



EVENT ABSTRACT

Influence of Neuro-Sensory-Motor Reflex Integration Technique on Immune Response of Patients with Herpes-Associated Multiforme Erythema

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Herpes-associated erythema multiforme is the most frequent form and occurs in 50-93% of patients with exudative erythema multiforme (EEM) [6, 8]. Erythema multiforme relapses in at least 30% of patients. A considerable number of causes for the infectious-allergic form of erythema have been detected, and clinical manifestations of infectious herpes are found in about half of patients [7]. The trigger role of herpes simplex virus in the pathogenesis of EEM gives objective reasons to proscribe acyclic nucleosides to such patients [1, 2]. In the literature of the field, one can find statements that the monotherapy of EEM by acyclic nucleosides is not effective enough [4, 5]. In many cases, psycho-emotional stress has a role in precipitating or triggering a herpes simplex relapse which comes prior to HAEM development. Because of what has been said, it appears important to study the connection between the immune system and the nervous system, and to search for new combined methods for adequate therapy to treat herpes-associated erythema multiforme, while taking into account the peculiarities of innate and adaptive functioning of the immune system.

This article uses the MNRI® (Masgutova Neurosensorimotor Reflex Integration®) therapeutic program developed by Dr. S. Masgutova, which includes diagnostic and therapeutic procedures [3].

The purpose of this study is to investigate the effect of the MNRI® therapeutic program on the innate and adaptive immune systems functions, and the peculiarity of cells cooperation in the immune response at the patients with HAEM.

Materials and Methods

In this research, two groups of patients were involved: Control Group-A – 15 healthy individuals (8 males and 7 females, age range of 18-54), and Research Group (B and C) – 31 patients (age range of 25-40 years old) with HAEM.

The duration of the HAEM disease varied from two to ten years with a frequency of relapse of one to two times per year. The laboratory DNA diagnostics identified the herpesviridae virus in these 27 patients.

The research group consisted of two other sub-groups: B) combined MNRI® and standard treatment – 16 patients (7 males and 9 females) and C) only standard treatment – 15 patients (8 males and 7 females).

Results of treatments of patients with HAEM in Group-B MNRI® therapy sessions for 14 days (6-8 hours daily) and standard treatment were compared with results of Group-C (standard treatment only: chemotherapeutic agents – acyclic nucleosides (acyclovir, Zovirax, viroleks, valacyclovir, and famciclovir). The Control Group-A of clinically healthy individuals served as

the criteria of the effect of both therapeutic programs. The patients were observed for one year and were evaluated before and after the MNRI® sessions.

Standard treatment (Group-C) included etiotropic treatment in the form of antiviral chemotherapeutic remedy-acyclic nucleosides (acyclovir, Zovirax, viroleks, valacyclovir, famciclovir). The etiotropic treatment was administered taking into account clinical and laboratory activation indicators of viral infections.

Determining the level of cytokines in the serum/plasma and blood of patients was determined by a flow cytometer Cytomix FC-500 (Beckman Coulter, USA) with the help of the test system Flow Cytomix Th1/Th2 11 plex (e-Bioscience, USA) according to the manufacturer's instructions. Lymphocyte subpopulation structure were determined by using monoclonal antibodies (Beckman Coulter, USA). The content of cells was determined by flow cytometer Cytomix FC-500 (Beckman Coulter, USA).

Results and Discussion

All observed patients were evaluated and measured for immunological function before treatments began. In the whole group the percentage of T-helper CD4+ was on the lower level of normal (38.6%). They also revealed a decrease in the relative number of CD8+ regulatory lymphocytes to 22.2%. In the content of the subpopulation of natural killer-cells, CD16+ changes were observed in the form of increasing to 19.6% (absolute number up – 544.2×10^6 cells/ml. Lymphocytes with CD95+ marker were initially reduced to 34.6%. In peripheral blood lymphocytes of patients, a very low activation level of molecules CD25+ was noticed – 2.4%. The cytokine profile in the blood serum of patients at the beginning of the study showed a reduction of the IL-2 ($9.1 \pm 0.2\%$), IFN- γ ($18.4 \pm 1.1\%$) with increased IL-10 ($51.8 \pm 14.6\%$) in comparison with the healthy subjects.

The failure of IFN- γ in the system of the observed patients showed a lower level in the serum with the reduction of induced production. The patients with induction showed increased production of IL-5 and IL-12 (up to 267.8 ± 55.2 and 6559.3 ± 1798.2 pg/ml, accordingly) that may indicate that there are stored immunocompetent cells to induce switching B lymphocytes to IgA synthesis and activation of antigen-presenting cells.

Results of Treatments

Additionally, all patients, which were the basis for including the MNRI® method into the combined therapy (Group-B) showed impairment of the innate immune system. The goal of including this combined therapy was to correct immunological disorders and subsequent removal of the trigger factor. Our study revealed that the role of the trigger factor in all patients was the reactivation of the viral infection.

As a result of applying the MNRI® therapy, the duration and severity of the disease significantly decreased (14 patients), which coincided with the dynamics of laboratory indicators of the herpes virus infection activation. Two patients also demonstrated similar result, but not on a significant level. In the group of traditional medical treatment (Group-C), only 6 patients demonstrated similar results with lower level of significance.

During the MNRI® test we observed, for example, a consistent significant increase of CD4+ lymphocyte population up to 42.1%, CD8+ up to 27%, and CD25+ up to 3.7% with the CD16+ reduced to a normal range (18.1%) in 14 patients out of 16, and in Group-C non-significant increase of the same lymphocyte population in 5 patients out of 15.

The evaluation of the dynamics of the humoral immunity showed a decrease of IgA levels to normal levels after MNRI® therapy in the same 14 patients. The level of circulating immune complexes, which was significantly higher than normal prior the treatment, tended to decrease. Studying the serum levels of cytokines after the therapy revealed that MNRI® therapy enhanced the lowered baseline level of IL-2 in serum and IFN- γ to a normal level in the same patients of Group-B. Major producers of IL-2 are CD4+ T-lymphocytes. IL-2 causes two principal physiological effects: to induce antigen-dependent proliferation of all types of T-cells and to promote the differentiation of certain functional lymphocyte subpopulations – cytotoxic lymphocyte and regulatory T cells. The principal biological effects of IL-2 signal was stimulation of T-cell and NK-cell proliferation. It is known that the immune defense against viruses is formed with the participation of many mechanisms of innate and adaptive immune systems and is implemented by using four main factors: interferon type I, natural killer cells, cytotoxic T cells, and neutralizing antibodies. Therefore, the tendency of increasing IL-2 during

immunotherapy serves to enhance antiviral protection, and thereby helps to eliminate the trigger factor of the erythema development in the observed patients. IFN- γ is produced by immune T- lymphocytes subpopulations Th1, CD8+ CTLs, and NK- cells. IFN- γ is the most potent activator of macrophages. It also activates NK- cells, and induces the MHC I and MHC II protein cells expression, thereby facilitating antigen presentation (including virus) to T- lymphocytes, which leads to the formation of the antiviral immune response. IFN- γ which is produced by CD8+ cytotoxic T-lymphocytes contributes to the antiviral action of these cells. The MNRI® therapy increased IFN- γ production to the normal level (452.7 pg/ml) and reduced initial elevated levels of induced IL-4 and IL-5 production.

The observed patients initially had nine times higher levels of induced IL-5 production. IL-5 is produced by a subpopulation of immune CD4+ T- lymphocytes and mast cells, and promotes the differentiation and activation of eosinophils. IL-5 is described as a differentiating factor of B- lymphocytes. The increased IL-5 levels in the observed patients on one hand, may have a positive effect. This is accomplished by increasing levels of IgA which helps to increase mucosal defense. On the other hand, a significant increase in IL-5 levels can contribute to the formation of an allergic reaction. Considering that HAEM is a manifestation of a hypersensitivity reaction, reduction of the induced production of IL-5 during the course of therapy has a beneficial efficacy of the MNRI® therapy.

After 12 months of monitoring the patients with HAEM, our research revealed a reduction of 2.7 times in the HAEM relapse rate and, in general, a reduction of clinical symptoms during relapses in Group-B (MNRI® combined with traditional medical treatment). The traditional medical treatment reduced the relapse rate by only 1.5 times. As a result of MNRI® therapy, we saw positive changes in the clinical and laboratory indicators of HSV infection activation, which is reflected in the reduction of herpes simplex relapse and reduction of laboratory indicators of active viruses.

In summary, based on our data, the use of the MNRI® therapeutic program allows correction of damaged mechanisms of the immune system and activation of the mechanisms of innate immunity in patients with HAEM. MNRI® therapy also helps to reduce the severity and duration of herpes simplex relapses by acting to influence the trigger factor and exerting a positive influence on the HAEM pathogenesis.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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