

# Polyfunctionality of Neurons: The Blocking of Extreme Pathological Afferentation Leads to an Improvement of the Higher Functions of the Brain

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**Abstract**—In this paper, a possible mechanism for improving the functional state of the brain regions maintaining locomotor, visual, auditory, and higher functions of the brain during the correction of the generalized spastic syndrome (botulinotherapy with Xeomin) in patients in the vegetative state (VS) is discussed. If the vegetative state is considered as a stable pathological condition (SPC) of the brain, then, in terms of the theory of the structural–functional organization of brain systems with rigid and flexible elements (N.P. Bechtereva), the therapy led to an unbalance of SPC, functional liberation of neurons, redistribution of their functions to ensure other activities, and the formation of new interneuronal connections. Taking into account the functional variability of neurons (S.V. Medvedev), the blocking of the neuromuscular transmission in spastic muscles reduces the abnormal afferent and efferent hyperactivity of motor and sensory neuronal circuits, which liberates the brain for other activities. Clinically, this allows considering botulinotherapy of drug-resistant muscle spasticity in patients in VS and minimal consciousness not only as a symptomatic treatment but also as indirect neuroprotection.

**Keywords:** vegetative state, recovery of consciousness, botulinotherapy, neuroprotection

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## INTRODUCTION

A vegetative state (VS) is a way out of a coma; when awakened patients show no signs of awareness of themselves and others. Until recently, the prognosis of emerging from VS was not known; however, it was assumed that different pathophysiological mechanisms underlie apparently similar clinical manifestations.

Considering VS as a stable pathological state (SPS) of the brain (according to Bechtereva [1]), we were the first to show that there are two masks of VS: true, with a poor prognosis, and functional, with a fairly favorable prognosis [2]. Favorable prognosis in functional VS is determined by the fact that persistent disturbance of consciousness in this case is the consequence of SPS, which can be unbalanced. As a result, the old interneuronal connections are switched off and new interneuronal connections are formed. The imbalance is reached by abolishing the factors that continue to have a pathological effect on the central nervous system (CNS) in the course of the disease of the brain—the factors that perpetuate the SDS. Clinically, it is manifested in an improvement of the patient's neurological status.

Among the frequent and obvious clinical components of VS, the most important is a rough and usually generalized increase in the muscle tone, with spastic paralysis, abnormal postures, and a probable significant pain component. The development of these locomotor disorders is primarily determined by the lesions

of neurons and their connections in the CNS. Considering the VS as a manifestation of SDS, we assumed that continuous pathological afferentation from spastic muscles stabilizes the SPS of the brain.

In clinical practice, the correction of muscle spasticity is regarded solely as a symptomatic treatment that facilitates primarily patient care, and the treatment procedure is usually selected empirically. For this purpose, various pharmaceuticals (sirdalud, baclofen, and mydocalm), with the central and/or peripheral action and oral administration are commonly used in high doses and different combinations. However, their effectiveness is often minimal, and the side effect of a lowered blood pressure with a decreased cerebral perfusion also limits their use. In the last decade, the complex of symptomatic antispastic (and antidistonic) treatments includes intramuscular (local) application of botulinum toxin; however, botulinotherapy is usually limited to certain body parts and muscle groups [3].

The effect of pharmaceuticals with the central action cannot be predicted, taking into account the changes in the functional activity of neurons in the SPS structure. On the contrary, the effect of botulinum toxin, which blocks the neuromuscular transmission in a peripheral organ, is more reliable in this context. On this basis, it is reasonable to correct the drug-resistant generalized spasticity with abnormal postures in VS patients with extended botulinotherapy, by injecting botulinum toxin into all spastic muscles. With

allowance for cachexia and inflammatory and immunopathological conditions in our patients, they were injected with the botulinum toxin preparation free of complexing proteins, Xeomin (Mertz Pharmaceuticals, Frankfurt on Main, Germany) [3], in a total dose of 600–800 units.

In addition to the antispasmodic effect, which lasted for 7 or 8 months (in some cases, 10 months), with a stable hemodynamics and absence of complications, we noticed changes in the neurological symptoms, including those not associated with the nonmotor neurons, as well as an improvement in the level of consciousness and communicative activity of patients.

In six patients administered with Xeomin, the standard therapy was not changed (or was not performed at all), and other types of treatment were not performed either. This made it possible to distinguish the clinical neurological and neurophysiological changes developing in the brain against the background of suppressed muscle spasticity at the peripheral level.

For two or three weeks of observations after administering Xeomin, all six patients showed an improvement of the following parameters: mobility (by 3–6 points) and the associated alternative communication (by 3–4 points), as well as visual responsiveness (by 1–5 points), auditory perception (by 2–8 points), and verbal communication (by 1–2 points). The parameters were estimated using the Loewenstein communication scale (LCS) [4]. The clinical dynamics corresponded to the changes in the glucose metabolism in the brain, recorded during a dynamic positron emission tomography (PET) study using 18-fluorodeoxy glucose (18-FDG) [5], which was performed one day before and two or three weeks after the Xeomin administration.

**Clinical example no. 1.** Patient K., 38 years old. Diagnosis: vegetative state. Drug-resistant generalized muscle spasticity with abnormal postures.

The vegetative state was the result of a severe traumatic brain injury (TBI) with the primary lesion of the basal ganglia and brainstem at the mesencephalic level, which was suffered seven months earlier. All attempts of pharmacological treatment of the generalized spasticity were ineffective.

On admission to the Institute of the Human Brain, Russian Academy of Sciences, the muscular spasticity of the patient corresponded to 4–5 points according to the modified Ashworth scale [6], and the VS of this patient was estimated as 8 points according to the LCS scale. Three weeks after the injection of 800 units of Xeomin (other therapy was not performed in this period), the muscle tone was reduced to 1–2 points, and the level of communicative activity increased to 20 points according to LCS, which corresponded to the transition to the small consciousness state. We also observed an improvement in other characteristics, such as mobility (general motor responses, appearance of attempts to turn the head and eyes, improved swallowing), visual responsiveness (appearance of

blinking reflex, awakened look, periodically fixed eyes, and attempts to follow with eyes), and auditory perception (appearance of a response to voice and rare attempts to execute a command). At the same time, according to the PET data, a relative increase in the energy metabolism in the cerebellum and brainstem was detected.

**Clinical example no. 2.** Patient C., 24 years old. Small consciousness (emerging from VS). This patient had drug-resistant generalized spasticity with abnormal positions of hands and feet, as well as visual and oculomotor disturbances.

Two years ago, the patient suffered a severe head injury with gross damage to the frontal and occipital lobes and a diffuse axonal injury of the brain, which resulted in the VS (11 points on LCS). During the 14 months of observation and complex treatment at the Institute of the Human Brain, Russian Academy of Sciences, this patient twice received botulinotherapy because of spasticity. Each time, he showed improvement in the level of consciousness and communication.

On admission to the Institute, this patient had the following characteristics: small consciousness (60 points according to LCS); spasticity, 4 points in the muscles of the distal segments of limbs and 2–3 points in other muscles (according to the Modified Ashworth Spasticity scale). Two weeks after the administration of 700 units of Xeomin (the other therapy remained unchanged for three months), this patient showed a decreased muscle tone persisting in some muscles to a maximum of 2 points. The level of communicative activity increased to a total of 73 points on the LCS. An improvement in the following characteristics was also observed: mobility (improvement in the arbitrary movements of the limbs, movements of the head and eyes, movements of facial muscles and tongue, and swallowing), visual responsiveness (appearance of the blinking reflex), auditory perception (improved perceptions of commands and recognition of objects), alternative communication (including the appearance of ideatory and ideomotor praxis), and verbal communication (improved articulation as well as the quality and meaning of verbal communication). In addition, the cognitive activity and attention of this patient also improved, and his emotional range broadened. According to PET data, a relative increase in the energy metabolism in the cortex of the left temporal and parietal-occipital regions was observed in the period of observation.

The above examples illustrate the clinical manifestations of a change (improvement) in the functional state of the neurons and/or interneuronal connections that ensure not only movements but also visual, auditory, and higher mental functions when muscle spasticity in patients is alleviated. This paradoxical, at first glance, result can be explained in terms of Bekhtereva's theory [7, 8] postulating that complex activities are ensured by a structural-functional system with components of varying degrees of flexibility (system with rigid and flex-

ible components), supplemented with the concept on the spatial distribution of this system in the brain and its principle variability in time [5, 9, 10].

Taking into account the fact that neurons may be elements of two or more systems and be involved in ensuring different types of activities, the behavior of a specific neuron (or a specific region of the brain) would not necessarily be reproduced under changed conditions (which is particularly important when SPS is unbalanced): a neuron can be involved in the provision of other activities, be switched off, or play a different role in ensuring the activity of interest. Probably, during the formation and maintenance of muscle spasticity, different neurons in the brain were reprofiled to ensure this one type of activity. The blockade of the neuromuscular transmission, caused by the injection of botulinum toxin into the spastic muscles, led to a reduction of the pathological afferent and efferent hyperactivity of motor and sensory neuronal circuits. This apparently entailed the functional liberation of the neurons in the CNS, redistribution of their functions for providing other types of activities, and the formation of new interneuronal connections.

In her last papers, Bechtereva [11, 12] noted that, by forming new interneuronal interactions in the brain, the supertask–brain–state of the body positive feedback is achieved. This idea is based on the fact that the state of health of the organs and systems of the body during implementation of an intense intellectual activity, supertask, is maintained at an appropriate level. The results of our clinical observations, pointing to the reprofiling of neurons in an apparent connection with the normalization of the state of muscles, to some extent, confirm the existence of this feedback.

From the standpoint of clinical medicine, it should be noted that extended botulinotherapy in patients in a state of VS and small consciousness should be regarded not only as an effective symptomatic treatment of drug-resistant muscle spasticity but also as a physiologically substantiated and reasonable indirect effect on the CNS, optimizing its functional state and broadening the capabilities of neuroplasticity (mediated neuroprotection).

Our data require a thorough in-depth analysis and further development. The existence of a positive feedback between the brain (with the possibility of neuronal reprofiling) and the body's state broadens the notion of the SPS of the brain and opens new ways for unbalancing SPS both in VS and in other chronic diseases of the CNS.

## CONCLUSIONS

Thus, our data showed an improvement in the functional state of the brain's regions that ensure locomotor, visual, auditory, and higher mental functions as a result of the peripheral reduction of long-term generalized muscle spasticity in patients in the vegetative state.

These results can be understood taking into account the functional variability of neurons: apparently, the reduction of the pathological afferent and efferent hyperactivity of sensory and motor neuronal circuits led to the functional liberation of brain neurons, redistribution of their functions to ensure other activities, and the formation of new interneuronal connections. This reprofiling of the neurons of the brain, associated with changes in the functional state of muscles, can be regarded, to a certain extent, as evidence for the existence of a supertask–brain–state of the body positive feedback.

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