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Effectiveness of Use of Immunomodulators in the Treatment of Episcleritis in Children and Adolescents with Tuberculosis

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Abstract The authors consider the effectiveness of use of immunomodulators in the treatment of episcleritis in children and adolescents with tuberculosis. It was found that in preschool children (4-6 years old), the effects of the use of immunomodulators were statistically insignificant both in comparison with the initial levels and relatively to the control group. Significant changes in indicators were detected starting from the age of 7-10 years old and with increasing age the effects were consistently reliable. Gender differences in the levels of indicators in different age groups and for various characteristics are not unambiguous, but higher levels of indicators were more often observed in girls compared to boys, while differences in indicators before and after the treatment were more pronounced in boys. From the above it follows that the use of immunomodulators, taking into account individual sensitivity in children and adolescents with tuberculosis for the treatment of episcleritis, is advisable and leads to normalization of pro- and anti-inflammatory interleukins.

Keywords Children, Adolescents, Episcleritis, Tuberculosis, Interleukins, Immunomodulators

1. Introduction

Episcleritis is a disease in which the connective layer between sclera and conjunctiva (episclera) becomes inflamed. The pathogenesis of episcleritis is unknown [1,5]. It is assumed that the immune system plays a decisive role in the pathogenesis of this pathology [2]. Multiple data point to likely antigenic stimuli in scleral lesions [3].

Most cases of episcleritis are associated with autoimmune diseases. However, it is still unknown whether the innate or adaptive immune system plays a predominant role in idiopathic forms of these diseases [4].

Tuberculosis may be the only systemic association with episcleritis and scleritis [5].

Purpose of the study: to study the effect of immunomodulators on the course of episcleritis by changing the immunological parameters of tears in children and adolescents with tuberculosis.

2. Material and Methods of the Research

80 children and adolescents with episcleritis, suffering from tuberculosis, who were treated at Andijan regional anti-tuberculosis dispensary, were examined. The children ranged in age from 4 to 17 years old. All children were divided by age into 4 groups: 4-6 years old, 7-9 years old, 10-14 years old and 15-17 years old. There were 10 boys and 10 girls in each age group. As a control group, children of the same age groups and gender ratio with tuberculosis, but without any inflammatory eye diseases, were examined.

To identify the peculiarities of changes in local immunological parameters in the composition of the tear fluid, an ELISA study was carried out for pro-inflammatory interleukin - tumor necrosis factor (TNF-α) and anti-inflammatory - interleukin 10 (IL-10) using test systems from Vector-Best JSC, Russia, also transforming growth factor-β1 (TGF-β1) using test systems "DRG" Germany. In addition, protease inhibitors α-1-anti-trypsin and α-2-macroglobulin were determined using test systems “Sentinel” Italy.

The day before tear collection, patients did not receive any drops. Before collecting tear fluid, lacrimation was induced (they were given a cut onion to smell). Tear fluid was collected immediately with sterile disposable glass capillaries from the inferior conjunctival fornix into a sterile, labeled Eppendorf. In the same way, tear fluid was collected from the conjunctival cavity and the other eye simultaneously. The manipulation was carried out until 1.0 ml of tear fluid

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accumulated in the Eppendorf. The obtained material was stored in the freezer at the temperature of -20.0℃ until the stage of laboratory research.

The choice of immunomodulator for treatment was made after determining individual sensitivity to immunomodulators. The study was carried out on lymphocytes isolated from blood taken from the antecubital vein of patients. To determine the sensitivity of lymphocytes to immunomodulators, the so-called "stress test" was carried out using the studied drugs, according to the change of the functions of E-rosette formation. Sensitivity to the drugs most often used in pediatric clinical practice was determined: cycloferon, thymalin, immunomodulin, immunal, interferon, polyoxidonium.

Statistical processing was carried out using the method of variation statistics with the calculation of average values and their average errors, as well as relative values and determination of the reliability coefficient of the difference between the compared Student-Fisher values (t). Differences were considered statistically significant at $p<0.05$ or less.

3. Results and Its Discussion

To identify the characteristics of changes in local immunological parameters in the composition of the tear fluid, the study of TNF-α and IL-10, TGF-β1 was carried out. Each patient examined, taking into account the maximum indicator of individual sensitivity, was prescribed appropriate immunomodulator internally for the treatment. Oftalmoferon was used topically, daily, by instilling 2 drops into the affected eye 3 times a day for 30 days, until the symptoms of the disease disappeared.

The children were divided by age into 4 groups: 4-6 years old, 7-9 years old, 10-14 years old and 15-17 years old, 10 boys and 10 girls.

Studies have shown that in boys aged 4 to 6 years old, suffering from tuberculosis with episcleritis, the result of TNF-α in the tear fluid before the treatment was not significantly higher compared with the same indicator without episcleritis and amounted to 156% relatively to it (Table 1).

After the treatment with immunomodulatory drugs, the level of TNF-α did not significantly decrease, but remained higher compared to the same level without episcleritis. Moreover, the TNF-α value after the treatment was 117% relatively to the control group. These changes indicate the absence of significant decrease in TNF-α under the influence of treatment with immunomodulators in children aged 4 to 6 years old suffering from tuberculosis with episcleritis. At the same time, in the same age group of girls, the level of TNF-α before the treatment was significantly higher than in the control group and amounted to 142%. After the treatment with immunomodulators, the indicator decreased statistically insignificantly, but was not significantly higher compared to the results in the absence of episcleritis, reaching 122%. These results indicate more intense increase in TNF-α in boys than in girls, and that the effect of immunomodulators on this indicator was not significantly greater. Based on the results of average TNF-α values in both sexes, the value of this indicator after the treatment was 120%, while before the treatment their ratio was 148% (Table 1).

In boys aged 4-6 years old with episcleritis suffering from tuberculosis, the IL-10 indicator after the treatment with immunomodulators was 77% relative to the group without episcleritis. After the treatment with immunomodulators, the level of IL-10 increased unreliably, but also remained unreliably lower than the group of children without episcleritis, their ratio was 65%. These results indicate a slight increase in IL-10 in tear fluid under the influence of immunomodulators in boys aged 4-6 years old suffering from tuberculosis with episcleritis. On the contrary, in this group of girls the level of IL-10 was 82% after the treatment and 73% before the treatment relatively to the control group. These changes indicate that the effect of immunomodulators in terms of IL-10 in boys is not more pronounced than in girls. When considering the mean values for boys and girls, the post-treatment and pre-treatment ratios to control scores were 80% and 70%, respectively.

At the same time, in the study of TGF-β1 in boys aged 4-6 years old, suffering from tuberculosis with episcleritis, it was found out that in boys this indicator before the treatment was 68% relatively to the control, but after the treatment under the influence of immunomodulators it increased and amounted to 85% relatively to the control. These results indicate that in boys aged 4-6 years old suffering from tuberculosis with episcleritis, under the influence of immunomodulators, there is an unreliable increase in TGF-β1. In addition, in this group of girls, the level of TGF-β1 after the treatment was 84% relatively to the control group, which was not significantly higher than before the treatment (70%). The average TGF-β1 value for both sexes was 69% before the treatment and 85% after the treatment relatively to the control group (Table 1).

During the study, the boys aged 7 to 9 years old suffering from tuberculosis with episcleritis showed a higher level of TNF-α in the tear fluid compared to the boys of the same age without episcleritis; their ratio was 161%. After the treatment with immunomodulators, the ratio of TNF-α levels to the control group decreased to 126%. The differences in indicators before and after the treatment were not statistically significant. However, in girls, the level of TNF-α after the treatment with immunomodulators significantly decreased relatively to the initial level ($p < 0.05$), but remained high, amounting to 113% compared to the control group, while the ratio of the initial level to the control group was 153%. This indicates that the effects of immunomodulators in reducing TNF-α are more pronounced in girls than in boys. When analyzing the average TNF-α values in all children of both sexes after the treatment with immunomodulators, the level decreased statistically significantly ($p<0.05$), and the ratio to the control group was 118%. The baseline to control ratio was 155%. These results indicate that immunomodulators are effective in reducing TNF-α levels in children suffering from tuberculosis with episcleritis, with the effect being more pronounced in girls.

Table 1. Changes in the indicators of pro-inflammatory (TNF-α), anti-inflammatory (IL-10) interleukins and TGF-β1 in the tears of children of the examined groups

Age groups	Indicators studied	Comparison groups	Boys	Girls	Total
4-6 years old	TNF-α pg/ml	1	3,6±0,31	4,6±0,39	4,1 ±0,35
		2	5,6±0,62*	6,5±0,79*	6,1±0,58*
		3	4,2±0,39	5,6±0,47	4,9±0,38
	IL-10 pg/ml	1	4,4±0,38	4,8±0,44	4,6±0,32
		2	2,8±0,25*	3,5±0,29*	3,2±0,21*
		3	3,4±0,27	3,9±0,33	3,7±0,25
	TGF-β1 ng/ml	1	39,8±3,5	34,7 ±3,1	37,3±2,8
		2	27,1±2,4*	24,3±1,9*	25,7±1,6*
		3	33,8±2,6	29,1±2,4	31,5±2,2
7-9 years old	TNF-α pg/ml	1	3,8 ±0,35	4,5±0,43	4,2±0,31
		2	6,1±0,57*	6,9±0,66*	6,5±0,52*
		3	4,8±0,44	5,1±0,46 **	4,9±0,41**
	IL-10 pg/ml	1	5,1±0,44	4,7±0,42	4,9±0,37
		2	3,0±0,28*	3,1±0,29*	3,1±0,23*
		3	4,1±0,38 **	4,0±0,35	4,1±0,32
	TGF-β1 ng/ml	1	43,9±3,7	49,4±4,2	46,7±3,1
		2	27,2±2,5*	32,1±2,9*	29,7±2,1*
		3	39,9±3,4 **	43,5±3,8**	41,7±3,2**
10-14 years old	TNF-α pg/ml	1	4,5±0,41	5,7±0,53	5,1±3,6
		2	8,4±0,81*	9,2±0,84*	8,8±0,75*
		3	7,0±0,61	6,2±0,58 **	6,6±0,59 **
	IL-10 pg/ml	1	5,4±0,49	4,9±0,46	5,2±0,39
		2	2,5±0,21*	2,9±0,26*	2,7±0,18*
		3	4,6±0,42 **	4,4±0,39 **	4,5±0,37**
	TGF-β1 ng/ml	1	54,1±5,1	47,7±4,3	50,9±3,9
		2	28,1±2,4*	27,1±2,2*	27,6±2,1*
		3	51,9±4,5**	44,8±4,1**	48,4±3,8**
15-17 years old	TNF-α pg/ml	1	4,8±0,39	4,1±0,36	4,5±0,32
		2	8,1±0,77*	6,5±0,58*	7,3±0,41*
		3	5,7±0,54**	4,7±0,42 **	5,2±0,40**
	IL-10 pg/ml	1	5,7±0,56	5,1±0,48	5,4±0,43
		2	3,1±0,23*	3,3±0,25*	3,2±0,17*
		3	4,7±0,42 **	4,5±0,41**	4,6±0,38**
	TGF-β1 ng/ml	1	58,4±5,3	53,4±4,8	55,9±3,4
		2	34,5±2,9*	33,6±2,7*	34,1±2,1*
		3	53,7±4,8 **	49,7±4,5**	51,7±4,2 **

Note: 1 – control group; 2 – patients with chronic episcleritis before the treatment;
3 – patients with chronic episcleritis after the treatment.
*- values significantly different from those of the control group.
**- significantly different values before the treatment to values after the treatment.

At the same time, the results of study of interleukin IL-10 in the boys aged 7-9 years old suffering from tuberculosis and episcleritis before the treatment were not significantly lower than those of boys without episcleritis, their ratio was 58%. After the treatment with immunomodulatory drugs, the rate was 81% relatively to the control group. After the treatment with immunomodulators, there was a significant increase in IL-10 ($p < 0.05$). The results obtained showed a significant increase in IL-10 in the tear fluid under the influence of immunomodulators in the boys aged 7-9 years old suffering from tuberculosis with episcleritis. At the same time, in this age group of girls, the IL-10 indicator after the treatment was 86%, which is not significantly higher than before the treatment - 67% relatively to the control group.

According to these results, the effect of immunomodulators was not significantly greater in boys than in girls. According to the average results for boys and girls, the IL-10 index after the treatment was 83%, which was also slightly higher than before the treatment - 63% relatively to the control group.

Meanwhile, in the study of TGF-β1 in the boys aged 7-9 years old suffering from tuberculosis with episcleritis, receiving immunomodulators, it was found out that the average value was significantly and reliably higher compared to the results before the treatment ($p < 0.05$). Regarding the group of children without chronic episcleritis, the TGF-β1 indicator in children of the main group was 62% before the treatment, and after the treatment the indicator was 91%. These changes indicate a significant increase in TGF-β1 under the influence of immunomodulators in the boys aged 7-9 years old suffering from tuberculosis and episcleritis. On the contrary, in the same age group of girls, all indicators were higher than those of boys, but their dynamics after the treatment coincided with the dynamics in boys - the indicator increased statistically significantly ($p < 0.05$). Relatively to the control group, the rate after the treatment was 88%, whereas before the treatment it was 65%. When examining the average level of TGF-β1 in boys and girls, it was found out that after the treatment the indicator was 89% relatively to the control group, which was also significantly higher than the ratio of indicators before the treatment, which was 64% (Table 1).

The study of interleukins in children aged 10-14 years old revealed that in boys suffering from tuberculosis with episcleritis, the result of TNF-α content in the tear fluid before the treatment was significantly higher than in children of the same age without episcleritis ($p<0.01$), and their ratio was 186%. After the treatment with immunomodulatory drugs, the indicator did not significantly decrease, but remained higher than in children of the same age without episcleritis, their ratio was 156%. These changes indicate a slight decrease in TNF-α under the influence of treatment with immunomodulators in boys aged 10-14 years old suffering from tuberculosis with episcleritis. At the same time, in girls of this group, after the treatment with immunomodulators, the level of TNF-α significantly decreased compared to the level before the treatment ($p <0.01$). The initial level of TNF-α in girls was significantly higher compared to the level of girls of the same age without episcleritis, their ratio was 161%. The indicator after the treatment decreased almost to the level of the control group and its ratio to the control was 109%. These results indicate that the level of TNF-α before the treatment relatively to the control group was higher in boys than in girls, but the effect of immunomodulators on this indicator was more significant in girls. According to the results, taking into account the average values of TNF-α in boys and girls, the ratio of the indicator after the treatment to control was 129%, and before the treatment - 173%. The decrease in TNF-α after the treatment was significant in comparison with the level before the treatment ($p<0.05$).

In the boys suffering from tuberculosis with episcleritis aged 10-14 years old, the level of IL-10 after the treatment with immunomodulators was 85% relatively to boys without episcleritis, and significantly higher than the result before the treatment ($p <0.05$), the ratio of which to the control was 46%. The results obtained indicate that the content of IL-10 in the tear fluid in boys with tuberculosis and episcleritis aged 10-14 years old was significantly increased under the influence of immunomodulatory drugs. At the same time, in this group of girls, the IL-10 result after the treatment was at the level of 90% relatively to the control group, which was significantly higher than the ratio of the indicator before the treatment to the control (59%). The increase in the indicator after the treatment with immunomodulators was statistically significant ($p <0.05$). These data indicate that the effects of immunomodulators in boys and girls are not significantly different. At the same time, the average indicator after the treatment in boys and girls was 87% relatively to the control group, while the ratio of the indicator before the treatment to control was 52% (Table 1).

The study of the level of TGF-β1 in children suffering from tuberculosis and episcleritis aged 10-14 years old showed that it was significantly higher in boys after the treatment with immunomodulatory drugs compared to the level before the treatment ($p <0.001$). The initial indicator was significantly lower than that of boys without episcleritis ($p <0.001$). Their ratio was 52%. After the treatment, the indicator significantly increased ($p <0.001$), its ratio to the control was 96%. This indicates that the use of immunomodulators contributes to significant increase in the level of TGF-β1 in boys suffering from tuberculosis with episcleritis aged 10-14 years old. In the same age group of girls, the TGF-β1 result after the treatment also significantly increased ($p<0.01$) and amounted to 94% relatively to the control group. Whereas before the treatment the ratio of the indicator to the control was 57%. Moreover, the changes were slightly less than in boys. When examining the average level of TGF-β1 in boys and girls combined, the result after the treatment was significantly higher ($p <0.001$) and was 95% relatively to the control group. The ratio of the indicator before the treatment and control was 54% (Table 1.)

In the study of children aged 15-17 years old, the result of the TNF-α content in the tear fluid after the treatment with immunomodulatory drugs in boys suffering from tuberculosis with episcleritis was significantly lower than the value before the treatment ($p <0.05$). Compared to the index in boys of the same age without episcleritis, the level remained higher and amounted to 118%. Whereas the indicator before the treatment correlated with the control group in the amount of 169%. These changes indicate that TNF-α was significantly reduced by the use of immunomodulators in boys suffering from tuberculosis with episcleritis aged 15-17 years old. In the same group of girls, trends similar to the group of boys were noted - the initial level of TNF-α in girls with episcleritis was significantly higher than in girls without episcleritis ($p <0.05$) and after the treatment significantly decreased ($p <0.05$), but remained slightly higher than control group level. Their ratio was 115%, whereas before the treatment the ratio with the control was 159%. The presented

data indicate that TNF-α levels are higher in boys than in girls, but the effects of immunomodulators do not differ significantly depending on gender. The ratio of the control group indicator to the total TNF-α indicator in boys and girls after the treatment was 115%, which is significantly lower than the ratio with the level before the treatment, equal to 162%.

When studying IL-10 levels in boys aged 15-17 years old with tuberculosis with episcleritis, the IL-10 result after the treatment with immunomodulators significantly increased ($p < 0.05$), but did not reach the level of the control group and amounted to 83% relatively to it. Before the treatment, the IL-10 level in boys with episcleritis was significantly lower than the control group ($p < 0.01$), their ratio was 54%. The results obtained indicate a significant increase in the content of IL-10 in the tear fluid under the influence of immunomodulators in boys with tuberculosis and episcleritis aged 15-17 years. On the contrary, in this group of girls, the level of IL-10 after the treatment with immunomodulators significantly increased relatively to the initial level ($p < 0.05$) and was more close in value to that of the control group, their ratio was 89%, which is significantly higher than the ratio before the treatment - 65%. Based on this, it was found out that the effect of immunomodulators on IL-10 levels in boys was not significantly greater than in girls. The ratio of the control group indicator to the average value of this indicator, taking into account both sexes, increased from 59% before the treatment to 85% after the treatment.

In boys aged 15-17 years old, suffering from tuberculosis with episcleritis, receiving immunomodulators, the level of TGF-β1 was 92%, which is significantly higher than before the treatment - 59%. These changes indicate a significant increase in the level of TGF-β1 in boys suffering from tuberculosis and episcleritis aged 15-17 years old under the influence of immunomodulatory agents. In the same group of girls, the dynamics of TGF-β1 levels after the treatment and relatively to the control group were similar to the dynamics in boys. The ratio of the indicator after the treatment to control was 93%, which is significantly higher than before the treatment - 63%, and its increase was slightly less than in boys. When examining the average values of TGF-β1 in boys and girls, the value after the treatment was 92% relatively to the control group, and before the treatment the ratio was 61%. The increase in indicators in all studied groups of children suffering from tuberculosis with episcleritis after the treatment with immunomodulators was statistically significant ($p < 0.05$).

4. Conclusions

In conclusion, we can note the patterns in the dynamics of interleukins, identified during their study in children and adolescents suffering from tuberculosis with episcleritis. It was found out that in preschool children (4-6 years old), the effects of the use of immunomodulators were statistically insignificant both in comparison with the initial levels and relatively to the control group. Significant changes in the indicators were detected starting from the age of 7-10 years old and with increasing age the effects were consistently reliable. Gender differences in the levels of indicators in different age groups and for various characteristics are not unambiguous, but higher levels of indicators were more often observed in girls compared to boys, while differences in indicators before and after the treatment were more pronounced in boys. From the above it follows that the use of immunomodulators, taking into account individual sensitivity in children and adolescents with tuberculosis for the treatment of episcleritis, is advisable and leads to normalization of pro- and anti-inflammatory interleukins.

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