Role of Human Fetal Tissue Transplantations in Rheumatoid Arthritis

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Cell-mediated immunity is studied in 15 patients with rheumatoid arthritis. Fetal therapy increases the absolute count of actively phagocytizing neutrophils, stimulates their functional activity, and increases the percentage of mature neutrophils.

Key Words: *rheumatoid arthritis; immune status; human fetal tissue transplantation*

Transplantations of human fetal tissue are proposed for treating immunodeficiencies [6]. Rheumatoid arthritis (RA) is an infectious allergic disease; total and organ reactivities play the decisive role in its development and outcome [3], and therefore this disease can be regarded as a pathogenetically justified model for assessing the efficacy of fetal cell effects.

Rheumatic fever affects both cell-mediated and humoral immunity [4]. The phagocytic activity of leukocytes is reduced during the active and latent periods of rheumatic process [1].

On the other hand, immunity disorders are associated with the production of sex hormones which influence normal differentiation, maturation, and motility of immunocytes, thus simulating an autoimmune disease [5].

Lymphocytes are the major cell type reacting to sex hormones. Specific gonadotropin receptors were revealed on T lymphocytes and macrophages [5], and hormonal disorders in RA patients are related to immunity disorders, which confirms the contribution of the pituitary-gonadal system to the pathogenesis of RA. In published reports the pathogenesis of rheumatic diseases is regarded as hyperestrogenization of the organism paralleled by androgen insufficiency. Therefore, the immune status of RA patients treated with sex hormones should be monitored. On the other hand, ineffectiveness of the traditional therapy of RA prompts the development of novel methods of therapy.

In this study we explored the possibility of using human fetal placental grafts for the treatment of RA.

The placenta produces proteohormones which, although much similar to the pituitary hormones, are not identical to them. Their main representative is chorionic gonadotropin; its maximum production is observed during the second and third months of pregnancy. Recently, a regulating hormone common for all gonadotropins was revealed, which increases the production and secretion of luteotropic hormone (LTH) and follicle stimulating hormone (FSH) [2]. Both hormones affect sex organs directly and through sex hormones by stimulating their production in the relevant organs. In men, FSH stimulates the seminal canaliculi and their growth and plays an important role at some stages of spermatogenesis, and LTH is responsible for the production of testosterone in the testicles. In women, FSH induces follicle growth in the ovaries and stimulates LTH effect on the production and secretion of estrogens.

MATERIALS AND METHODS

Cell-mediated immunity, neutrophil phagocytic capacity, phagocytic number, absolute phagocytic index, and concentrations of immunoglobulins in the sera of patients with RA were assessed before and after fetal tissue transplantation.

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TABLE 1. Immunological Parameters of Normal Subjects and RA Patients Before and After Transplantation of Human Fetal Placental Cells

Parameter	Normal controls	RA patients	
		before therapy	after therapy
Erythrocytes, 10^{12}/liter	4.8±0.7	3.6±0.64	4.66±0.053
Hemoglobin, g/liter	125±1.3	100.3±1.3	116.4±1.4
Leukocytes, mm^3	5630.0±560.5	6031.2±611.0	5730.0±296.0
Neutrophils, mm^3	3210.1±630.2	3652.5±315.6	3111.1±196
Neutrophil phagocytizing capacity:			
phagocytosis, %	73.5±5.6	49.3±2.6	69.3±3.6
phagocytic number	5.1±0.7	3.1±0.3	4.9±0.8
phagocytic capacity	2566.1±199.1	1956.1±126.2	2689.2±135.7
absolute phagocytic index	11322.2±741.4	6911.2±197.1	12112.3±816.3
Immunoglobulins, g/liter:			
IgA	2.3±0.3	2.6±0.05	3.0±0.4
IgM	1.9±0.2	2.4±0.06	4.3±0.2
IgG	5.7±0.8	13.6±1.3	18.9±1.4

Fifteen patients with RA (5 men and 10 women) aged 27-65 years with the disease lasting 3-15 years were included in the study. All the patients were treated with nonsteroid anti-inflammatory drugs.

Nine (60%) patients had moderate and four (26%) high activity of RA with pronounced insufficiency of the locomotor system; in two-thirds of the patients hemoglobin level varied from 80 to 105 g/liter, which indicated an active rheumatoid process.

Eight (53%) patients developed involvement of the hands and wrist joints. In 10 (67%) patients, muscle atrophy was moderate, in 5 (33%) patients polyarthritis was associated with pain and stable exudative changes in the joints, involving their dysfunction. The overwhelming majority of patients complained of the "morning constraint;" in 26% of them (n=4) RA was associated with high fever. The process ran a subacute course in 74% of cases, with disorders of the articular functions regarded as the first-degree functional insufficiency.

The control group consisted of 11 normal subjects.

Fetal tissue obtained from healthy women aged 15-40 years was used for transplantation. Before medical abortion all women were screened for viral infections (hepatitis B, cytomegalovirus, herpesvirus, and HIV), chlamydia, and toxoplasma, and the Wassermann test was carried out. Pregnancy terms (10-12 weeks) were determined from the date of the last menses, the height of elevation of the fundus uteri, and ultrasonic findings.

The preparation was made, and its sterility controlled simultaneously. The resultant suspension was injected intramuscularly in the operation room at 7-day intervals. The course consisted of 5 transplantations.

During fetal therapy the patients were administered no drugs, including those stimulating hemopoiesis.

RESULTS

The phagocytic capacity of neutrophils was markedly decreased in RA patients, and the total count of leukocytes increased in comparison with that in normal subjects (Table 1). The absolute phagocytic index of RA patients, which is an integral value depending on the activity of leukocytes and their total count, differed appreciably from that in the controls ($p<0.05$). Other characteristics of the neutrophil phagocytic capacity were less decreased, although the quantitative ratio of neutrophils in patients and normal subjects was virtually the same.

Moreover, the phagocytic capacity of neutrophils assessed from the absolute phagocytic index decreased with the duration of rheumatic process. After fetal therapy, the general status of 80% (n=12) patients improved, pain and morning constraint decreased and/or ceased, body temperature normalized, inflammatory changes in the joints reduced, muscles grew stronger, and hemoglobin levels in peripheral blood tended to increase: in the overwhelming majority (n=14) of patients hemoglobin increased from 100.3±1.3 to 116.4±1.4 g/liter, and the erythrocyte count from $3.6\pm0.064\times10^{12}$ to $4.66\pm0.053\times10^{12}$/liter.

After fetal tissue transplantation, a positive time course of changes in red blood correlated with a decrease in the activity of inflammatory process, pre-

paralleled by a decrease in leukocyte and neutrophil counts and a simultaneous increase in their functional activities (Table 1). The absolute count of actively phagocytizing neutrophils per mm^3 of blood corresponded to the normal values. By the end of the third-fourth week after transplantation the neutrophil phagocytic activity normalized.

Thus, the results permit a conclusion that fetal therapy effectively arrested RA symptoms, which was best of all seen in patients with exacerbated process; the treatment corrected immunity and stimulated hemopoiesis.

Despite the good results of fetal cell transplantation, some problems concerning differentiated effects of individual hormones on the immunity of RA patients are still unclear. It is evident that assessment of the immune status of RA patients should be complex, including studies of the cellular and humoral immunity and nonspecific defense factors.

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Exchange of Sialic Acid-Containing Compounds in Chronic Osteomyelitis

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Serum content of free, oligosaccharide and protein-bound sialic acids, seromucoid components, and activity of sialidase are measured in rabbits with osteomyelitis induced by intraosteal administration of *St. aureus*. During chronic stage of purulent osteomyelitis the content of oligosaccharide-bound sialic acids is increased, while the content of seromucoid hexosamines is decreased.

Key Words: *osteomyelitis; sialic acids; seromucoids*

Changes in the content of sialic acids (SA) and glycoproteins are associated with the intensity of osteomyelitis [1]. The evidence that SA of oligosaccharides, glycopeptides, and glycoproteins are involved in cell-to-cell contacts, reception, and immunomodulation [7] opens new prospects in the investigation of the metabolism of SA in osteomyelitis.

In this study we determined serum content of free, oligosaccharide-, and protein-bound SA (FSA, OSA, and PSA, respectively), seromucoid components (orosomucoids), and serum activity of sialidase in experimental chronic osteomyelitis.

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MATERIALS AND METHODS

Experiments were carried out on rabbits weighing 1.5-2.5 kg. Acute osteomyelitis was induced by injecting *St. aureus* into the upper third of the left femur [2]. The development of osteomyelitis was confirmed by clinical, laboratory, and roentgenological data [2]. The animals developed acute inflammation and local pathology of the upper shin on days 3-6 after the injection. Purulent fistulas formed on days 12-16. *St. aureus* colonies were grown from the pus. Destructive focus markedly increased in size after 21-30 days, and the process became subacute. The pathology became chronic (formation of stable fistulas) on days 35-40.

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