IMMUNOLOGICAL MARKERS OF LONG-TERM EFFECTS OF TREATMENT IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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The goal of this research was to study the clinical efficacy of course-based neurotrophic therapy in mild cognitive impairment (MCI) and the effect of therapy on immune parameters in patients, and to assess the prognostic value of the dynamics of immune parameters during the year after treatment. 20 patients with MCI receiving intravenous Cerebrolysin (20 infusions of 30 ml with increasing dose during the first four days) were examined. Neuropsychological and immunological examination was carried out immediately before the study, after 3 months., 6 months and after 1 year after the end of treatment. It was found that after therapy, patients had a long-term decrease in the severity of systemic inflammatory response, and that marked signs of systemic inflammation at the beginning of follow-up combined with a persistent decrease in the level of immunoglobulin G in dynamics were prognostic markers of MCI progression. In conclusion, it was shown that neurotrophic therapy has a good clinical effect and has a favorable immunomodulatory effect in aMCI, and the relationship between the dynamics of humoral immunity and systemic inflammation and the risk of progression of cognitive impairment in patients within 1 year after therapy was established.

Keywords: Alzheimer’s disease; immunoglobulin G; mild cognitive impairment; systemic inflammation; IL-8.

Introduction. Amnestic mild cognitive impairment (aMCI) is currently considered as possible earliest clinical stage of Alzheimer’s disease (AD). The risk of dementia in aMCI patients is about 15% per year (Busse et al., 2006). However, in some patients, cognitive disorders are stable or regress: the rate of cognitive recovery in aMCI reaches, according to various data, from 15 to 30% (Palmer et al., 2003). Thus, it is important to search for prognostic markers in aMCI. According to contemporary views, long-term latent activation of the mechanisms of innate immune response in the brain contributes to the progression of neurodegeneration in aMCI (Skaper et al., 2018). The relationship between markers of systemic inflammation and neuroinflammation in the early stages of AD, including aMCI, is being actively studied.

The aim of this work was to research the clinical efficacy of neurotrophic therapy with Cerebrolysin in aMCI, the effect of therapy on immune protection in patients, as well as to assess the prognostic value of the dynamics of immune parameters during follow-up.

Materials and methods. 20 patients (16 female, 4 male, age 54–84 years, mean age 72.6 ± 3.2 years), corresponding to the diagnosis criteria of aMCI (Petersen, Touchon, 2005), and 17 volunteers of the control group, comparable in
age and sex with the main group, were included into
the study. Patients of the main group underwent
1 course of therapy — 20 intravenous infusions of
Cerebrolysin of 30 ml with an increase in the dose
during the first 4 days (5, 10, 20, 30 ml) in 100 ml
of saline. The follow-up was conducted immedi-
ately before the study, after 3 months, 6 months,
and after 1 year after the end of treatment.

Clinical evaluation of the effectiveness was
carried out using neuropsychological scales CG1,
MMSE, MoCA-test. Immunological examination
included assessment of immunoglobulins IgA, IgM,
IgG, cortisol, C-reactive protein (CRP) (Chem-
medic), cytokines IL-2, IL-4, IL-8, TNFα (Vector-
best LLC) by enzyme immunoassay. Microsoft Excel
software was used for statistical processing. For com-
parison of group means student t-test was applied.
Differences were considered significant at \( p < 0.05 \).

**Results and discussion.** It was found that
7 patients who developed dementia or expressed
negative dynamics of cognitive functions in the
dynamics of observation had signs of systemic
inflammatory response in all cases (increase in the
level of C-reactive protein to values above 5 g/l
and increase in the level of 2 and more proinflam-
atory cytokines IL-1β, IL-8, TNFα). At the same
time, out of 13 patients whose cognitive functions
remained stable after 1 year of follow-up, only
7 had signs of systemic inflammation \( p < 0.05 \).
Thus, the presence of systemic inflammation at
the beginning of therapy was prognostically unfa-
vorable in MCI. It was also shown that in patients
who had no clinical effect after 3 months the level
of IL-8 significantly increased at this point. Of the
10 patients whose IL-8 levels were < 25 pg/ml,
9 had a marked clinical improvement after 1 year after treatment and 5 had minimal improvement.
Of the 10 patients who had IL-8 > 25 pg/ml, a
marked improvement was noted in 1, 3 had min-
imal improvement, and 6 had no clinical effect.
Thus, a link was found between an increase in the
level of IL-8 in dynamics and the lack of optimal
effect of therapy. It was also shown that in patients
who had systemic inflammation at the start of ob-
ervation there was a link between changes in the
level of total IgG during observation and cognitive
functions. Patients with aMCI who had no effect
of therapy after 6 months had a decrease in the
level of IgG at this point \( p < 0.05 \) compared to
the initial level. In addition, the decrease in IgG
at 6 months was a marker of further cognitive de-
cline. In the group of 7 patients with cognitive de-
cline after 1 year of follow-up, at 6 months there
was also a decrease in the level of IgG compared
to the beginning of observation \( p < 0.05 \) (Fig. 1).

**Conclusion.** It was found that detection of
signs of systemic inflammation with an increase in
IL-8 level above 25 pg/ml in patients with MCI 3 months after the start of observation was a mark-
er of the absence of favorable short-term dynamics
of cognitive functions during therapy. Progression of cognitive impairment in patients with MCI af-
fter 1 year of follow-up was associated with the
presence of systemic inflammation in combina-
tion with a decrease in the level of total IgG in
dynamics after 6 months and 1 year of follow-up.

**References**

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