NEUROPROTECTION IN CHRONIC BRAIN ISCHEMIA: CLINICAL AND IMMUNOLOGICAL FEATURES

YAKUTKHON MADJIDOVA, DURDONA USMANOVA

Tashkent Medical Academy, Tashkent Institute of Postgraduate Medical Education, Uzbekistan

ABSTRACT

The influence of neuroprotector cortexin with significant immunomodulating, anti-inflammatory, neurotrophic, and neuroprotective effects on subjective and neurological symptoms, as well as immunological parameters (IL-1β, TNF-a) in chronic brain ischemia is shown in the article.

UDC CODE & KEYWORDS

■ UDC: 616 ■ Chronic brain ischemia ■ Proinflammatory cytokines ■ Myelin basic protein ■ Antibody ■

INTRODUCTION

Cerebrovascular disorders are one of the topics of the day in neurology. The special importance they have in the elderly and senile age patients. The significant prevalence of chronic forms of cerebrovascular insufficiency, especially in the patients of older age groups, explains the practical importance of this issue [1,3].

According to Levin et al. (2004), chronic brain ischemia (CBI) or discirculatory encephalopathy (DE) is a syndrome of progressing multifocal or diffusive brain lesion expressing by clinical neurological, neuropsychological and/or cognitive disorders induced by chronic vascular cerebral insufficiency and/or repeated episodes of acute disorders of cerebral circulation [4].

Immunological mechanisms have significant value in the pathogenesis of CBI. At the same time, local inflammation, microcirculatory disorders, damage of hematoencephalic barrier and autoimmune aggression play the leading role in development of neurological deficit in CBI. In the case of autoimmune aggression, some researchers (Gerasimova et al., 2001; Skvortsova et al., 2005) noted the following accompanying signs as loss of immune tolerance, activation of cellular and humoral immunity, resulting in formation and increase of both organ-specific antibodies (antibody to myelin basic protein and nerve growth factors) and organ nonspecific antibodies (anti-DNA) [1, 5]. Proinflammatory cytokines (TNF-α, IL-1β) play the important role in the formation of neurological deficit in CBI that leads to the death of neurons and glia as well as to brain edema, aggravating clinical manifestations of disease. Start and development of the delayed death of neurons are induced by activated microglia which begins to secrete proinflammatory cytokines. They effect on the vascular endothelium and initiate the migration of leucocytes from vascular bed into ischemic brain tissue [2, 6].

The abovementioned data concerning pathophysiological mechanisms of the development of CBI are the evidence for use of new drugs in the comprehensive therapy of CBI. A drug of peptide structure cortexin is proved to be effective agent with specific action on the central nervous system, as well as with nootropic and neuroprotective effects [3].

The purpose of our research was to study clinical-immunological status and efficiency of cortexin in the treatment of patients with CBI (DE) of I-II stages.

Material and methods

We examined 78 patients with CBI (DE) of I-II stages who had been treated in department of neurology of the Sixth Tashkent Clinical Hospital: 36 (46%) males and 42 (54%) females at the average age of 58.3±0.6 years old. The patients were divided into 2 groups: I group included 46 patients who were treated with cortexin, group II consisted of 32 patients receiving only traditional therapy without cortexin. All patients underwent neurological and immunological examinations. Asthenic syndrome was studied on the scale of evaluation of asthenization level; psycho-emotional state was studied on the Spilberger anxiety scale of self-estimation; to study cognitive functions we used the MMSE (Mini-Mental state examination) test; attention and intellectual functions were investigated by the Schulte tables.

The levels of proinflammatory cytokins (IL-1β, TNF-α) were determined by method of immunoenzymatic analysis with use of commercial test-systems “Vector-Best” (Russia, 2010). These test-systems are based on the “sandwich” method of hard-phased immunoenzymatic analysis with use of horse-radish peroxidase as fermentative indicator. The material for examinations was blood serum in dose of 5.0 ml taken from cubital vein in the morning before breakfast. The levels of antibodies to myelin basic protein (MBP) in blood serum were determined by immunoenzymatic method with use of test-system “Navina” (Moscow).

Studies were carried out in dynamics at the 1st and 10th days of treatment. Cortexin was injected in dose of 10 mg intramuscularly in 0.5% solution of novokainum (2.0 ml) once a day within 10 days. The efficiency of cortexin was estimated on the basis of clinical and immunological data.

Statistical analysis of the results obtained was carried out with use of package of applied programs “Statistica 5.5 for Windows”, “Microsoft Office Excel-2003”. Reliability of differences between average values of parameters in groups was estimated with use of Student’s t-test.

Results of research and discussion

Clinical manifestation of CBI (DE) of stage I-II consisted of subjective and objective symptoms. Subjective symptoms were characterized by asthenic syndrome: general weakness, increased fatigue, reduced working activity, emotional liability, anxiety, and attention disorders. Cephalgia syndrome was noted frequently; headaches had character of tension (constricting, compressing, as "small hat") or ischemic-hypoxic (feeling of heavy head and impossibility to concentrate). Objective symptomatology was characterized by high-stem signs (anisocoria, convergence act disorder, symptoms of pyramidal insufficiency), vestibular ataxic syndrome such as dizziness, tottering gait, disorders in conducting coordinator tests. These signs were associated with signs of cognitive dysfunction: disturbances of memory, attention, and slowing thinking process.

Thus, headache was found in 38 (81.4%) patients of group I and in 29 (95.2%) ones of group II. 36 (92.1%) patients of group II and 27 (67.8%) of group I (P<0.001) complained of dizziness (frequently of non-systemic character). Sleep disorders were noted in 36 (83.1%) patients of group I and in 27 (57.1%) from group II (P<0.01), respectively. Noise in ears was observed in 31 (74.6%) patients of group II and in 24 (33.9%) of group I. Among asthenic signs, fatigue was diagnosed in 40 (88.1%) patients of group I and in 24 (60.3%) patients of group II, decreased working activity was registered in 47 (91.5%) and in 28 (66.7%) patients, respectively in groups I and II. Decrease in cognitive functions as memory reduction was revealed in 29 (71.2%) patients of group I and in 29 (90.5%) of group II (P<0.01), reduced attention was found in 38 (88.1%) and 30 (98.4%) patients (P<0.05), respectively.

The study of asthenization level after treatment has shown positive dynamics of parameters by 19.2% in group I receiving cortexin, and by 9.6% in group II receiving traditional therapy without cortexin (P<0.05), respectively.

The average parameters on the MMSE test after treatment noted dynamics of parameters by 9% in group I and by 3.5% in group II (P<0.05), respectively.

The analysis of rate of sensory-motor reactions and attention by the Schulte tables has shown positive dynamics after treatment by 9.2% in group I and only 1% in group II (P<0.01); parameters of emotional-personal spheres by the Spilberger test after treatment revealed dynamics of parameters by 18.8% and 11.1% in group I and II (P<0.05), respectively.

The level of basic proinflammatory cytokin IL-1β in patients of group I before treatment was 14.4±0.8 pg/ml, whereas after treatment – 12.0±0.5 pg/ml (P<0.05). Before treatment this parameter was 2.3 times higher than in control and after treatment 1.9 times. Obviously, this is connected with proinflammatory effect of cortexin (Table).

Table: Parameters of proinflammatory cytokines (IL-1β, TNF-a) in chronic brain ischemia before and after neuroprotection

Group	IL-1β		TNF-a	
	Before treatment	After treatment	Before treatment	After treatment
Control	6.24±0.72		2.15±0.21	
Group I (n=46)	14.4±0.8***	12.0±0.5***^	12.1±0.7***	8.0±0.3***^^
Group II (n=32)	14.9±0.6***	13.4±0.5***	10.4±0.7***	9.2±0.6***

Source: Authors. Notes: * - significant differences to control (*** - P<0.001); ^ - significant differences to parameters before treatment (^ - P<0.05; ^^ - P<0.01)

In patients of group II who received traditional therapy without cortexin the level of IL-1β before treatment was 14.9±0.6 pg/ml, and after treatment 13.4±0.5 pg/ml, the differences were insignificant. The parameter after traditional treatment differed from control in 2.1 times.

The level of TNF-α in peripheral blood of patients of group I before treatment was 12.1±0.7 pg/ml, and after treatment decreased in 1.5 times (8.0±0.3 pg/ml). It was noted TNF-α suppression after therapy with inclusion of cortexin. At the same time, the level of TNF-α before and after treatment was higher than in control in 5.5 and 4 times, respectively. In group II before treatment the level of TNF-α was 10.4±0.7 pg/ml, and after treatment 9.2±0.6 pg/ml, respectively.

Thus, the study of cytokine levels in CBI gives the information about functional activity of various types of immunocompetent cells, allows estimating dynamics of immunopathological process and development of disease.

At the first day of study patients observed high levels of antibodies to MBP (0.202 ng±0.011 un.opt.dens.). The determination of levels of antibodies to MBP at the 10^{th} day of treatment showed that in patients of group I receiving cortexin the this parameter was decreased significantly (P<0.05) and was 0.152 ng±0.02 un.opt.dens. (that is on 32.71% from the initial level). In group of patients receiving only traditional therapy the levels of antibodies to MBP were decreased by 18.6% (0.181 ng ±0.02 un.opt.dens.; P<0.05).

Thus, dynamic study of antibodies to MBP has revealed its reliable decrease after treatment. Decrease in the levels of antibodies to MBP indicated about remyelinization processes, and, consequently, about improvement of neurotrophic maintenance of neurons in the central nervous system as a result of treatment with cortexin.

The results obtained allow making a conclusion that cortexin has immunomodulating, anti-inflammatory and neurotrophic effects.

Thus, the important role in the pathogenesis of CBI (DE) belongs to immunological and neurotrophic mechanisms, in particular local inflammation, microcircular disorders, damage of hematoencephalic barrier and autoimmune aggression [3].

Taking into account subjective and objective neurological symptoms, as well as dynamics of immunological parameters, we achieved satisfactory clinical effect which was characterized by significant regress of neurological symptoms.

Conclusion

1. Cortexin has significant effect on correction of parameters of neuropsychological and cognitive spheres, improving state of patients with CBI (DE) and raising the quality of their life.

2. Cortexin resulted in decrease of the levels of proinflammatory cytokines that specifies its ability to reduce activity of immune inflammation, and also affects on neurotrophic maintenance by decrease of levels antibodies to MBP.

Thus, inclusion of cortexin in comprehensive treatment for CBI is a welcome therapy with significant immunomodulating, anti-inflammatory, neurotrophic, and neuroprotective effects.

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