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RESEARCH ARTICLE

Humoral immune status in patients with parasitic arthritis

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ABSTRACT

Introduction. The description of clinical manifestations of parasitic infestation includes joint damage manifested by arthralgia and arthritis, however, until today; the form of joint damage in parasitic infections is not clinically defined. The multitude of parasites creates a heterogeneous joint involvement, and the intensifying of specific manifestations would be an important premise in clinical diagnosis.

Objective. Assessment of immunological changes in the context of parasitosis and their ratio depending on the clinical variant of parasitic arthritis.

Material and methods. A group of 161 patients with parasitic arthritis was selected, established in two stages of compliance according to specific and serological criteria. The average age was 47.0±2.1 years, 72 men / 89 women. The average duration of joint syndrome was 50.4±15.6 months. The first group (97 patients) had parasitic arthritis of echinococcosis infestation, the 2nd (31 patients) – parasitic arthritis of *Toxocara cannis* and the 3rd (33 patients) had parasitic arthritis of *Giardia lamblia* infestation.

Results and discussion. IgA was increased above normal in all patients with parasitic arthritis (4.25±0.001; $p < 0.001$). IgM showed significant changes, depended on infestation agent ($p < 0.05$). Patients with normal IgG levels predominated, except for patients from the group with echinococcosis parasitic arthritis ($p > 0.05$). The amount of IgE exceeds normal values in *Echinococcus* parasitic arthritis (38.40 ng/ml), *Toxocara canis* (34.16 ng/ml), *Giardia lamblia* (45.06 ng/ml).

Conclusions. This suggests that the key aspects of immunity against parasites are mainly determined by the size of the harmful organisms that the immune system needs to combat. Macroorganism includes unique defense mechanisms that can be effective against multicellular helminths: high production of IgA and IgE and activation of key effector cells – eosinophils.

Keywords: parasitic arthritis, immunoglobulins, *Echinococcus*, *Giardia Lamblia, Toxocara Canis*.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Most authors attest that parasitic arthritis has a non-specific immunological response and until today, the most important reactions remain unclear.

The research hypothesis

Due to the fact of the difference in infesting agents, a different clinical manifestation of parasitic arthritis is assumed, with a varied expression of immuno-inflammatory syndrome.

The novelty added by the manuscript to the already published scientific literature

The presentation of variability in parasitic arthritis is based on the

fact of different immuno-inflammatory reactions generated by different parasitic agents. Thus, parasitic arthritis in *Echinococcus* is characterized by the most severe development, followed by *Giardia lamblia,* and then *Toxocara cannis.*

Introduction

The immunological nature of parasitosis has always been of major interest, and there is existing literature that documents elevated levels of immunoglobulins, particularly IgA. [1-3]. Thus, the authors stipulate that the increase in the blood level of IgA is evidentiary for the hypothesis of infectious triggers in the mucous tunics in parasitic arthritis [2, 4]. Cases of IgA-induced nephropathies in patients with parasitic arthritis have been described [3, 5, 6]. Similarly, it is known that IgG and IgM have a protective effect and are able to damage the body of helminths, to conjugate the enzymes secreted by them, to form precipitation around their membranes, disrupting the physiological processes of the parasite. Many authors note that helminths secrete a complex of carbohydrates, which stimulate the production of IgE antibodies. One of the functions of IgE is to stimulate the formation and migration of eosinophils towards parasites for the fight against them. In this case, it appears that parasitic invasions at the initial stage are always accompanied by an increase in immunoreactivity in two ways – activation of the general mechanism of IgE antibody production and synthesis of specific IgE antibodies [1, 3, 7]. Perhaps this is why parasitic invasions are accompanied by an increase or manifestation of the hypersensitivity of the host organism, and with successful treatment – a decrease in all systemic inflammatory manifestations, including musculoskeletal [3, 8].

The most active processes of immunogenesis of helminthiasis are IgE-mediated inflammation, proliferation of eosinophils, cytotoxic action, increase in the activity of effector cells, that is, a cascade of reactions, aimed at the death and elimination of parasites, but not the development of persistent immunity [5, 9]. An active manifestation in the fight against helminths is hyper-eosinophilia, hyper-IgE production, release of mast cells mediators, hypersecretion of mucus, secretion of interleukin characteristic of allergies and systemic inflammatory immuno-pathological processes.

In recent years, the main antiparasitic mechanism, the effector cells of which are eosinophils, and the humoral side expressed by immunoglobulins, have been well studied. But, till this day, remains a great conundrum the development and progression of parasitic arthritis, generated by persistent immunopathological reactions. Likewise, it is necessary to mention the heterogeneity of clinical and laboratory manifestations, which presents a great diagnostic difficulty. Late diagnoses, in turn, increase the rate of morbidity and invalidation.

Thus, the study of the immunopathology of parasitic arthritis will allow to broaden the range of clinical assessment and will contribute to the elaboration of international consensus in classification and diagnosis criteria.

The wide prevalence of helminthiases *Echinococcus*, *Giardia lamblia* and *Toxocara canis* in the Republic of Moldova, the duration of the life cycle of parasites in the host body, the variety of clinical manifestations caused by them, the severity of complications and consequences determine the extreme relevance of this problem, with the need to detect solutions. A particular interest is the study of the specific anthelmintic immune response, which provokes osteo-articular pathological changes, as well as the development of diagnostic criteria and prognosis indicators.

The purpose of the study: Assessment of immunological deviations in the context of parasitosis and their ratio depending on the clinical variant of parasitic arthritis.

Materials and methods

This study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (No. 83, from 19.06.2018), according to the WMA Declaration of Helsinki. A group of 161 patients with parasitic arthritis was selected, established in two stages of compliance according to specific and serological criteria. The first stage included the correspondence of the diagnosis in accordance with the criteria of osteoarticular damage of the inflammatory type. The second stage of definition of diagnosis concerned the compliance in accordance with the positive results of the serological or parasitological diagnosis confirmed positive. The average age was 47.0±2.1 years, 72 men / 89 women. The average duration of joint syndrome was 50.4±15.6 months.

Patients were divided into 3 groups by the pathogen of infestation and the clinical variant of parasitic arthritis. The first group (97 patients) included parasitic arthritis on the background of echinococcosis infestation, the 2nd (31 patients) – of *Toxocara cannis* and the 3rd (33 patients) group included parasitic arthritis of *Giardia lamblia* infestation.

The patients from the studied groups were subjected to a detailed evaluation, carried out according to a program of complex paraclinical examination, with quantitative determination of IgA, IgM, IgG and IgE, with the assessment of specific anthelmintic cellular immunity: eosinophils, degranulation capacity etc. The data obtained was processed through statistical package StatSoft ver. 8.0.

Results

The assessment of the level of immunoglobulins in the blood revealed the increase of the average IgA indices above the normal physiological values (4.25±0.001; $p < 0.001$) in all patients with parasitic arthritis (Table 1).

The average indices of IgG level were within the reference range in all the subjects, but they were at the upper limit of normal value and showed no differences between the studied groups ($p > 0.05$). However, a slight tendency towards decreasing IgG concentration was observed in patients with *Giardia lamblia* parasitic arthritis compared to the other studied groups, but these differences, are not statistically significant ($p > 0.05$).

Table 1. Immunoglobulins level in peripheral blood in parasitic arthritis

Immunoglobulins	Parasitic arthritis *Echinococcus* n = 97	Parasitic arthritis *Toxocara canis* n = 31	Parasitic arthritis *Giardia lamblia* n = 33	Normal values
IgA level, g/l	4.5±0.17**	4.07±0.21**	4.39±0.12**	0.9-3.5
IgG level, g/l	1.25±0.3	1.23±0.4	1.19±0.7	0.8-2
IgM level, g/l	1.99±0.017	1.64±0.032	2.09±0.011*	0.6-2.1

Note: ** - p < 0.05; ** - p < 0.001.*

The average indices of IgM levels in the blood showed significant changes (p < 0.05) (see Table 1). As well as in the case of IgG, in parasitic arthritis, patients with physiological levels of immunoglobulins predominate (91%), except for a tendency of their elevation in the groups of patients with parasitic arthritis *Echinococcus* and *Giardia lamblia* compared to *Toxocara canis*. However, the differences were not statistically significant (p > 0.05).

Our study has shown that IgE is the only antibody that increases systematically and reaches the maximum values in the evolution of all 3 helminthiases. Its amount exceeds normal values by more than 10 times - with *Echinococcus* (38.40 ng/ml), 9 times - with *Toxocara canis* (34.16 ng/ml), 11 times - with *Giardia lamblia* (45.06 ng/ml) (see Table 2).

Table 2. IgE level in peripheral blood in parasitic arthritis

Immunoglobulins	Parasitic arthritis *Echinococcus* n = 97	Parasitic arthritis *Toxocara canis* n = 31	Parasitic arthritis *Giardia lamblia* n = 33	Normal values
Ig E (ng/ml)	38.40±0.16*	34.16±0.23*	45.06±0.12**	<4

Note: *p < 0.05; **p < 0.01

As far as eosinophils are concerned, the results of this study were generally consistent with the literature. Thus, absolute values of eosinophils in peripheral blood resulted in significant eosinophilia in all three groups of patients studied, but significantly higher in patients with echinococcal infestation, followed by *Giardia lamblia* and then *Toxocara canis* (see Table 3). A significant increase (relative to the norm) in the content of leukocytes of the eosinophilic series in the blood of the examined patients was observed (up to 45.43±8.71%, p = 0.001 - in patients with *Echinococcus*; in patients with *Giardia lamblia*, eosinophilia was determined in 60% of cases and was recorded at the level of 39.51±1.76%, p = 0.019) (see Table 3).

Table 3. Eosinophils number (%) and the capacity of degranulation (%, abs)

Eosinophil content, %	Parasitic arthritis *Echinococcus* n = 97	Parasitic arthritis *Toxocara canis* n = 31	Parasitic arthritis *Giardia lamblia* n = 33
Absolute indexes, $x10^9$/L (M±m)	4.55±0.97**	3.35±0.72*	4.0±0.56**
Relative indexes, % (M±m)	45.43±8.71***	33.5±0,3*	39.51±1.76**
Degranulation capacity, % abs	7.79±2.04%*** 0.21±0.01 G/l*	6.05±1.13%* 0.27±0.03 G/l*	6.37±0.83%* 0.07±0.00 G/l**

Note: ** - p < 0.05; ** - p < 0.01; *** - p < 0.001*

Another factor that causes a significant increase in the bactericidal function of eosinophils may be an increase in their ability to degranulate and undergo cytolysis. This affirmation is confirmed by the results of our study, which revealed a significant increase (in relation to the norm) in the content of eosinophils with affected morphological properties (without antigenic stimulation: in patients with echinococcosis 7.79±2.04% (p < 0.001) and 0.210±0.010 G/l (p < 0.05), respectively, with giardiasis 6.37±0.83% (p < 0.05) and 0.070±0.000 G/l (p < 0.01) at a rate of 2.54±0.05% and 0.002±0.00 G/l) (see Table 3). When *Toxocara cannis* antigen was added to *in vitro* samples, the absolute and percentage number of eosinophils in peripheral blood with altered morphological properties was found to be greater than the mean values of these parameters (6.05±1.13% (p < 0.05) and 0.270±0.030 G/l (p < 0.05)). It should be noted that changes in the morphology of leukocytes of the eosinophilic series were mainly in the nature of cytolysis: swollen cells were 2 or more times larger than the size of neutrophils, granules were visualized next to the cells. Along with this, increased vacuolization of the nucleus and cytoplasm of eosinophilic granulocytes was recorded.

Discussions

At the present time, the following hypothesis is accepted „atopy has appeared as an evolutionary adaptation to the increased antigenic load, but in the absence of timely antigenic exposure, it does not protect, but leads to the development of allergic and autoimmune diseases" [2, 5, 9]

As known, the production of common serum immunoglobulins IgE and IgG is regulated by IL-4 [6, 8, 10]. These immunoglobulins, and especially IgE – are an important

physiological regulator of immunological homeostasis [2-4], a fact also proven by our study. As can be seen by our results, but also from the data of the specialized literature, in helminthiases the protective role of antibodies of the IgE class is the most important. Numerous data according to which the level of antibodies of the IgE class in helminth infection is significantly increased, suggest that IgE actively contributes to the protection of the host against parasites.

In helminthiases, there is often a 100-fold increase in IgE titers [3, 8, 11].In our study, we obtained similar results. Numerous studies show that IgE class antibodies activate mast cells and induce the release of mediators from them, which are able to act directly on the parasite by increasing vascular permeability and releasing eosinophilic chemotactic factor, which can lead to the accumulation of adjuvant antibodies (IgG and IgA) and cells that directly affect the parasite [1, 4].

It has been established that the characteristic features of antiparasitic immunity are primarily due to the size of pathogenic objects against which the immune system must act, a fact assumed by some scientists [5, 7]. Macroorganism includes unique defense mechanisms that can be effective against multicellular helminths: high IgE production and activation of eosinophilic – effector cells. It is known that an increased content of granulocytes is one of the first, and sometimes the only sign of the pathological process caused by helminthic invasion. According to the authors, in the acute phase, the content of eosinophils reaches 20-40%, sometimes up to 90% [6, 9]. At the same time, in the chronic stage, according to various authors, eosinophilia occurs in about half of the patients – from 44 to 59% [2, 4, 7].

Eosinophils involved in the fight against helminths along with mast cells, begin to secrete various cytokines. However, it is known that the "processes occurring along the line mastocyte – eosinophils also have a significant impact on the formation of allergic reactivity with a significant impact on the musculoskeletal system" [3, 8].

Eosinophils perform various functions in helminthiases and differ from other cells by the presence of granules that are intensely stained with acid dyes, especially eosin. One of the main functions of eosinophils is cytotoxicity [4, 10]. The products of the granules of these cells can participate both in oxygen-dependent lysis, when toxic oxygen metabolites are released, and independent of oxygen, which is mainly associated with the release of a large base protein, eosinophilic cationic protein and peroxidase [6, 11]. These mechanisms can act both in isolation and synergistically, which in this case ensures the maximum efficiency of the lysis [8, 9].

Conclusions

Therefore, it has been established that the characteristic features of antiparasitic immunity are primarily due to the size of pathogenic objects against which the immune system must act. Human organism includes unique defense mechanisms that can be effective against multicellular helminths: high production of IgA and IgE and activation of key – eosinophilic – effector cells.

The assessment of the level of immunoglobulins in the blood revealed the increase in the average indices of IgA in all patients with parasitic arthritis ($p < 0.001$).

The average indices of the IgG level were presented within the limits of the norm in all the investigated groups, but they were posted at the upper limit of normal and showed no differences between the studied groups ($p > 0.05$). However, a slight tendency towards a decrease in IgG concentration was observed in patients with *Giardia lamblia* parasitic arthritis compared to the other studied groups, but these differences are not statistically significant ($p > 0.05$).

The average indices of IgM levels in the blood showed significant changes ($p < 0.05$). In parasitic arthritis, patients with physiological levels of immunoglobulins predominate, except for a tendency to their elevation in the groups of patients with parasitic arthritis through *Echinococcus* and *Giardia lamblia* compared to *Toxocara canis*.

The most active processes of immunogenesis of helminthiasis are IgE-mediated inflammation, proliferation of eosinophils, cytotoxic action, increased activity of effector cells. It is such a cascade of reactions, aimed at the death and elimination of parasites, and not the development of persistent immunity. Our study have shown that, most visibly in the evolution of all 3 helminthiases, IgE systematically increases and reaches a maximum. Its quantity exceeds the normal range more than 10 times with *Echinococcus*, 9 times - with *Toxocara canis* and 11 times - with *Giardia lamblia*.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

This study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes No. 83, from 19.06.2018).

Abbreviations

ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASRI – Bath Ankylosing Spondylitis Radiology Index; CRP – C-reactive protein; DAREA – Disease Activity REactive Arthritis; FC – functional class; VAS – visual analogic scale.

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