels in women were generally low [8]. Several similar studies have confirmed these findings [9–11].

The Russian researchers showed, for the first time, that CDC patients of reproductive age had normo- or hypogonadotropic failure [12]. Two clinical cases of patients with CDC after tubal pregnancy were published. The hormonal and instrumental study results revealed that 1 patient was diagnosed with hypogonadotropic normoprolactinemic ovarian failure and the other had normogonadotropic normoprolactinemic ovarian failure [13].

Melatonin

Due to the preservation of the sleep-wake cycle rhythm in patients with CDC, many studies are focused on sleep analysis in this group of patients. Melatonin is known as a hormone that is responsible for the production of circadian rhythms in the body.

Circadian rhythms are endogenously generated by the suprachiasmatic nucleus of the hypothalamus. Melatonin functions as an endogenous synchronizer that is capable of stabilizing and intensifying circadian rhythms. Additionally, melatonin has antioxidant, anti-inflammatory, oncostatic, and anticonvulsant effects, and is also involved in blocking apoptosis [14].

An endogenous circadian rhythm of melatonin production peaks at approximately 02:00–04:00 [15].

Studies indicate wide variability among patients with CDC in their ability to exhibit physiological sleep and respond to external temporal changes. The preservation of circadian rhythms is assumed to be a positive prognostic marker and an indicator of the compensated physiological state of patients with VS/SAW [16]. In 2014, for the first time, the comparative secretion of melatonin was studied in 6 patients (4 males aged 33.3 ± 9.3 years and 2 females aged 38 and 47 years) with VS/SAW and healthy volunteers. The study was conducted on two consecutive nights, thus at the first night, all participants lay in bed and blindfolded in a dimly lit room (55 lux) from 22:00 to 08:00, and at the second night, patients were exposed to monochromatic (470 nm) blue light, which is effective in suppressing melatonin secretion. No significant changes were found in the plasma melatonin levels during an overnight melatonin suppression test in patients with VS/SAW [17].

A.A. Belkin et al. studied the levels of melatonin in 10 patients with CDC over time [18]. A positive correlation was found between the blood melatonin levels and neurological improvement.

M. Kanarskii et al. published study results in which they analyzed the level of melatonin in 22 patients with CDC and 11 healthy volunteers. A direct correlation was revealed between the amount of melatonin and the level of consciousness ($rs = 0.86$ at $p < 0.05$). This study also revealed a correlation between the low levels of melatonin and the severity of brain injury with possible damage to the retina through the transdegenerative mechanism [19].

A study by F. Gobert et al. in 2 patients with CDC collected urine samples for sulfatoxymelatonin every 2 h for 24 h. The scientists discovered circadian rhythm deregulations. After 7–8 months, a repeated neurological assessment was performed, and these patients switched to MCS. The authors predicted a possible exit from the CDC after the circadian rhythm regulation [20].

BDNF

Neurotrophins are significant proteins in the nervous system function, which regulate cell proliferation and differentiation and processes of neuron survival and death, and are involved in the mechanisms of neuronal plasticity.

BDNF is a neurotrophin involved in the regulation of growth, development, differentiation, and survival of cell populations, and the processes of their adaptation to external influences [21].

Neurotrophins, such as BDNF, can promote the survival and death of neurons based on various physiological factors and pathological conditions. BDNF in adults promotes neurogenesis and activates survival signaling through the kinases of the tropomyosin receptor (Trks) [22, 23], and its precursor, proBDNF, binds to the p75 neurotrophin

receptor (p75NTR), which is a molecule similar to the tumor necrosis factor receptor. Activation of the p75 neurotrophin receptor by proBDNF can induce apoptosis of neurons under various conditions [24, 25]. During synaptogenesis, p75NTR is widely expressed, namely during brain development and in the post-traumatic period, and is activated after brain injury, including CCI and cerebral hypoxia, and the associated overexpression can result in neuronal death.

BDNF expression is sensitive to influences, such as stress, trauma, hypoglycemia, ischemia, and brain damage, and is modulated by a large number of pharmacological agents targeting a wide variety of neurotransmitter systems [26]. Disorders in the genetic and epigenetic control of metabolism, transport, or transmission of the BDNF signal contribution to the development of several neurological and mental disorders, including Alzheimer's disease [27, 28], Huntington's disease [29], Parkinson's disease [30], neuropathic pain [31], schizophrenia [32], severe depressive disorders [33], and addiction [34].

BDNF is involved in the neuronal and synaptic reorganization of the brain. In animal models of CCI, BDNF expression is activated in the hippocampus and cerebral cortex [35, 36]. Some studies show that BDNF secretion in the brain immediately decreases after CCI, and the level of BDNF decreases more in patients with a worse CCI outcome [36–38].

S. Bagnato et al. [39] compared BDNF levels in the blood serum in 18 patients with VS/SAW and MCS. The comparison group consisted of 16 healthy people of the same gender and age. In 12 patients with VS/SAW and MCS (7 males and 5 females, with mean age 38.9 years) and healthy volunteers (9 males and 7 females, with mean age 38.6 years), BDNF levels in blood serum were compared before and after verticalization with ErigoPro robotic lower limb training. Serum BDNF levels were significantly lower in patients with VS/SAW and MCS (median 1141 pg/mL; 25% and 75%, 1016 and 1704 pg/mL, respectively) than in the control group (median 2450 pg/ml; 25% and 75%, 2100 and 2875 pg/ml; $p < 0.001$). BDNF levels measured before and after verticalization in the group of patients with CDC and healthy patients remained ($p = 0.5$). Moreover, BDNF levels did not differ between patients with VS/SAW and MCS ($p = 0.2$), as well as between patients with traumatic and non-traumatic brain injuries ($p = 0.6$). BDNF levels positively correlated with time from the moment of brain injury ($p = 0.025$).

E.G. Yazeva et al. determined the level of BDNF in patients with CDC. The main group included 26 patients (16 males and 10 females, with an average age of 27 years, from 23 to 41 years), wherein 14 had VS/SAW and 12 had MCS. The comparison group consisted of 21 healthy volunteers. The groups were comparable by age and gender. Serum BDNF level in healthy volunteers averaged to 54 pg/mL (40–62 pg/mL), which was significantly higher in patients with CDC ($p < 0.01$) and amounted to 770 pg/mL (640–950 pg/mL). No significant difference was found in the BDNF level in the blood serum among the patients with VS/SAW and MCS [40].

Our study results revealed that the BDNF levels in the blood were significantly higher in patients with MCS than those with VS/SAW.

APO-1 Fas receptor

Apo-1 is a cluster of differentiation 95 (CD95), a member of the tumor necrosis factor receptor superfamily. The Fas receptor is located on the cell surface and its activation leads to apoptosis. The mechanisms underlying cell death after CCI are not fully understood. Apoptosis is considered one of the mechanisms that contribute to the significant and long-term loss of neuronal cells after CCI. The study measured the level of APO-1 in the cerebrospinal fluid and blood serum in 10 patients (4 females, 6 males, aged 18–65 years) with severe CCI daily for 15 days after injury. The comparison group included 5 healthy volunteers. APO-1 was not detected in the cerebrospinal fluid, whereas an increased level was detected in the blood serum of patients after CCI at a concentration of 56–4327 mU/mL. Activation of the Fas-mediated apoptosis pathway may partially be a direct result of the initial trauma. However, a long-term increased level of sFas in the cerebrospinal fluid can be due to the ongoing inflammatory response to trauma and delayed apoptotic cell death [41].

According to our findings, the level of APO-1 in the blood was higher in patients with VS/SAW than in those with MCS. No APO-1 was found in the cerebrospinal fluid.

Fas-L

Fas-L is a molecule that triggers the process of programmed cell death by binding to the apoptosis receptor APO-1 (aka Fas, aka CD95), that is, Fas-L is an inducer of apoptosis. As a result of its action, the protein damages the tissues and is involved in the pathogenesis of certain diseases, and an increased level is found in neoplastic processes, CCI, and other diseases. Fas-L can also transmit non-apoptotic signals. Mesenchymal stem cells are multipotent cells derived from various adult tissues. The mesenchymal stem cells from different tissues share common properties; however, they also have tissue-specific characteristics. Previous studies demonstrated massive apoptosis after Fas-L treatment with bone marrow mesenchymal stem cells both *in vitro* and *in vivo*. Fas-L-induced responses were studied in the stem cells that are derived from Human adipose tissue [42]. These cells responded to Fas-L administration with simultaneous apoptosis and proliferation,

resulting in a doubling of cell counts and a phenotypic shift, including a decreased CD105 expression and an increased CD73 expression, combined with an increased potential for bone tissue differentiation. Treatment with freshly isolated stem cells increased the count of fibroblasts-forming large colonies, which are probably produced by the progenitor cells of early stem cells. Fas-L-induced apoptosis and proliferation signaling are revealed to be independent of each other. Thus, Fas-L signaling in stem cells leads to their expansion and phenotypic shift toward a stronger stem cell state. These responses are believed to ensure the survival of adipose-derived stem cell progenitor cells in a Fas-L-rich environment during tissue damage and inflammation, and may also increase the survival of these cells after *in vivo* administration.

Another study examined Fas-L expression by immunoglobulin A in the cerebral cortex, thalamus, and hippocampus of mice after CCI, and results were assessed using an image analysis system. Mice were injured by fluid percussion and euthanized 15 and 30 min, 1, 3, 6, and 12 h, and 1, 4, 7, and 14 days after the injury. Fas-L expression was detected 1 h after injury, which significantly increased after 3 h, reached a maximum after 12 h from injury, then decreased gradually after 4 days, and returned to normal after 14 days from injury [42]. Apoptosis that is mediated by Fas-L occurs, not only around the brain injury but also in the brain tissues away from the traumatic area. The Fas-L expression regularity can be used as one of the markers of brain injury.

Our study found no significant differences in the Fas-L level in the blood and cerebrospinal fluid in patients with MCS and VS/SAW.

Glutamate

Glutamic acid (glutamate) is a well-known neurotransmitter, wherein an increased level in the synapses leads to a disease that is clinically similar to amyotrophic lateral sclerosis. After severe CCI, synaptic glutamate levels immediately increase [43]. Excess glutamate in synapses, in turn, activates the corresponding N-methyl-D-aspartate receptors and the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, which promote excess calcium influx into the neuronal cells. Oxidative stress occurs, which leads to mitochondrial dysfunction, lipid peroxidation, and protein and DNA oxidation. As a consequence, the nerve cells die [44]. The occurrence of major depressive disorder after CCI is also associated with the impaired modulating role of glutamate [45].

A.L. Yasen et al. determined the concentration of glutamate in the brain using proton magnetic resonance spectroscopy in 9 patients (including 5 females aged 20.7 ± 2.3 years) immediately after CCI and within 2 months of restoration [46]. The control group included 9 healthy volunteers comparable by gender, age, weight, and height. Glutamate values were similar between the groups ($p = 0.57$), but significantly different over time ($p = 0.01$). The concentration of glutamate was lower in the CCI group compared to the control group, 72 hours after injury ($p = 1.02$). The authors suggested that changes in glutamate concentrations in the brain may be local and based on the time elapsed after CCI.

Our study revealed a significant difference in the level of glutamate in the cerebrospinal fluid. The values were lower in patients with VS/SAW than those with MCS. This is probably due to the CDC duration. Patients with VS/SAW had the state of CDC for 1–12 months (on average 4 ± 3 months), whereas 1–6 months for those with MCS (average 3 ± 2 months).

Protein group S100

S100 proteins represent a group of low molecular weight calcium-binding proteins. The count of S100 proteins increases at the initial stages of the development of chronic cerebral ischemia and reflects chronic neurodegenerative processes in the brain tissues [47]. This group of proteins is essential for cell growth and differentiation, as well as transcription, proteins phosphorylation, secretion, muscle fiber contraction, and other processes. They regulate the cell cycle and apoptosis and are involved in oncogenesis. Proteins of the group S100 in the brain are predominantly produced by astrocytes. At nanomolar concentrations, S100 stimulates *in vitro* growth of neurites in the neurons of the cerebral cortex and ganglia of the dorsal roots of the embryonic chicken [48, 49]. These data suggest that S100 may be a neurotrophic factor during nerve development and regeneration.

An increased S100 protein level in the blood and cerebrospinal fluid is noted in traumatic brain injury [49, 50]. Concentration determination of S100 in the blood diagnosed a severe degree of injury in patients with CCI, and patients with a low level of this marker and a mild severity of CCI may not undergo computed tomography of the brain, thereby avoiding up to 30% of unnecessary examinations. Scientists found that an increased S100 protein level of >0.1 μg/L is a sensitive marker of pathological changes on brain computed tomography [51].

Unfortunately, the insufficient specificity and the presence of extracerebral sources of the S100 protein in the peripheral blood limit its diagnostic value. Moreover, elevated serum S100 levels were found in patients with extracranial pathologies, such as trauma and burns [52]. A study was conducted among 94 patients, which revealed no relationship between the concentration of S100 in the blood serum and the severity of CCI [53]. This marker has not been previously studied in patients with CDC, which necessitates further research.

CONCLUSION

The examination results of patients with different levels of disorders of consciousness during the pituitary gland MRI revealed no significant differences between the groups in the volume of the pituitary gland. Additionally, no pituitary space-occupying lesions and other possible causes of the formation of ovarian insufficiency were found. The hormonal study revealed hypo- and normogonadotropic ovarian function failure; however, the analyses of gonadotropin levels revealed no significant differences in different groups based on the level of consciousness. No significant differences were found between the groups with different levels of consciousness in the melatonin level examination in the blood serum and urine. Nevertheless, several examined patients retained a nocturnal peak in melatonin secretion, which may indicate a high potential for further recovery of consciousness according to the literature. The APO-1 level was below normal in 50% of patients; however, this marker was increased by 80 times in 1 patient. Serum APO-1 and BDNF levels in patients with MCS were significantly higher than those with VS/SAW. Serum Fas-L was determined in all patients, and its increased level may be due to the continuing inflammatory response to trauma and delayed apoptosis. The level of glutamate was higher than the reference values in 50% of patients, but only 1 female patient had a CCI, and the level of glutamate was within the normal range in 2 patients after CCI. No significant changes were determined in the serum glutamate levels between the groups with different levels of consciousness (VS/SAW and MCS). The level of glutamate in the cerebrospinal fluid in patients with VS/SAW was significantly lower than those with MCS. Increased activity of neurons and astrocytes, as well as greater neuroplasticity of MCS patients, compared to the VS/SAW patients, can probably be suggested. The S100 protein level was determined only in a small group, thus an in-depth study of this marker is required.

Further research and accumulation of data on patients with CDC and highly informative markers will predict outcomes, as well as develop new effective approaches to the rehabilitation of consciousness in this category of patients.

ADDITIONAL INFORMATION

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