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Prognosis for Recovery from a Vegetative State

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Summary

The prognosis for recovery from a vegetative state (VS) remains underdeveloped.

Objective. To determine the feasibility of prognosis for recovery from a vegetative state based on clinical comparison of 18- fluorodeoxyglucose-PET (18FDGPET) and MRI (SCT) data.

Materials and methods. We compared and analyzed retrospectively cerebral PET and MRI (SCT) scans and relevant prognostic criteria (including revised coma recovery scale — CRS-R scores) prospectively during 6–84 months of follow-up in a cohort of 39 VS patients. All VS cases were of different etiologies, lasting for more than 2 months after brain damage (including 18 patients in chronic VS).

Pairwise comparison of groups was used (significance level $P<0.05$) and multiple comparison for three groups with a Bonferroni correction at $P<0.017$ was employed.

Results. Three patterns were identified when comparing 18FDGPET and MRI (SCT) neuro-images: pattern I — the area of functional alterations was larger than the area of structural damage, pattern II — complete matching of areas of structural and functional alterations, III — mixed pattern. Pattern I (69% of cases) was more common than patterns II (18%), and III (13%), $P<0.001$. There were no differences in VS etiology, VC duration, CRS-R scores, patients' gender and age between the groups of patients each falling into one of patterns. The outcome in a group with pattern I patients (all of them recovered from VS) was better than in other two groups exhibiting patterns II or III, each, $P<0.001$. In a group of patients with pattern III the recovery was better than in pattern II (all patients remained in VS), $P=0.018$. The increases in the total CRS-R score values were as follows: 12,1±4,46; Me=12 (4–19), $N=27$ (patients with a pattern I); 0±1,54 (–2–1, $Me=0$, $N=7$ (patients with a pattern II); and 5,20±4,09/ $Me=4$ (1–10), $N=5$ (patients with a pattern III). Significant increases in neurological improvement were revealed in pattern I patients with non-chronic VS versus chronic VS, $P=0.003$.

Conclusion. Clinical comparison of PET/MRI (SCT) data showed certain potential to predict patient's recovery from VS in 87% of cases. A retrospectively confirmed favorable prognosis in patients with pattern I was established in 69% cases, unfavorable (pattern II patients) was defined in 18% cases, regardless of other prognostic criteria, including chronic VS. Therefore, the data confirms the feasibility and clinical relevance of neurophysiological justification as a candidate approach for evaluating the prospect of recovering patients from VS.

Keywords: chronic disorders of consciousness; chronic vegetative state; recovery from a vegetative state; prediction; potential for recovery of consciousness

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Significant advances in emergency medicine in the treatment of acute severe brain injury have been shown to have some drawbacks. With increasing survival comes increasing disability, including the most severe and still poorly understood chronic disorder of consciousness (CDC) [1, 2]. Chronic disorder of consciousness, diagnosed 4 weeks and later after brain injury, refers to the first stages of recovery from coma. It includes the vegetative state (VS), characterized by wakefulness without awareness, and the minimally conscious state (MCS), with minimal signs of conscious behavioral responses, further subdivided into MCS (-) and MCS (+) based on their manifestations. The next stage, emergence from MCS with recovery of functional communication, is not related to CDC [1, 3, 4].

The VS, as well as any stage of recovery from coma, may turn out to be the final stage of recovery of consciousness, although the patient's survival may last for years and decades, which raises many medico-social, economic, as well as ethical prob-

lems [2, 4–6]. In this context, the prediction of outcome, especially in terms of improvement of consciousness, becomes a crucial issue [4, 6, 7]. Over the past two decades, significant progress has been made in diagnosing, predicting, and promoting recovery of consciousness in patients with CDC [8]. However, with an arsenal of prognostic factors and criteria proposed on the basis of virtually all diagnostic modalities used in the study of the brain, many of which are becoming increasingly complex [7–11], there is no reliable pathogenetic and clinically relevant prognosis, nor is there such a treatment [3, 4]. The main prognostic criteria remain clinical and epidemiological [4]. This is largely due to the lack of a universally accepted neurophysiological concept explaining the mechanisms of VS development and recovery [12].

Despite the fact that an empirical approach that does not rely on pathogenesis may undermine the prognostic component of the obtained data [13], multicenter studies and an integrated approach, particularly with the use of non-activation functional neuroimaging [14–16], are expected to provide a breakthrough in prognostication. Previously [17], we proposed using the correlation of structural (MRI, spiral CT) and functional (18FDG-PET) brain abnormalities to determine the potential for recovery of consciousness when considering VS from the perspective of Natalia Bekhtereva's theory of stable pathological state (SPS) of the brain. Although this parameter is critical in determining a valid prognosis [8], the efficacy of such a prediction has not been proven.

The aim of this study was to assess the utility of prediction of recovery from VS based on clinical correlation of 18FDG-PET and MRI (SCT) data.

Materials and Methods

In patients with CDC (VS) admitted for comprehensive diagnosis and treatment in the Department of Anesthesiology and Intensive Care of the Clinic of N. P. Bekhtereva Institute of Human Brain of the Russian Academy of Sciences (IHB RAS) from 2007 to 2016, we performed a retrospective analysis and correlation of 18FDG-PET and MRI (SCT) data, as well as several known prognostic factors, criteria, and follow-up data. All examinations and treatments were carried out with the patients' relatives/guardians' written informed consent. The Ethics Committee and Academic Council of IHB RAS approved the protocol for comprehensive examination and treatment.

We evaluated a consecutive sample of 39 patients with VS who underwent 18FDG-PET and MRI (or spiral CT if MRI was contraindicated) for a detailed assessment of neuropsychiatric status during their first hospitalization at the IHB RAS before specialized treatment, which served as a baseline.

Unknown follow-up was considered a criterion for non-inclusion. Follow-up data were evaluated at 6 months and beyond (up to 7 years) by determining the maximum level of consciousness achieved during this period. The duration of a single hospitalization in the IHB RAS was at least 1 month (usually 1–3 months). Repeated hospitalizations, including multiple hospitalizations with the whole set of examinations, occurred in 26 patients.

Classification of VS according to etiology and duration into chronic (in traumatic etiology >12 months from the onset of brain injury, in non-traumatic etiology >3 months) and non-chronic types, as well as determination of the level of consciousness and its changes according to the Coma Recovery Scale-Revised (CRS-R) were performed in accordance with international guidelines and criteria approved in the Russian Federation [1, 3, 4, 18].

Traumatic VS (VS_t) was diagnosed in 23 of 39 patients (13 women, 26 men; age 29.8 10.5 years (min 14 — max 54, *Me*=27), and non-traumatic VS (VS_{nt}) in 16 patients.

Chronic VS was observed in 18 patients (VS_t 9 and VS_{nt} 9). The actual duration ranged from 18 months to 10 years after brain injury in VSt and from 6 months to 5 years in VS_{nt}.

In the remaining 21 patients (14 VS_t and 7 VS_{nt}), the actual time of VS was >2 months (up to 12 months for VS_t, up to 3 months for VSnt) after the brain injury. For clarity, it was further referred to as non-chronic VS.

The cause of VSnt was hypoxic-ischemic and anoxic brain injury in 13 patients, inflammatory in 2 patients, and toxic in 1 patient. TBI was severe in all 23 patients with VSt (severe brain contusion with/without brain compression in 23 patients, diffuse axonal damage grade II–III in 20 patients), 17 of whom underwent various neurosurgical procedures. Prior to admission to the IHB RAS, all 39 patients received intensive care in specialized hospitals for at least 2 months from the time of the brain injury and were subsequently hospitalized either for life-threatening complications or (less frequently) for rehabilitation. The rest of the time, patients remained at home or in care facilities. Various complications were recorded in all patients during the first 6 months of VS (purulent/septic in 39, paroxysmal sympathetic hyperactivity syndrome in 39, hypertensive hydrocephalus in 17, epileptic syndrome in 18, and others). MRI (SCT) revealed progressive brain atrophy of varying degrees in the thalamus, subcortical nuclei, and cerebellum in all 18 patients with chronic VS; no change (improvement) in consciousness was documented from the time of coma recovery. In 11 patients, a benzodiazepine test [12] was performed. All patients were in critical condition with compensated vital functions when admitted to IHB RAS.

MRI was performed on 1.5 Tesla (General Electric) before 2009 and 3 Tesla (Philips Achieva 3T)

since 2009. Sequences used: T2VI (weighted images); T2-FLAIR WI; T1 WI non-contrast and, if necessary, with contrast enhancement (Gadadiomide from Omniscan). Spiral CT was performed on a Gemini TF Base scanner (Philips, Netherlands). 18FDG-PET was performed with a PC2048-15B (Scanditronix) or Gemini TF Base (Philips) PET scanner.

The functional status of brain regions was determined using the glucose metabolic rate (GMR) with evaluation of images in each image acquisition by visual and semi-quantitative methods. The value of GMR within the physiological range [19] was defined as «normal», and the value outside the reference values (regardless of intensity) was defined as «abnormal». The study was performed in a standardized manner under identical conditions. The correlation (congruency/non-congruency) of the areas of structural (MRI, SCT) and functional (PET) abnormalities in separate brain regions was checked visually. In particular, areas of functional impairment (PET) and areas of structural lesions (1.5T MRI or 3T MRI or SCT) were identified and then matched based on the topographic anatomy of the brain.

The congruence of functional and structural abnormalities was confirmed if the anatomical localization of the lesion coincided (with precision down to the details of individual structures such as gyrus, subcortical nuclei, brainstem, determined by generally accepted known anatomical landmarks) and if the area of abnormalities differed by no more than 15–20%. Image fusion using high-end software was carried out in some cases (when the area of abnormality was small) for clarification and quantitative comparison of lesion areas on PET and MRI (SCT) images. In cases where it was possible to perform repeated (multiple) PET scans, changes in metabolic abnormalities between consecutive PET scans were identified if the increase/decrease in metabolism exceeded the physiological variation of this parameter for the corresponding structure (usually 7–15% [19]) and/or the change in area of GMR abnormalities exceeded 20–25%.

Treatment options for patients were not considered. Treatment was based on clinical need, which is generally consistent with current guidelines and protocols [3, 4, 20, 21]. In addition, diagnosis and treatment of low-grade infection were performed [22], and high-dose multi-pattern botulinum therapy (IncobotulinumtoxinA) was used to treat generalized spasticity and dystonia [23].

Clinical data were analyzed with Statistica for Windows V11.0. Non-parametric methods were used. Frequency variables were compared using χ^2 and χ^2 with Yates correction (for small groups), Fisher's criterion. To evaluate quantitative parameters, means, errors of means, standard deviations, data range (min-max), medians, descriptive statistics (absolute and relative frequencies, ratios) were calculated. Quantitative parameters were compared using Mann–Whitney, Wald, median χ^2 criteria. Pairwise comparisons of groups were performed (differences were considered significant at $P<0.05$). For additional confirmation of some correlations, multiple comparisons of groups were performed with Bonferroni correction for three groups; differences at $P<0.017$ were considered significant. Spearman's rank correlation coefficients were calculated.

Results

Clinical correlation of PET and MRI (SCT) data revealed the following 3 variants of brain damage (without taking topography into account).

Variant I was identified when the area of energy metabolism disturbance exceeded the area of structural damage. In addition to a gross decrease (up to absence) of metabolism directly in the areas of structural damage, perifocal and/or visually preserved brain areas also showed varying degrees of metabolic abnormalities (Fig.)

Variant II was confirmed when the area of energy metabolism disorder was completely equal to or smaller than the area of structural damage (Fig.)

Variant III (mixed) was characterized by a combination of variants I and II in different anatomical structures. This variant was recognized in cases that did not fall under variants I and II.

The frequency of the three variants of PET/MRI (SCT) correlations, as well as the characteristics of VS corresponding to these variants with the follow-up data on change of consciousness are shown in the Table.

Variant I was significantly more frequent than II ($P<0.001$) and III ($P<0.001$). The frequency of variants II and III did not differ ($P=0.54$). Patients classified into the different correlation variants did not differ in gender ($P=0.79$ or more), age ($P=0.47$ or more), duration of VS (non-chronic/chronic) ($P=0.74$ or more), occurrence of VS of different etiology (traumatic/non-traumatic) ($P=0.29$ or more), total CRS-R score ($P=0.88$ or more). Inflammatory epilepsy was characteristic of all patients with variant III.

The outcome for variant I (all recovered from VS) was better than for variant II ($P<0.001$) and variant III ($P<0.001$), and for variant III better than for variant II (all remained in VS) ($P=0.018$).

The best outcome in terms of increase in total SRS-R score was also with variant I (vs II, $P<0.001$, vs III, $P=0.001$) and the worst with variant II (less increase in total score than variant III, $P=0.035$). Outcomes were better with variant I ($P<0.001$) than with variant II for both chronic and non-chronic VS, and with variant III for non-chronic VS ($P<0.001$).

In patients with variant I, the increase in total CRS-R score at baseline was less in chronic VS than in non-chronic VS ($P=0.003$). In variant II, the increase in score did not differ according to the duration of VS ($P=0.84$), while in variant III there was

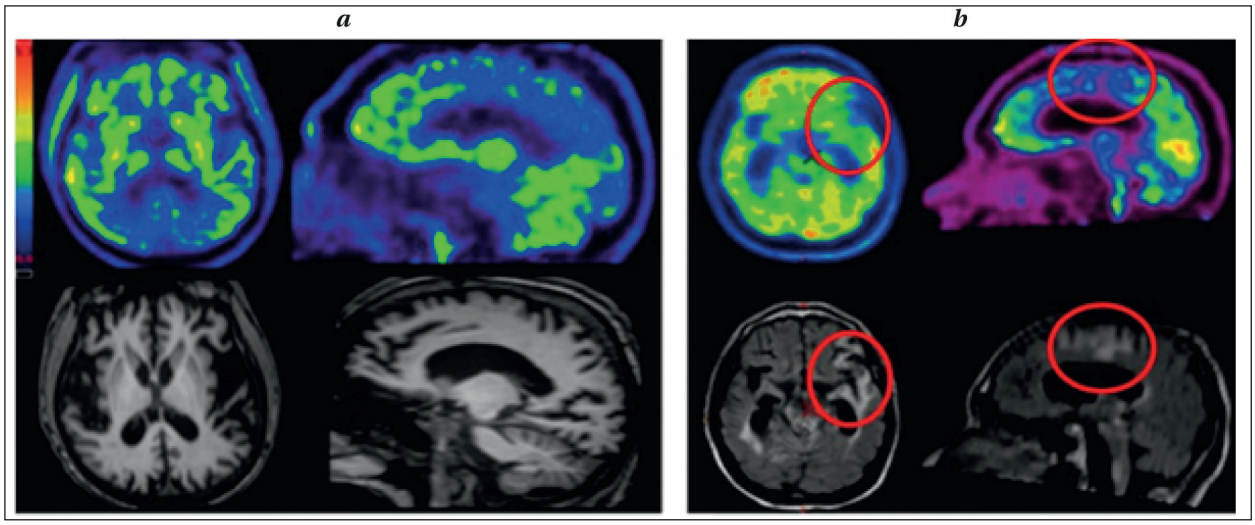

Fig. Standardized evaluation and comparison of individual 18F-FDG PET images (top row) and MRI/CT (bottom row) for prognostic purposes.
Note. *a* — variant I: areas of reduced glucose metabolism (PET) are significantly more extensive than corresponding areas of structural damage (MRI, T1). *b* — variant II: areas of reduced glucose metabolism (PET) coincide with areas of structural damage (CT). At the time of examination, both patients are in chronic traumatic VS.

a trend toward a greater increase in cases of chronic VS (P=0.052).

In a multiple comparison of groups with Bonferroni correction, all outcome parameters were better in patients with variant I than in patients with variant II and III (P<0.017). The worse outcome in variant II compared to variant III was observed only as a trend in «remained in VS/recovered from VS», which is the key prognostic parameter.

Thus, variant I (69% of patients) was prognostically favorable. In a pairwise comparison of the groups, the differences in outcome were significant for variant II (18% of patients) and III (13% of patients). The differences in the course of neurological recovery in these patients were indirectly confirmed by the trend toward worsening of the key index in multiple comparisons with few observations. This allowed us to consider variant II as prognostically unfavorable (Fig.), and variant III as equivocal. Taking into account the above, the accuracy of prognosis (favorable/unfavorable) was actually 87%, of which the prognosis was favorable in 69% of patients, unfavorable in 18%, and equivocal in 13%.

Changes in PET parameters in combination with clinical characteristics were analyzed in 26 of 39 patients in VS.

In the variant I group, 21 patients (12 VS_t, 9 VS_{nt}) were followed up with improvement of consciousness. In all patients, normalization of energy metabolism (PET) was observed over time, consisting of reduction of the area of abnormal metabolism (usually beyond the area of structural damage) and/or improvement of GMR. In 18 patients (chronic and non-chronic VS of various etiologies), PET changes were recorded before and/or simultaneously with the appearance of behavioral signs of awareness. In addition, in one of these patients, clinical and neuroimaging parameters obtained at the time of improvement in consciousness were compared with postmortem morphological data (acute cardiac death), which has been reported in detail separately [23]. In the other three patients (all with chronic VS of different etiology), the initial improvement in GMR did not exceed the level of physiological variability, but became evident after clinical changes. In all patients, GMR improvement did not occur in all brain regions and was not immediate. Initially, when the metabolic disorders persisted, the improvement of this parameter occurred gradually with the improvement of consciousness (in our observations, during repeated courses of treatment). If patients' consciousness did not change or even worsened over time (compared to the previous examination), GMR did not change and sometimes decreased. Changes in the energy metabolism of all or some brain regions were manifested in the evolution of neurological symptoms and/or electrophysiological parameters [23].

In the variant II group, 4 patients who remained in VS were followed up. In 2 patients (VS_t), PET data and level of consciousness did not change over time. In the third patient (VS_t), an episode of minimal improvement was observed, when inconclusive and transient eye fixation occurred without changes in PET parameters. At the insistence of the relatives, treatment was discontinued and only nursing care was provided. One year later, in the control study, the level of consciousness corresponded to VS. There were negative changes (compared to baseline data) in the CRS-R score with an increase in the area of structural and functional damage.

The fourth patient, who had already been in VS for 5 years at the time of admission to the IHB

Table. Variants of PET/MRI (CT) correlation: frequency, characteristics, and outcomes of VS.

Parameter, units	Values in compared groups,			*P*		
	I	II	III	I / II	I/ III	III/ II
Frequency, *N* (%)	27 (69)	7 (18)	5 (13)	<0.001; <0.017	<0.001; <0.017	>0.05; >0.017
Characteristics of VS cases						
Sex (female/male), *N*	9 : 18	2 : 5	2 : 3	>0.05; >0.017	>0.05; >0.017	>0.05; >0.017
Age, years *M*±σ (min–max), *[Me]*	30.44±9.85 (17–54), [27]	31.28±13.90 (15–54), [26]	24.40±9.15 (14–39), [23]	>0.05; >0.017	>0.05; >0.017	>0.05; >0.017
VS_{nc} : VS_c, *N*	14 : 13	4 : 3	3 : 2	>0.05; >0.017	>0.05; >0.017	>0.05; >0.017
VS_t : VS_{nt}, *N*	15:12	4:3	4:1	>0.05; >0.017	>0.05; >0.017	>0.05; >0.017
CRS-R , total score, *M*±σ (min–max), *[Me]*	4.11±1.37 (1–6), [4]	4.0±0.82 (3–5), [4]	3.80±1.64 (2–6), [3]	>0.05; >0.017	>0.05; >0.017	>0.05; >0.017
Follow-up: △ CRS-R, *M*±σ (min–max) [Me]						
All VS cases	12.1±4.46 (4–19), [12]	0±1.54 (–2–1), [0]	5.20±4.09 (1–0), [4]	<0.001; <0.017	<0.01; <0.017	<0.05; >0.017
VS_{nc}	14.28±4.45 (7–9), [15]	0.25±1.15 (–2–1), [0]	4.33±4.93 (1–10), [2]	<0.001; <0.017	<0.001; <0.017	>0.05; >0.017
VS_c	9.7±3.19 (4–14), [11]	0.33±0.58 (0–1), [0]	6.50±3.53 (4–9), [6.5]	<0.001; <0.017	>0.05; >0.017	>0.05; >0.017
P-value for VS_{nc} / VS_c	<0.01	>0.05	>0.05*	—	—	—
Follow-up: maximal consciousness						
Remained in VS: Recovered from VS, All VS cases, *N*	0 : 27	7 : 0	2 : 3	<0.001; <0.017	<0.001; <0.017	<0.05; >0.017*
MCS(-) : MCS(+) : EMCS						
All VS cases, *N*	7 : 14 : 6	0 : 0 : 0	2 : 1 : 0	n/p	n/p	n/p
VS_{nc}, *N*	1 : 8 : 5	0 : 0 : 0	1 : 0 : 0	n/p	n/p	n/p
VS_c, *N*	6 : 6 : 1	0 : 0 : 0	1 : 1 : 0	n/p	n/p	n/p

Note. MCS — minimally conscious state; EMCS — emergence from minimally conscious state; VS — vegetative state; VS_c — chronic vegetative state; VS_{nc} — non-chronic vegetative state; VS_t — vegetative state of traumatic etiology; VS_{nt} — vegetative state of non-traumatic etiology; CRS-R — Coma Recovery Scale Revised; △CRS-R — increase in CRS-R score; n/p — not performed. Statistical significance level *(P)* for pairwise comparison of groups: <0.001 — strong difference; <0.01 — marked difference; <0.05 — difference; >0.05 — no difference; >0.05* — trend for difference (*P*=0.052). Additionally with Bonferroni correction for the three groups: <0.017 — significant difference; >0.017 — no difference; >0.017* — trend for difference (*P*=0.018). The exact *P*-values are shown in the text.

RAS, had brain areas with reduced GMR outside the structural damage according to the history data in the stage of non-chronic VS. The result of the benzodiazepine test suggested a favorable prognosis [12], which was the reason for initiating intensive pharmacotherapy. Brain metabolism recovered to normal and remained unchanged according to the results of repeated PET scans. However, the expected improvement in consciousness never occurred until the patient's death.

In the variant III, a patient was observed in chronic VS. Over time, the area of reduced GMR decreased and consciousness improved to MCS(-). In the following three years of survival, despite treatment attempts, the level of consciousness and PET parameters did not change.

Data on energy metabolism of individual brain regions were not evaluated in this study.

The results of the application of some prognostic factors and criteria were reported. Only 17% of 18 patients with chronic VS remained in this state (1 VS_t and 2 VS_{nt}), contrary to expectations. All (18/18) patients with chronic VS had signs of brain atrophy, 78% (14/18) had absent or extremely weak pupillary reaction to light, 44% (8/18) had the «rabbit snout» sign. No significant differences were found in the etiology of VS, with 22% (5/23) of patients with VS_t and 25% (5/23) with VSnt remaining in VS, *P*=0.87. The mean total CRS-R score remained <6 in all 39 patients, with no significant differences between those who later remained in VS (3.63±0.74 (3–5, *Me*=3.5, *N*=8)) and those who recovered to MCS (4.16±1.39 (1–6, *Me*=4, *N*=31), *P*=0.21. The prognosis according to benzodiazepine test results (accurately determined in 10 of 11 patients) was poor in 8 but confirmed in only one (for variant II); favorable in 2 but confirmed in one (for variant I).

Discussion

Most studies on predicting outcome in VS do not specifically define criteria for functional recovery, return to normal life (which is the strategic goal of rehabilitation), and even recovery from VS [4]. We focused on the latter, i. e., defining the potential to achieve at least MCS, which expands the possibilities for further treatment.

The baseline characteristics and medical histories of the patients with VS were generally not different from those reported in the literature [24]. However, our patients had some specific features related to the duration and outcome of VS. During the first 4 weeks after brain injury, the prognosis

for recovery from VS is considered «cautious» (although the prognosis for VS is less favorable than for MCS) [3, 4].

In the patients studied, the duration of impaired consciousness exceeded 2 months, and almost half of them had chronic VS, which significantly reduced their chances of improving consciousness [3, 4]. Moreover, cases of chronic VS corresponded to the so-called permanent VS (no change in chronic VS_t and VS_{nt} for more than 6 and 3 months, respectively), when recovery is highly unlikely, which is a reason to consider discontinuing life support [4].

Therefore, a rather high percentage of patients with improved consciousness attracts attention, which, on the other hand, served as a reference point for evaluating the accuracy of the proposed prognostic method. Consciousness improved in 77% (30/39) of the patients, with 71% (15/21) in non-chronic VS and 83% (15/18) in chronic VS. These results, as well as the proportion of patients with a confirmed favorable prognosis (favorable in 69%, unfavorable in 18%), are more positive than those reported by several other investigators. In comparison, the prognostic significance of the benzodiazepine test, according to its developers, was confirmed in 76% of VS cases, of which only 28% had a favorable prognosis [12]. Other data suggest that only 20% of patients with chronic VS can be expected to improve their level of consciousness [5].

Traumatic etiology of VS is considered to be prognostically more favorable than non-traumatic (the most unfavorable being anoxic) [4, 25]. According to the literature, the frequency of recovery from VS was independent of the etiology of the brain injury. This is consistent with the results of a recent multicenter study to identify predictors of short-term outcome [15].

All patients had cerebral and extracerebral complications in the early and later periods after brain injury [4, 26]. Most had CRS-R scores <6 points [18, 27], many, especially in chronic VS, had the «rabbit snout» phenomenon and absent pupillary response to light [24], which are considered negative prognostic signs. While some investigators believe that clinical assessment of CDC is fundamental for prognostication [28], it is worth noting that even the absence of all brainstem reflexes during prolonged continuous lung ventilation is not an obligatory attribute of brain death, nor does it exclude the presence of awareness (the so-called «responsive unawakefulness syndrome») [29].

All patients with VS had a variety of structural brain damage, including damage to the corpus callosum, brainstem (including dorsolateral oral areas), or corona radiata, and damage to the left (dominant) or both frontal lobes, all of which have a negative prognostic value [3]. In chronic VS (regardless of etiology), all patients had marked brain atrophy [30], sometimes involving the thalamus and cerebellum [25]. All of these structural changes were found in patients with variant I neuroimaging correlations, thus reducing their prognostic value. Furthermore, brain regions known to be uniquely associated with consciousness have not been identified [11, 29].

A number of factors considered positive, such as young age [4, 25] and early advanced treatment [31], were only implemented in variant I, although they occurred with equal frequency in all variants, including variant II. This suggests that they may be more important in predicting survival or survival time than neurological recovery.

In line with the notion that disorders of consciousness are mainly determined by functional rather than structural brain abnormalities [32], many neurophysiological prognostic criteria based on electrophysiological parameters, PET and functional MRI data have been proposed [7, 8, 10, 12, 13]. After analyzing the literature data, we conclude that the detection of patterns more expected in MCS and emergence from MCS are mostly considered positive in VS. Their detection may be of diagnostic value (given the high risk of erroneous clinical diagnosis of VS [1, 3, 4, 18]) or may serve as a predictor of recovery from VS, reflecting the spontaneous or induced [33] reorganization of the persistently impaired functional state of the brain [34].

Neurophysiological parameters were recently found to be generally better predictors of the transition from VS to MCS than from VS/MCS to emergence from MCS. However, their prognostic value has often not been confirmed [35]. For example, P300 (evoked brain potentials) [35, 15] and fMRI activation patterns, which are classic from a neurological point of view, have not proven their «favorability» [35]. Electrophysiological parameters, whose ineffectiveness we have previously shown, were not evaluated [23], but it should be noted that the benzodiazepine test [12] had no prognostic value in patients with variant I.

Although the usual prognostic criteria proved to be of little value in predicting recovery from VS in variant I, it should be stressed that they mostly focus on a rather short period from the time of brain injury, whereas markers of late recovery have not yet been identified [7]. On the other hand, since in variant I the extent of recovery from non-chronic VS was greater than from chronic VS, it is possible that all (or some) of the criteria known from the literature are essential for predicting the extent of recovery of consciousness and/or function. This assumption, which is in line with current requirements [4], warrants further investigation with a data set for pathogenetic therapy.

Most patients, especially in chronic VS, have only reached MCS levels when consciousness improved. However, the fact of transition from VS to

MCS increases not only the likelihood of further recovery but also the availability of treatment [4, 36]. We believe that the improvement of patients' consciousness (especially in chronic/permanent VS) is related to the applied therapeutic approaches, which, as well as the prognosis, are based on Natalia Bekhtereva's theory of the stable pathological state (SPS) of the brain. Evidence of the effectiveness of these methods was reported earlier [22, 23].

From the perspective of the above-mentioned theory [17, 37], VS seems to be the result of activation of the brain's protective response, which, after stabilization, is transformed into a new entity, i.e., SPS. Without going into the underlying mechanisms, we emphasize that the SPS cannot be destroyed, but only destabilized and unbalanced, which is clinically reflected (in VS patients) in the transition to the next level of consciousness, which in turn represents a new SPS, and so on. Visualization of brain regions with impaired functional state outside of structural lesions (evidence of SPS) means that there is a potential for improvement of consciousness, which is prognostically positive (variant I), while the absence of such regions (variant II) corresponds to an unfavorable prognosis. Variant III, which was identified due to the high sensitivity and low specificity of PET [1, 19], later transformed into variant I or II, especially after appropriate treatment.

Confidence in the above concepts is crucial. In the pairwise comparison of the groups, the differences in the results in patients with all variants of the neuroimaging correlations were found to be significant. However, from a formal point of view, it is important to identify only the favorable variant I, which predominates in the patient population. No significant differences were found for the key parameter (recovery from VS) for variants II and III in the intergroup comparison with Bonferroni correction, but a trend towards differences was revealed, probably due to the small number of such patients.

Based on the SPS theory of Natalia Bekhtereva, specific characteristics of the PET method and documented follow-up data, we concluded that variant II is prognostically unfavorable and variant III is equivocal.

In the available literature, we did not find similar prognostic approaches or results, suggesting a potential for improvement of consciousness in most cases of VS. The frequency of the three prognostic variants may change as the number of observations increases. However, given the available data on brain energy metabolism in CDC, no fundamental changes are expected.

Typically, energy metabolism abnormalities in VS are described on PET as larger in area and more severe than those in MCS, and MCS as more extensive than recovery from MCS [1, 12]. When correlated with MRI, the area of abnormal metabolism decreases to the limits of the structural lesion area as consciousness improves [38]. In fact, this «common» description corresponds to variant I, confirming its frequency (69% according to our data). On the contrary, there are only a few confirmed cases of VS in which the cerebral cortex metabolism appears to be relatively preserved [1, 32]. This corresponds to the less common variant II (18%).

«Unusual» cases of VS (in variant II) give reason to believe that PET does not prove the presence of consciousness. It can be explained by the unique characteristics of brain neuroplasticity [32]. However, there is a lack of information in the literature about «normal» neuroplasticity (in variant I).

Based on the follow-up of patients classified as variant I (death upon improvement of consciousness) [23], it can be assumed that «typical» improvement of consciousness is associated with activation of axonogenesis and so-called functional neurogenesis with the appearance of scattered newly formed cells in those brain regions where functional improvement occurs (clinically and according to PET data). In variant II, if activation of neurogenesis and axonogenesis occurs, it is most likely aberrant. Further research is needed, but the structural and functional changes noted above in variant I do not contradict the theory of SPS, but only broaden the scope of its application.

From a clinical point of view, the following aspects are important A favorable prognosis (potential for recovery of consciousness) may go unrealized or even become unfavorable for many reasons, including inadequate therapy, as demonstrated by the history of our patients.

Many patients who recovered from MCS remained severely disabled, especially when recovering from chronic long-term VS. According to the data of international studies [24, 39], this was due, among other things, to «medical neglect».

Patients with CDC frequently experience inadequate palliative care, poor rehabilitation, and even segregation in the treatment of chronic diseases [39, 41], owing to a variety of neurological complications and comorbidities [40]. This does not contribute to the improvement of patients' general condition and consciousness.

Despite the lack of a widely accepted approach to the treatment of VS, we believe it is reasonable to classify patients with variants I and III (favorable and uncertain prognosis, regardless of VS duration) into a «target group» for adequate observation and reasonable therapeutic measures.

Given the good prognosis, the inclusion of variant I in the «target group» is self-explanatory. Despite the uncertain prognosis, the inclusion of variant III in this group is also justified. However, only 5 patients had variant III, according to our data. Consciousness improved in three of them,

and they recovered from VS: two reached MCS (-) and one reached MCS (+).

Unfortunately, only one of these three patients had follow-up PET scans when their consciousness improved or stopped improving during their survival years. All patients with variant III, on the other hand, had inflammatory epilepsy, which could have influenced the change in metabolic parameters during the PET scan [22].

The presented analysis of PET/MRI (SCT) data demonstrated the ability to predict recovery from VS in 87% of cases with either a favorable (69%, variant I) or unfavorable (18%, variant II) prognosis, regardless of other factors and criteria. In contrast, the examination of functional and structural brain abnormalities, unlike several published studies [1, 14], was based on the standard evaluation of individual PET and MRI/SCT images used for routine diagnostics. The utilization of scanners of different models to evaluate both structural and functional changes in the brain of patients does not impact the accuracy of the semi-quantitative assessment of the correlation between the volumes of structural and functional brain lesions [42–44]. This approach, which takes into account the variability in localization and volume of brain lesions in patients with VS [1, 12], greatly facilitates the translational aspect of research.

Functional neuroimaging is now required in addition to standardized clinical assessment and EEG when investigating patients with CDC [18]. 18FDG-PET is considered one of the most informative imaging techniques for studying brain function [1, 12, 14].

Additionally, other factors are important: all necessary tomographs are readily available, MRI and SCT can be used interchangeably if there are contraindications to MRI, and visual comparison of data is straightforward. However, a model based on non-activation fMRI, which has a similar accuracy rate (88%) in predicting the potential for regaining consciousness within a year, can only be utilized if there are no contraindications to MRI and if the structural brain damage is minimal (less than 30%). Furthermore, this model relies on three key epidemiological criteria (etiology, timing, age) [16].

Limitations. Firstly, we cannot guarantee that the prognostic criteria generated will be relevant for patients in the earlier stage of VS, specifically within 2 months after the brain injury. Additionally, it is uncertain whether the unfavorable prognosis (variant II) will remain consistent as medical technology advances.

This study did not evaluate the significance of criteria based on non-activation fMRI or laboratory data. The study did not examine the potential timing of improvement in consciousness due to the involvement of different clinical factors including complications, treatment, and nutrition.

Conclusion

We determined three prognostic variants of neuroimaging correlations reflecting the potential for emerging from VS during the period of more than 2 months after brain injury based on the results of standard evaluation and correlation of individual 18FDG PET and MRI (SCT) images of the brain used in routine diagnostics of CDC and considering VS from the position of N. P. Bekhtereva's theory of stable pathological state of the brain. Variant I involves functional abnormalities that outnumber structural abnormalities and has a favorable prognosis (69% of cases). Variant II has a complete overlap of these abnormalities and an unfavorable prognosis (18%), whereas variant III has a «mixed» presentation and uncertain prognosis (13%).

A retrospective analysis of prognosis based on neuroimaging correlation variants revealed that it predicted recovery from VS in 87% of cases (69% and 18% in variants I and II, respectively) independent of other prognostic criteria, including chronic VS.

Given the pathophysiologic validity, availability, and ease of assessment, it is reasonable to use PET/MRI (SCT) prognostication in clinical practice, with patients in VS with I and III variants assigned to the «target group» for active monitoring and implementation of relevant therapeutic strategies.

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