Tenoten in the Therapy of Patients with Moderate Cognitive Impairment

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Tenoten is a new anxiolytic and antidepressant based on antibodies to brain-specific protein S-100B. Experimental studies demonstrated the effect of tenoten on mechanisms of neuronal plasticity and manifestations of higher nervous activity. Tenoten is clinically comparable with amitryptiline, sertraline, and phenazepam, but does not produce potent sedative relaxation effect typical of these drugs. The study demonstrated considerable improvement of the control over brain frontal compartment effector functions. Tenoten is recommended not only at the stage of moderate cognitive impairment, but also in manifest cerebrovascular pathologies characterized by pronounced impairment of the regulatory functions of the frontal compartments of the brain.

Key Words: *tenoten; moderate cognitive disturbances; cerebrovascular diseases*

Tenoten extends the line of drugs based on low-dose antibodies to Ca^{2+}-regulating family of brain-specific proteins S-100 [2]. In the 60s, pilot studies of the nature and physiological role of S-100 protein family showed that it participates in basic functions of the nervous system: maintenance of membrane potential, generation and transmission of nerve pulses, modification of synaptic activity, neuronal plasticity and some manifestations of the higher nervous activity such as learning capacity, memory, and affective volitional functions [11].

The involvement of S-100 family proteins into nervous activity was identified primarily with antibodies to this protein. Being a physiologically active product, the antibodies reflect the dynamics of an internal process and considerably modulated all forms of nervous activity in experimental models and under pathological conditions. The therapeutic and diagnostic functions of antibodies were most pronounced in the analysis of the dynamics of alcohol dependence and autoimmune syndrome.

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This was the first stage in investigations of the functions of anti-S-100 antibodies.

As extension of this trend, the antibodies were used not only as the markers of S-100 functions, but primarily as potential modifiers of nervous activity, *i.e.* potential drugs. The use of the results of fundamental studies of the role and functions of antibodies to one of the most effective Ca^{2+}-regulating proteins and application of the technology of low-dose and ultra-low-dose drugs preparing led to the creation of a new drug Proproten-100 in 2001.

Clinical randomized placebo-controlled double-blind studies of Proproten-100, first recommended as an antiabstinent drug, revealed anxiolytic and antidepressant properties of this preparation [1,3]. After modification of antibody potency ratio (C_{12}+C_{30}+C_{200}) in experimental studies [4] and then in clinical trials, a principally new anxiolytic tenoten was approved and recommended for clinical use.

Experimental analysis of tenoten was carried out *in vitro* and *in vivo* on neuronal structures of various organization levels: organotypic culture of the nervous tissue, cultured brain slices, cultured neuroblastoma C-1300 cells, semi-intact preparation of the nervous system from higher invertebrates, and on the models

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of long-term sensitization and under conditions of alternative choice in animals. The new drug possesses a wide spectrum of activities, the most important of them are antihypoxic effect [6] and desensitizing effect on mechanisms of learning and memory [5,7,11]. Unexpectedly, the preparation exhibited properties of a genetic inductor realizing its desensitizing effect via intracellular signaling Ca^{2+}-dependent MAP/NRK-kinase systems involved into mechanisms of depressions [9].

In the present pilot open non-randomized selective clinical study we analyzed therapeutic efficiency of tenoten in patients with cognitive impairment of vascular genesis.

MATERIALS AND METHODS

The study included 56 ambulatory patients (20 men and 36 women) aging 28-78 years (mean age 56.7±1.3 years) with clinical symptoms of moderate cognitive impairment (MCI). Apart from MCI symptoms (the patients complained of forgetfulness in day-to-day life, impaired "mechanic" memory, excessive tension in solving mental tasks), most patients were characterized by background asthenia (inhibition and lability of mental processes, impairment and rapid exhaustion of attention) and the presence of concomitant psychosomatic and autonomic disorders (hyperhidrosis, palparation, gasp, dizziness, agitation, anxiety, depressed mood). Cognitive deficit developed primarily against the background of chronic cerebral ischemia, in some cases in combination with brain damage aftereffects.

The following criteria developed in Memory Laboratory, Mayo Clinics (Rochester) were used for MCI diagnosis: memory impairment (reported by the patients and their close relatives and colleagues), low indexes of mnestic functions (data of neuropsychological testing), preserved general cognitive potential, the absence of limitations in everyday life, and the absence of dementia (Mini-Mental State Examination Score ≥24).

The patients received 2 tablets of tenoten 3 times a day 30 min before meal or 1 h after meal. The treatment course lasted for 2 weeks. No undesirable effects caused by administration of tenoten were recorded.

All patients signed informed consent for participation in the study.

The presence of focal neurological symptoms and signs was evaluated during standard neurological examination. Clinical diagnosis was confirmed by computer or magnetic resonance tomography and/or duplex scanning of the carotid and vertebral arteries, when possible.

The following tests were used:

- Clock drawing test (CDT) [13];
- Verbal fluency test (VFT) [12];
- Mini-Mental State Examination (MMSE);
- Frontal Assessement Battery (FAB), a method of MCI diagnosis against the background of pathology of the frontal cortex or subcortical structures, when MMSE can be little effective [10];
- Hamilton Depression Rating Scale (HDRS), a differential diagnostic test excluding pseudodementia in depressive patients.

The patients were selected by screening for the presence of cognitive deficit (CDT) and compliance with MCI criteria. The history of the disease and data of clinical examination and neurovisualization were taken into account. Neuropsychological testing (MMSE, FAB, VFT, HDRS) was performed 3 times: before treatment and after 1 and 2 months of tenoten therapy.

We used descriptive and analytic statistical methods, including regression analysis. The parameters were compared using nonparametric Wilcoxon test (for 2 independent samples) and Friedman test (for 3 independent samples); statistical hypotheses were verified using standard criteria (χ^2).

RESULTS

Comparison of MMSE scores by Wilcoxon and Friedman tests revealed significant differences as soon as 1 month after the start of treatment ($p<0.001$, Table 1). The positive dynamics of the mean MMSE score

TABLE 1. Results of Tests before and after Treatment of Patients with MCI (*M±m*)

Term of testing	Mean total score		
	MMSE	FAB	VFT
Before treatment	26.11±2.02	16.61±1.56	17.93±7.30
After 1 month of treatment	26.75±1.76	16.89±1.40	18.86±7.08
After 2 months of treatment	27.36±1.52	17.16±1.09	19.66±7.17

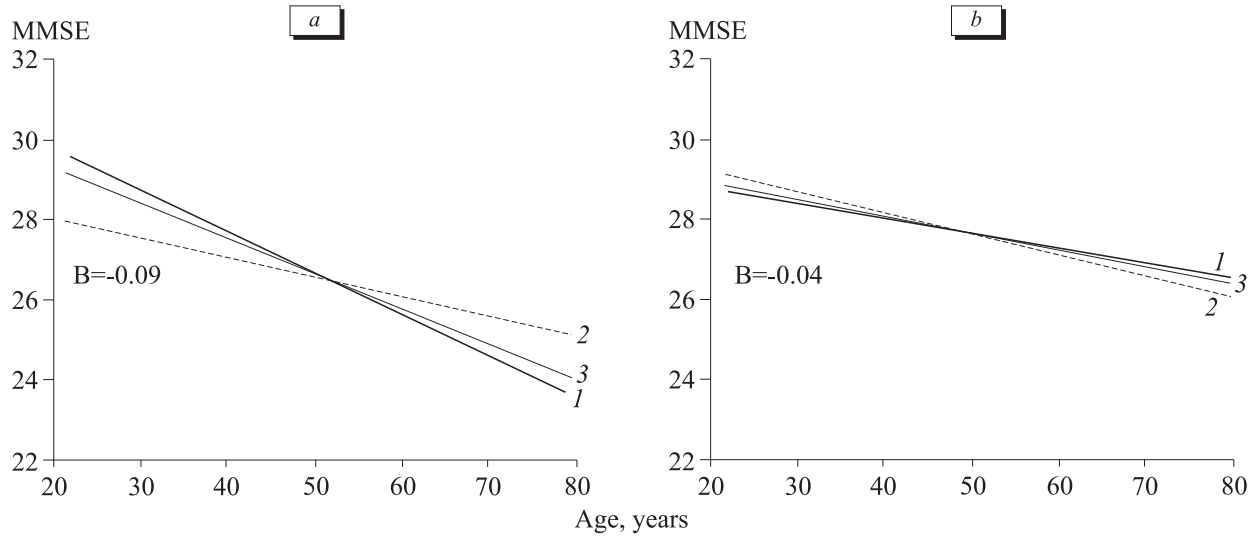

Fig. 1. Regress of the total MMSE score: slope of regression curve before (a) and after treatment (*b*). *1)* women; *2)* men; *3)* total.

was also observed after 2-month treatment with the preparation ($p<0.001$).

Analysis of testing by individual cognitive parameters of MMSE scale revealed significant increase in temporal ($p=0.003$) and spatial ($p=0.001$) orientation scores. No significant changes in other parameters of the cognitive sphere were noted after treatment, except visual spatial perception ($p=0.04$).

The significance of the increase in the total FAB score after 1- ($p=0.03$) and 2-month ($p=0.01$) tenoten treatment was confirmed by comparing the corresponding parameters of the paired samples using Wilcoxon test (Table 1).

Improvement of the regulatory functions of the frontal cortex is confirmed by increased lability and rate of associative processes (VFT) against the background of treatment ($p<0.001$, Table 1).

The regression analysis performed by us clearly demonstrated age-related impairment of cognitive functions (Fig. 1). The regress of the total MMSE score with age was statistically significant both before ($p=0.001$) and after treatment ($p=0.044$), but the slope of the regression curve decreased against the background of treatment. These changes were more pronounced in female patients.

Impairment of cognitive function involves several neurotransmitter systems. The progressive memory impairment is primarily associated with increasing acetylcholine deficit.

According to the theory of dynamic localization of higher nervous functions (A. P. Luriya), the function of the frontal lobes consists in programming of voluntary activity and in control over execution of the selected program. One of the primary symptoms of frontal dysfunction in dyscirculatory MCI is sluggish thinking; the patients spent long time and makes considerable efforts for solving various mental tasks requiring attention mobilization. Difficulties in switching attention from one stage of activity to the other are also typical. However, the patients experience no considerable limitations in day-to-day live and professional activity [9].

Comparison of the rating of cognitive status parameters in patients before and after tenoten therapy revealed significant improvement of the control over effector functions of the frontal cortex of the brain (FAB, $p<0.001$), verbal associations (VFT, $p<0.001$), and the absence of significant changes in consolidated memory parameters (MMSE, $p=0.292$). This proves the positive effects of tenoten of integrative functions of the brain. In light of this, it seems interesting that tenoten administered for a long time produces a more pronounced effect on regulatory functions associated with frontal compartments of the brain and on their relationships with lower structures. Our findings suggest that tenoten can be used not only at the early stages of MCI, but also in the treatment of patients with advanced cerebrovascular pathologies, when impairment of regulatory functions of the frontal cortex became more pronounced. Thus, *in vitro* and *in vivo* studies proved that tenoten exhibits a wide spectrum of psychotropic activities and low toxicity.

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