ejpmr, 2019,6(7), 39-43

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ASSESSMENT OF THE FORMATION OF IMMUNOLOGICAL DISTURBANCES IN MEN WITH AZOOSPERMIYA

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Article Received on 30/04/2019 **Article Revised on 20/05/2019** **Article Accepted on 10/06/2019**

ABSTRACT

A study was conducted to study the state of the immune system in 132 men with primary infertility. It was revealed that this contingent had an imbalance in the content of some parameters of the immune system. Thus, the level of CD3 + - and CD4 + lymphocytes was reduced, the killer activity was increased. The content of CD20 + lymphocytes and the concentration of IgG and IgA were elevated. The level of pro-inflammatory cytokines (IL-2, IL-6, TNFα) in the examined patients was elevated. The results indicate the important pathogenetic role of the immune mechanisms in men with primary infertility.

KEYWORDS: Male infertility, immunity, cytokines.

INTRODUCTION

Male infertility is a multifactorial syndrome, including a wide range of disorders, a symptom of many different pathological conditions affecting both the sexual and other body systems: endocrine, nervous, circulatory, immune. One of the factors of male infertility is the absence of the sperm duct, the cause of which can be cystic fibrosis, in which there are mutations of the CFTR protein gene (cystic fibrosis transmembrane regulator). Aplasia of the vas deferens occurs due to congenital anomalies of the Wolf duct. Clinical manifestations of the usual form of cystic fibrosis are quite characteristic. Genetic disease leads to a significant increase in the viscosity of secretions produced by exocrine glands. Thus, in men with cystic fibrosis, seminal fluid becomes viscous and cannot pass through the vas deferens during ejaculation. More than 95% of men with cystic fibrosis have obstructive azoospermia. Most have bilateral congenital obstruction of the proximal part of the vas deferens or epididymis.

Changes in the reproductive system affect the work of the immune system. Observed disruptions in the immune response, relating to cellular and humoral links, as well as cytokine synthesis.

The aim of the study

The aim of the study was a comprehensive clinical and immunological examination of men with primary infertility of unknown origin.

MATERIALS AND RESEARCH METHODS

132 men of reproductive age were examined at the Department of Nephrology and Urology of the Tashkent Institute for the Advancement of Physicians. The basis for the diagnosis of primary infertility was clinical and laboratory studies, which included: taking history, seminal fluid, semen, determination of the level of sex hormones, as well as ultrasound scrotum, kidney and Doppler sonography of the spermatic cord. The control group consisted of 20 healthy men, married and having children.

Immunological studies were conducted by studying the subpopulation composition of lymphocytes using monoclonal antibodies of the LT series (Sorbent LLC, Russia). The concentration of immunoglobulins and proinflammatory cytokines in serum was determined by ELISA. Used the test system of JSC "Vector-West (Russia).

For statistical calculations, standard programs were used (MS Excel 2002, Statistica 6.0). The degree of reliability of differences between groups was assessed by the Fisher-Student test. Differences were considered statistically significant at $P < 0.05$; $P < 0.01$; $P < 0.001$.

RESULTS AND DISCUSSION

132 men aged 28 to 45 years old and married for more than 3 years were examined. Analysis of clinical data showed that 44 of them had chronic prostatitis category B, 75 category A, testicular hypoplasia was found in 90 men, hypogonadotropic hypogonadism in 10, and hypergonadotropic hypogonadism in 66 people.

Normogonadotropic state was observed in 36, urinary tract infection in 72. Varicocele (left and right) in 57 men. Klinefelter syndrome (confirmed by a genetic test) in 2 men. Cryptorchidism was observed in 4 and operations on the reproductive organs were carried out in 5 men examined.

An analysis of the anamnestic data showed that a number of concomitant diseases were observed in men with primary infertility.

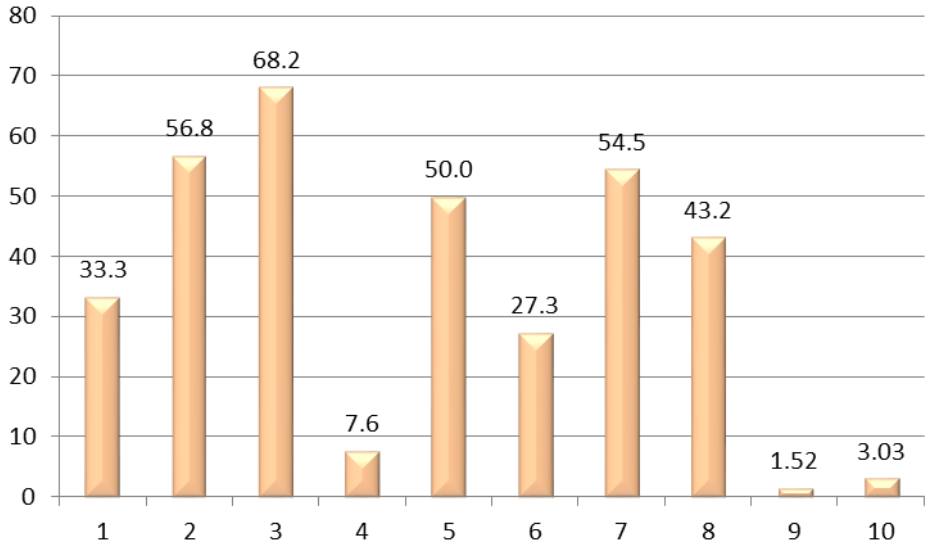

Fig. 1: Clinical characteristics of the examined men, %.

1. Chronic prostatitis category A
2. Chronic prostatitis category B
3. Testicular hypoplasia
4. Hypogonadotropic hypogonadism
5. Hypergonadotropic hypogonadism
6. Normogonadotropic state
7. Urinary tract infection
8. Varicocele
9. Klinefelter syndrome
10. Cryptorchism

Diseases of the gastrointestinal tract in 27.8%, allergic diseases in 19.6%, diseases of the cardiovascular system in 10.9%, diseases of the broncho-pulmonary system (upper and lower respiratory tract) in 38.7%, 2, 5% were diabetic.

Thus, in the men examined by us with primary infertility, the somatic and urological history is burdened by chronic diseases, a high frequency of sexually transmitted infections, and a pronounced hormonal imbalance.

Analysis of the results of the studies showed that the relative content of T-lymphocytes was significantly reduced relative to the values of the control group (49.8 ± 0.8% versus 55.6 ±1.3% in the control).

Table 1: Indicators of cellular immunity in the examined men, (M ± m).

Indicators,%	Control group	Patients
CD3 +	55.6 ± 1.3	49.8 ± 0.8 *
CD4 +	32.3 ± 0.8	28.4 ±0.6 *
CD8 +	21.5 ± 1.1	24.6 ± 1.0
CD16 +	12.6 ± 0.9	22.8 ± 0.8 *
CD20 +	24.3 ± 1.0	33.1 ± 0.7 *

Note: * Values are reliable in relation to the control group. (P <0.05-0.001)

Analysis of the results of studying the subpopulation composition of lymphocytes showed a decrease in the level of T-helper / inducer (28.4 ± 0.6% versus 32.3 ± 0.8% in control, P <0.05) and a tendency to increase in T-suppressor / cytotoxic lymphocytes. CD4 + lymphocytes, by performing their helper function, help, firstly, B cells to turn into an antibody-producing plasma cell; secondly, CD8 + lymphocytes - into a mature cytotoxic T-cell; third, macrophages exercise the effects of hypersensitivity. These functions of T-lymphocytes / helper cells are realized due to the fact that they, in turn, are divided into two subpopulations - Th1 and Th2 types, which perform different helper functions due to the production of different cytokines-interleukins.[4] The cytotoxic immune response plays an important role in protecting the body against intracellular pathogens and

includes a non-specific link, NK cells, and an antigen-specific link of the adaptive immune response, CTL.[3] Reliably increased expression of CD16 antigens on lymphocytes in the examined patients (22.8 ± 0.8% compared with the control -12.6 ± 0.9%) may indicate the presence of antigenic load.

The B-system is represented by the quantitative content of B-lymphocytes with a CD20+ molecule and the level of immunoglobulins of the classes IgG, IgA, IgM. CD20 + - lymphocytes are directly involved in specific immune defense reactions of the body.[3] Comparative characteristics of the content of circulating CD20 + cells showed that in patients the level of these cells was significantly increased (33.1 ± 0.7% vs. 24.3 ± 1.0% in control, P <0.05). The results obtained suggest that there is an activation of the B-cell element of the immune system against the background of an imbalance in the population of T-lymphocytes.

The study of the concentration of the main classes of immunoglobulins G, A and M showed an increase in the synthesis of Ig G (15.38 ± 0.86 mg /% versus 9.65 ± 0.69 mg /% in the control) and IgA (1.87 ± 0.65 mg / % versus 1.34 ± 0.5 mg /%), (P <0.05). As for Ig M, its content did not differ from the data of the control group.

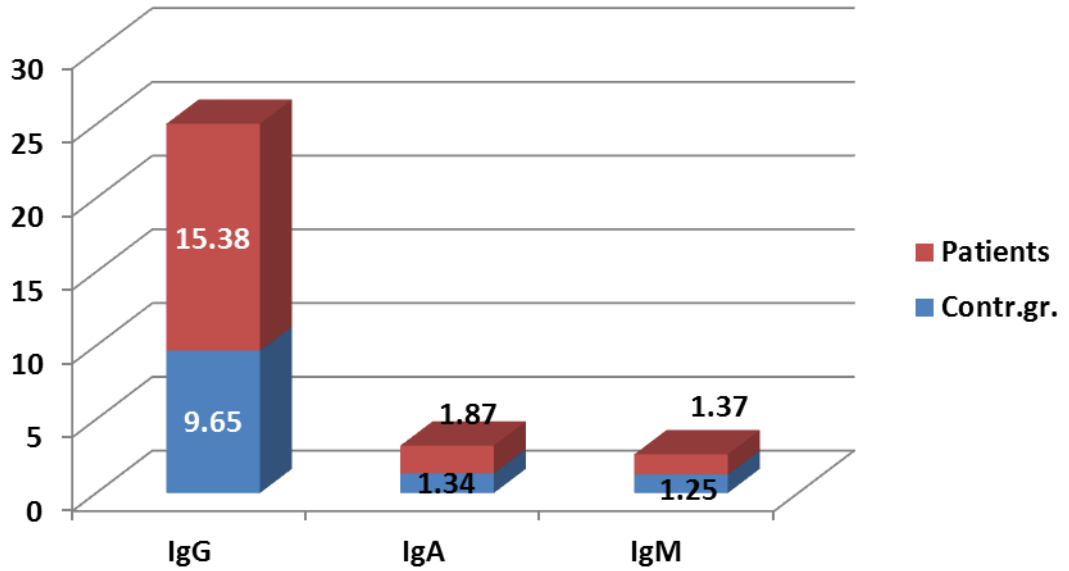

Fig. 2: The level of immunoglobulins in the examined men, (g / l).

It is known that the central regulators of immunological homeostasis in the body include cytokines, which have an extremely wide range of biological effects. In the inflammatory process, the nature of interactions in the system of "immune competent cytokine cells" often changes, which may underlie the violation of the mechanisms for the implementation of the body's defense.[5] From this point of view, it is of interest to study the relationship of disorders in the immune system and the severity of the pathological process in men with infertility.

As our studies have shown, the level of pro-inflammatory cytokines in men with infertility was significantly higher than the control group (Fig. 3).

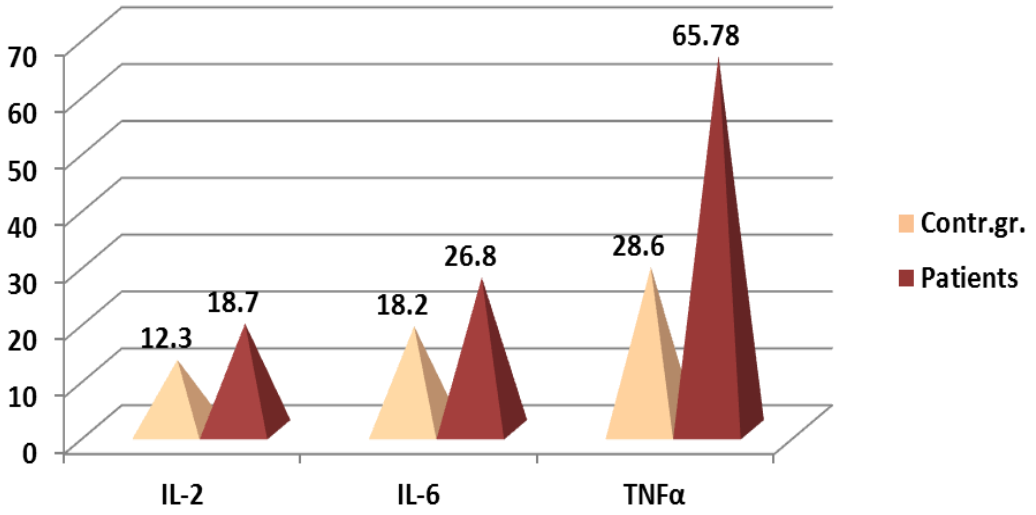

Fig. 3: The level of cytokines in the examined men, (pkg / ml).

Thus, the level of tumor necrosis factor (TNFα) in men with infertility was 2.3 times higher than the values of men who made up the control group (P <0.001). TNFα is known to belong to the family of cytokines that cause apoptosis of cells. At the same time, it plays a key role in protecting the body against pathogens. TNFα regulates many biological processes, including proliferation, differentiation and death of various cells, inflammatory reactions, innate and acquired immunity, as well as the formation of the structure of various organs and tissues, including secondary lymphoid organs.[1-7] However, the violation of the mechanisms controlling the protective inflammatory response can lead to the development of chronic diseases.

The study of the synthesis of IL-2 showed its significant increase in men with infertility (P <0.01). Interleukin-2 (IL-2) has a pronounced ability to induce the activity of almost all clones of cytotoxic cells. He was the first interleukin to reveal this ability. According to the literature, the participation of IL-2 is equally important for the induction of specific T-killers, and for the activation of non-specific mechanisms of the anti-inflammatory process.[5,6]

Interleukin 6 (IL-6) is a glycoprotein that is a multifunctional cytokine that coordinates immune and acute phase inflammatory responses, as well as oncogenesis and hemopoiesis. Produced by cells of the immune system as well as cells that have no direct relationship to the immune system: fibroblasts, keratinocytes, chondrocytes, stromal cells of endometrium, Leydig cells in the testis, pituitary follicular-stellate cells and vascular smooth muscle cells, endothelial cells and synovial. IL-6 can also be secreted by tumor cells of various histological nature. Receptors for IL-6 are found on both lymphoid and non-lymphoid cells. One of the main functions of IL-6 is the regulation of the maturation of antibodies producing B-lymphocytes and the production of immunoglobulins. IL-6 performs the function of a mediator of protective processes against infections and tissue damage. In addition, it is able to inhibit the synthesis of pro-inflammatory cytokines (IL-1β and TNF), can have a hormone-like effect on the liver, maintaining glucose homeostasis, stimulates the secretion of somatotropic hormone and suppresses the secretion of thyroid-stimulating hormone, has pyrogenic properties, reduces albumin and prealbumin synthesis.

In our studies, the serum IL-6 content in men with infertility was elevated (P <0.001).

The revealed changes indicate a pronounced activation of the cytokine immunity in infertility of various origins. It is known that TNF-α is a pluripotent cytokine, which is mainly produced by monocytes and macrophages and performs essential functions. During the start-up period of inflammation, it activates the endothelium, increases the expression of adhesion molecules on endothelial cells and promotes adhesion of leukocytes to the endothelium, activates leukocytes (granulocytes, monocytes, lymphocytes), induces the production of other proinflammatory cytokines that have synergistic with TNF-α action. Elevated levels of IL-6 are associated with chronic and acute inflammatory conditions. Therefore, by the level of TNF-α, IL-6 and IL-2, one can indirectly judge the activity of the inflammatory process as a whole.

CONCLUSION

Thus, the conducted studies have shown that in the examined contingent of men with infertility, along with other clinical and laboratory changes in the body, there are deviations in the state of the immune system. The important role of functional disorders on the part of such effector cells as macrophages involved in antigen processing and its presentation to the naive T-helper lymphocyte cannot be ruled out, because at this stage a number of regulatory events occur that determine the direction of the immune response.[3]

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