ДИНАМИКА ПОКАЗАТЕЛЕЙ КЛЕТОЧНОГО ИММУНИТЕТА ПРИ КОМПЛЕКСНОМ ЛЕЧЕНИИ ОСТРОГО ОПТИЧЕСКОГО НЕВРИТА

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Резюме. Увеличение частоты развития оптического неврита среди населения трудоспособного возраста, а также неутешительный прогноз для зрения ввиду развития атрофии зрительного нерва определяет высокую социальную значимость данной проблемы. Целью работы является анализ влияния «Имунофана» на показатели клеточного иммунитета и клинические симптомы болезни в комплексном лечении оптического неврита, ассоциированного с герпесвирусной инфекцией. В исследовании приняли участие 37 человек (37 глаз) с острым оптическим невритом, ассоциированным с герпесвирусной инфекцией. Схема лечения включала назначение раствора дексаметазона по убывающей схеме, 1% раствора препарата «Эмоксипин» 0,5 мл и 12,5% раствора препарата «Дицинон» 0,5 мл через ирригационную систему, имплантированную в ретробульбарное пространство, в комбинации с назначением лекарственных средств нейропротекции («Пикамилон» и «Семакс») в течение 10 дней. Все пациенты были разделены на 2 группы. Основная группа – 20 пациентов, которым в схему лечения был добавлен препарат «Имунофан». Группа сравнения – 17 пациентов, лечение которых проводили только по вышеописанной методике. Курс лечения составил 10 дней. Анализ данных продемонстрировал более значимую положительную динамику показателей клеточного иммунитета, получавших иммунотерапию. Наши исследования показали эффективность данного препарата в комплексном лечении оптического неврита, ассоциированного с герпесвирусной инфекцией, что подтверждено ускорением купирования воспаления, более значимым повышением зрительных функций у пациентов, получавших «Имунофан», и меньшим процентом развития атрофии зрительного нерва. В этой группе пациентов в более ранние сроки произошли и оставались стабильными на протяжении всего срока наблюдения изменения показателей клеточного звена иммунитета. По нашим данным, меж-

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групповая оценка иммунорегуляторного индекса показала его более быстрое нарастание у пациентов группы сравнения, получавших препарат «Имунофан», и достигала нормальных значений уже спустя 6 месяцев после лечения. Клиническая эффективность препарата «Имунофан» в комплексной терапии оптического неврита, ассоциированного с герпесвирусной инфекцией, характеризовалась сокращением сроков купирования признаков воспаления в зрительном нерве в 2 раза и более, увеличением максимально корригированной остроты зрения 4,5 раза, снижением частоты возникновения рецидивов оптического неврита в 2 раза при сроках наблюдения 12 месяцев.

Ключевые слова: оптический неврит, герпесвирусная инфекция, кортикостероидная терапия, иммуномодулирующая терапия, показатели клеточного иммунитета, имунофан

DYNAMICS OF CELLULAR IMMUNITY INDICATORS IN THE COMPLEX TREATMENT OF ACUTE OPTIC NEURITIS

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Abstract. An increase in the incidence of optic neuritis among the working-age population, as well as an unpromising prognosis for vision due to the development of optic nerve atrophy, determines the high social significance of this problem. The aim of the work is to analyze the effect of Imunofan at the parameters of cellular immunity and clinical symptoms of the disease in the complex treatment of optic neuritis associated with herpes virus infection. The study involved 37 people (37 eyes) with acute optic neuritis associated with herpes infection. The treatment regimen included the appointment of a dexamethasone solution according to a decreasing scheme, a 1% solution of the drug Emoxipin 0.5 mL and a 12.5% solution of the drug Dicynone 0.5 mL through an irrigation system implanted in the retrobulbar space, in combination with the neuroprotection drugs (Pikamilon and Semax) for 10 days. All patients were divided into 2 groups. The main group consisted of 20 patients who received Imunofan to the treatment regimen in addition. The comparison group included 17 patients who were treated only according to the method described above. The course of treatment lasted 10 days. The analysis of the data showed a more significant positive dynamics of cellular immunity parameters in those who received immunotherapy. Our studies showed the effectiveness of this drug in the complex treatment of optic neuritis associated with herpes infection, what is confirmed by the acceleration of inflammation relief, a more significant increase in visual functions of patients treated with Imunofan, and a lower percentage of optic nerve atrophy. In this group of patients, changes in the parameters of the cellular link of immunity occurred earlier and remained stable throughout the entire period of observation. According to our data, an intergroup assessment of the immunoregulatory index showed its faster increase in patients of the comparison group who received Imunofan, and reached normal values already 6 months after treatment. The clinical effectiveness of Imunofan in the complex therapy of optic neuritis associated with herpes infection was characterized by a reduction in the period of relief of signs of inflammation in the optic nerve by 2 times or more, by an increase in the maximum corrected visual acuity by 4.5 times, and by a decrease in the incidence of recurrence of optic neuritis by 2 times over a 12 months observation period.

Keywords: optic neuritis, herpes virus infection, corticosteroid therapy, immunomodulatory therapy, indicators of cellular immunity, imunofan

Introduction

According to the literature, optic neuritis (ON) reaches 30-40% in the structure of inflammatory diseases of the visual pathway [1]. An increase in the incidence of ON among the working-age population and a disappointing prognosis for vision due to the development of optic nerve atrophy (ONA) determines the high social significance of this problem [1].

Along with CNS diseases, including autoimmune damage to the optic nerve, acute and chronic bacterial and viral infections, including herpesvirus infection (HVI) [5, 6, 10, 11], are of great importance in the etiology of ON.

HVI causes changes in the systemic and local immune status, which is determined by the characteristics of the antigenic structure of the pathogen, the level of antigenic load, the production of antibodies, and the rate of elimination of the antigen by the immune system.

Glucocorticoid therapy is the main and rapid way to block immune-mediated inflammation mechanisms in the optic nerve, but at the same time it can lead to a weakening of the immune defense and increased replication of the herpes simplex virus [3, 4, 13].

In connection with the immune imbalance, the possible formation of resistance to antiviral chemotherapy, most authors adhere to the principles of complex treatment for ophthalmic herpes and the appointment of etiotropic chemotherapy and immunocorrective therapy [4, 8, 9].

The aim of the work is to analyze the effect of Imunofan in the complex treatment of ON associated with HVI at the parameters of cellular immunity and clinical symptoms of the disease.

Materials and methods

We examined 37 people (37 eyes) with acute unilateral ON associated with HVI, aged 17 to 36 (average 26.5) years. Inflammation of the optic nerve proceeded in the form of intraocular neuritis.

The clinical study did not include patients with ON within the background of multiple sclerosis and other neurodegenerative diseases of the CNS, Devic's disease and severe concomitant somatic diseases.

According to the results of laboratory serological studies of blood serum by ELISA method in the process of clarifying the etiological diagnosis of ON IgM antibodies to herpes simplex virus were identified in 23% of cases, in all 37 patients HVI was confirmed with an increase in the titer of IgG antibodies to herpes simplex virus by 4-5 times.

The avidity index of IgG antibodies at the time of admission to the hospital in 23 (61.5%) patients with ON was 31-49%, which indicated that they had a late stage of primary infection; in the remaining 14 patients (38.5%) the avidity index IgG antibodies ranged from 56 to 72% and indicated a chronic persistent HVI.

The standard treatment regimen included the introduction for 10 days through an irrigation system implanted in the retrobulbar space of Dexamethasone solutions in a decreasing pattern (course dose of 60 mg), 1% solution of Emoxipin 0.5 mL and 12.5% Dicynone 0.5 mL [13].

Antiviral chemotherapy with Acyclovir (orally 0.4 mg 5 times a day) was prescribed 2-3 days after receiving positive laboratory results of the study for the presence of HVI. In 7 patients with concomitant chronic inflammatory pathology of the upper respiratory tract, the treatment was supplemented with intravenous injections of the antibiotic Ciprofloxacin 100 mg daily for 7 days.

The patients were divided into 2 observation groups: the 1st main group (n = 20), which standard treatment was supplemented by intramuscular injections of Imunofan 50 mcg daily for 10 days. 2nd comparison group (n = 17), which patients received standard treatment without Imunofan. The formed groups were comparable in terms of sex, age, severity of the inflammatory process in the optic nerve ($p > 0.05$).

Ophthalmological examination methods included: visometry (sign projector Carl Zeiss Jena, Germany); ophthalmoscopy (indirect non-contact lens with a lens of 90 diopters) with the calculation according to the severity of the clinical signs of the inflammatory process in the optic nerve in scores of the total clinical inflammation index (TCII), which is characterized by a score of the degree of severity of the ophthalmoscopy picture (0 – no symptom; 1 – mild; 2 – moderately expressed; 3 – sharply expressed); static computer perimetry (Humphrey, Germany). The morphological status of the optic disc (OD) was studied by optical coherence tomography (OCT) (Cirrus HD-OKT 4000, Carl Zeiss Meditec AG, Germany), the thickness of the peripapillary retinal nerve fiber layer (RNFL) was measured.

Immunophenotyping of lymphocytes was performed with an assessment of $CD3^+$, $CD4^+$, $CD8^+$, $CD22^+$. The studies were carried out on the basis of the Research Institute for the Protection of Motherhood and Childhood in Khabarovsk. The results of an immunological blood test, obtained at the regional blood transfusion station in 20 healthy people who donated blood for the first time, were taken as normal indicators.

Cellular immunity testing was performed before the start of treatment, 1.5 months after treatment, then after 6 and 12 months of observation.

Statistical analysis of the obtained results was carried out using the computer program Microsoft Excel with the identification of the significance of the difference according to the Student's criterion.

Results and discussion

When evaluating the results of immunoenzymatic typing of lymphocytes in patients of both groups, a deficiency in the absolute and relative content of $CD3^+$ lymphocytes and $CD4^+$ lymphocytes was initially determined. In turn, most of the examined patients (75%) had an increase in the absolute and relative content of $CD8^+$ and $CD22^+$ lymphocytes.

Comparative dynamics of clinical-functional and morphometric parameters in patients with ON with various treatment methods is shown in Table 1.

Analysis of the data presented in Table 1 showed that after 10 days of inpatient treatment, more sig-

nificant positive dynamics was noted in the clinical course of ON in patients of the main group. Thus, the best corrected visual acuity (BCVA) by this observation period increased by 4.5 times against the initial one, while in patients of the comparison group it increased only by 3.25 times ($p < 0.05$).

In the comparison group, 10 days after treatment, the thickness of RNFL was 116.32±4.51 μm, which is statistically significantly higher than that of the main group – 96.5±3.4 μm ($p < 0.05$).

One month after treatment, in patients of the main group, the RNFL thickness indicator reached values that was not significantly different from that of the intact eye ($p > 0.05$), while in the comparison group, only by the 3rd month of observation. At the same time, it should be noted that in 4 patients of the comparison group, by the 3rd month of observation, the thickness of the RNFL tended to decrease by 10-15 μm compared with the intact eye, which indicated the development of partial optic nerve atrophy (ONA).

A more rapid completion of the inflammatory process in the optic nerve in patients of the main group compared to the comparison group was also evidenced by the dynamics of the decrease in TCII. So, after 1 month of observation, TCII in patients who did not receive immunotherapy still remained on average level of 4.5±0.1 points, in patients of the main group, TCII was significantly lower (1.9±0.1 points), while after 2 months after treatment, clinical signs of inflammation of the OD were already completely absent in patients of both observation groups.

At the end of 12 months after treatment, the majority of patients (85%) of the main group had stable results. Only 1 patient in this group showed a trend towards a decrease in BCVA by 0.1-0.2 of the previously achieved level. Ophthalmoscopically, these patients were diagnosed with decoloration of the temporal half of the OD, according to OCT, a decrease in the thickness of RNFL by 8-10 μm, which was regarded by us as evidence of the development of postneuritic partial ONA, which was later confirmed by the results of electrophysiological studies.

In the comparison group, 12 months after treatment, partial ONA occurred in 4 cases (23.5%), which was supported by the data of ophthalmoscopy, OCT and electrophysiological studies. This condition was accompanied by a decrease in BCVA by 0.2-0.4 from the previously achieved level. Only one patient in the comparison group had a relapse of ON and one case of acute ON in the fellow eye in the absence of such cases in the main group.

Table 2 shows the indicators of cellular immunity of patients in groups.

Analyzing the data in Table 2, it can be seen that in patients with OH who received Imunofan as part of complex treatment, the indicators of cellular immunity normalized already 6 months after treatment and remained stable throughout the entire observation period, while in patients who did not receive immunotherapy, data results were achieved only 12 months after treatment. Intergroup assessment of the immunoregulatory index showed its faster increase in patients of the main group.

An analysis of the literature data points to the huge role of the herpesvirus family in the development of human infections common in nature [2, 4, 9, 10, 12].

The etiological role of HVI in the occurrence of ON is insufficiently presented in the ophthalmological literature, which significantly limits the possibilities of effective therapy. There is an opinion that in patients with infectious and inflammatory diseases of herpetic etiology, due to concomitant secondary immunodeficiency, antiviral chemotherapy without restoring the adaptive-compensatory capabilities of the immune system is ineffective. In such clinical situations, according to researchers, a positive result

TABLE 1. DYNAMICS OF FUNCTIONAL AND MORPHOMETRIC INDEXES IN DIFFERENT METHODS OF IMMUNOTHERAPY, M±m

Index	Before treatment	After treatment				Intact eye control
		10 days	1 month	3 months	12 months	
Main group, n = 20 people						
BCVA	0.16±0.02	0.63±0.02	0.72±0.03	0.75±0.02	0.77±0.03	1.00±0.05
Thickness of PRNFL, μm	129.5±5.5	96.5±3.4*	92.3±2.1*	88.5±5.2*	87.2±5.1	87.5±5.6
TCII, points	13.1±0.3	3.7±0.2*	1.9±0.1*	–	–	
Comparison group, n = 17 people						
BCVA	0.14±0.02	0.52±0.05*	0.65±0.01*	0.72±0.05	0.71±0.03	1.00±0.05
Thickness of PRNFL, μm	130.7±3.3	116.32±45.00	110.0±3.2	90.1±4.9	87.3±3.2	87.5±5.6
TCII, points	13.2±1.4	6.5±0.1	4.5±0.1	–	–	

Note. *, reliability of intergroup differences $p < 0.05$; BCVA, best corrected visual acuity; PRNFL, peripapillary retinal nerve fiber layer; TCII, total clinical inflammation index.

TABLE 2. INDEXES OF CELLULAR IMMUNITY OF PATIENTS DEPENDING ON THE THERAPY

Index	Before Treatment	After treatment			Control group
		1.5 months	6 months	12 months	
Main group, n = 20 people					
T lymphocytes (CD3), %	61.95±0.08#	68.72±0.71*	68.98±0.34*	68.88±0.11*	70.02±1.41
T helpers (CD4), %	30.25±0.16#	33.01±0.14#	38.01±0.32*	37.82±0.10*	38.41±1.22
T cytotoxic (CD8), %	27.91±0.02#	25.99±0.05*	24.97±0.02#	25.72±0.07	25.94±0.05
IRI	1.05±0.01#	1.38±0.02#	1.45±0.01*	1.44±0.02	1.46±0.05
Comparison group, n = 17 people					
T lymphocytes (CD3), %	61.28±0.04#	64.21±0.29* #	65.04±0.09* #	65.91±0.04* #	70.02±1.41
T helpers (CD4), %	31.06±0.23#	33.16±0.32#	34.23±0.19* #	33.70±0.06* #	38.41±1.22
T cytotoxic (CD8), %	28.00±0.08#	26.40±0.02*	24.21±0.03* #	25.28±0.03	25.94±0.05
IRI	1.19±0.21#	1.22±0.01* #	1.37±0.01* #	1.35±0.02	1.46±0.05

Note. *, statistically significant differences between the compared groups; #, statistically significant differences from the control group, $p < 0.05$; IRI, immunoregulatory index.

of antiviral etiotropic therapy can only be guaranteed by immunomodulatory therapy [4, 8, 10, 11].

There are a few works in the literature concerning the use of Imunofan in ophthalmology in the treatment of endogenous uveitis in adults [6] and children. However, we have not found any works on the use of Imunofan in the treatment of patients with optic neuritis of HVI etiology in the available literature.

Our studies have shown the effectiveness of this drug in the complex treatment of ON associated with HVI, which was confirmed by the acceleration of inflammation relief, a more significant increase in visual functions in patients treated with Imunofan, and a lower percentage of ONA. In this group of patients, changes in the parameters of the cellular link of immunity occurred earlier and remained stable throughout the entire period of observation. According to our data, an intergroup assessment of the immunoregulatory index showed its faster increase in patients of the comparison group who received Imunofan, and reached normal values already 6 months after treatment.

Conclusion

The clinical effectiveness of Imunofan in the complex therapy of ON associated with HVI was characterized by a reduction in the period of relief of inflammation signs in the optic nerve by 2 times or more, by an increase in the BCVA by 4.5 times, and by a decrease in the incidence of recurrence of ON by 2 times over a 12 months observation period.

Restoration of cellular immunity indicators was detected already by the 3rd month of observation.

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