Allergoreactivity as a Predictor of the Severity of HIV Infection

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ABSTRACT

Introduction: Different types of allergic conditions develop in the half of patients infected with HIV due to the immune system dysfunction. Increased prevalence of allergic conditions in HIV infected patients lead us to conduct the study of allegro reactivity by carrying out skin tests to different types of allergens including an allergen to Candida.
Objective: To study the immediate type skin reaction in response to subcutaneous injection of different allergens including Candida allergen in patients infected with HIV at different stages of the disease.
Method: One hundred HIV infected patients were investigated. The control group consisted of 10 healthy individuals and 10 patients with different clinical forms of atopic allergy. Subcutaneous tests were done in the patients forearm.
Results: Allergic skin test results to different allergens were characterized by wide variability at all clinical stages: from absence of immediate hypersensitivity reaction to a strong positive reaction. The patients at the 4th stage of the disease despite the high level of IgE had immediate hypersensitivity reaction of the less intense compared to HIV infected patients at the 2nd stage of the disease. Test results to Candida allergen showed a positive reaction in patients with a rapid progression of HIV/AIDS before the development of the clinical picture of candidiasis.
Conclusion: Development and extent of the immediate hypersensitivity reaction changes with the progression of HIV/AIDS. Analysis of the immediate hypersensitivity reaction to Candida allergen may be used as an indicator of development and progression of candidiasis in HIV infection. The skin test results should be taken into consideration before initiating the antiretroviral therapy in order to avoid the development of allergic drug reactions to this class of medications. Results of allergotests may help in prediction of HIV progression.

Keywords: HIV infection, immediate hypersensitivity reaction, lymphocytic count, allergic reaction

INTRODUCTION

According to UNAIDS Report on the global AIDS epidemic 2010, Eastern Europe and Central Asia are the only regions where HIV prevalence clearly remains on the rise. The number of people living with HIV infection has almost tripled since 2000 and reached an estimated total of 1.4 million in 2009 compared with 760 000 in 2001. There were an estimated 76 000 AIDS-related deaths in 2009 compared with 18 000 in 2001. (1).Uzbekistan faces one of the biggest pandemic of HIV/AIDS in Central Asia. (2,3,4,5,6)

Global character of HIV/AIDS necessitates in-depth research of pathogenesis of these pathological conditions.(7,8) The pathophysiology of HIV infection is associated with unique clinical, diagnostic, and therapeutic features. (9, 10,11)

HIV infection causes the deficiency of T and B immunity, deficiency of the compliment system and phagocytes that lead to cell – mediated immune deficiency.(12) The immune dysfunction caused by HIV infection increases the likelihood of allergy and other immune-mediated diseases in many patients. Anergic condition with manifestation of allergic, auto-allergic and immune-complex pathological processes is also developed in patients.(13,14,15) Half of the patients infected with HIV have different types of allergic conditions mainly in the form of allergic rhinitis, adverse drug reactions, hay fever, atopic dermatitis, and angioneurotic edema. (16)

During the progression of HIV infection there can be observed the immune disregulation which lead to the development of various bacterial, fungal and viral infections in patients.(9, 12 17) Candidiasis is commonly developed in HIV infected patients once their CD4 level count drops below 350. As the result, manifestation and the progression of candidiasis may increase the suspicion of the presence of human immune deficiency virus infection in the patient.

Increased prevalence of allergic conditions in patients infected with HIV lead us to conduct the study of allegro reactivity of such patients by carrying out skin test to different allergens including an allergen to Candida.

GOAL OF THE RESEARCH

To study the immediate type skin reaction in response to subcutaneous injection of different allergens including Candida allergen in patients infected with HIV at different stages of the disease.

MATERIALS AND METHODS

One hundred HIV infected patients aged from 18 to 72 years were investigated. Forty four patients (48%) had a latent stage of HIV infection, 37 patients (40.6%) had secondary clinical symptoms, and 10 patients (11%) had AIDS. All patients were divided according to WHO clinical staging of established HIV infection. We also used a WHO immunological classification for established HIV infection dividing patients according to CD4 values.

All patients were registered in the Republic Centre of AIDS. The diagnosis of all patients was confirmed clinically and by the laboratory methods of enzyme multiplied immunoassay and Western blot.

Control group included 10 healthy individuals and 10 patients with different clinical forms of allergy.
All patients underwent the following investigations: Complete Blood Count, Urinalysis, Blood Sugar, biochemistry including BUN, LFT, and skin tests with atopic allergens.
Immunological condition of the patients was determined by the levels of IgA, IgM, IgG, and IgE. Level of immunoglobulins A, M and G was determined by the standard method of Mancini, radial immunodiffusion with mono specific serum antibodies to immunoglobulin A, M and G, made by Research Institute of Epidemiology and Microbiology (Moscow, Russia).
Subcutaneous injections of the allergens were done in the patients forearm. We used allergens made by Medical Immunology Ltd. Moscow and Microvita Ltd.
Analysis of the immunity of HIV infected patients was done according to the clinical stages. Cellular immunity was determined according to the level of leukocytes, lymphocytes, the general pool of T lymphocytes (CD-3), T helper cells (CD-4) and cytotoxic T cells (CD-8), CD-4/CD-8 ratio (immune regulator index – IRI) and B lymphocytes (CD-72).

RESULTS

Level of leukocytes and lymphocytes at different stages of HIV/AIDS.

In asymptomatic stage of the disease the level of lymphocytes on the average was not differ from the data of the control group – 32.85±0.78 % ($P \geq 0.05$), with wide scope of individual values from 21% to 50%. Absolute number of lymphocytes was 1941±148 cell/µl, with individual variation between 714 cell/µl and 2930 cell/µl. The stage of persistent lymphadenopathy was characterized by small reduction of lymphocytes to 28.9±0.69%, with variation between 17% and 46% and absolute number between 544 and 3190 cell/µl (average 1627±64 cell/µl).
The patients at the second clinical stage had in average 29±0.92% of lymphocytes with variation between 20% and 39%. Absolute number of lymphocytes was reduced more significantly to 1560±88 ($p<0.05$) cell/µl, with variation between 754 cell/µl and 2610 cell/µl.
The third clinical stage was characterized by the reduction of lymphocytes to 25.93±0.86%, with the variation between 18% and 37%. Absolute number of lymphocytes was between 576 cell/µl and 2024 cell/µl, in average at 1270±76 cell/µl ($p<0.05$).
The patients of the fourth clinical stage had in average 17,46±0,97% of lymphocytes with variation between 8% and 30%. The absolute number was 953±98 cell/µl with the variation between 288 and 1920 cell/µl.

Subpopulation of T lymphocytes at different stages of HIV/AIDS.

The relative and absolute number of CD3-lymphocytes was decreased at all clinical stages in HIV infected patients compared to the control group (table 1). At the first clinical stage the amount of CD3 was in average 52.19±1.12% ($p<0.01$) with individual variation between 30% and 78%. Absolute number was between 390 cell/µl and 2558 cell/µl, in average at 938±51 cell/µl.
At the stage of generalized lymphadenopathy the average of CD3 level was not differ from the level at asymptomatic stage and were lower compared to the control group ($p <0,001$).

At the second clinical stage the number of T lymphocytes was the similar with asymptomatic stage. At the third clinical stage the absolute number of T lymphocytes was less than at the second clinical stage ($p<0.05$).

The fourth clinical stage was characterized by significant T immune deficit of both relative and absolute number of CD3 T lymphocytes ($P<0.001$). The decrease of CD3 T lymphocytes at all clinical stages of HIV infection was due to the decrease of T helpers lymphocytes that carry CD4 receptor. CD4 T lymphocytes are the prime target for HIV and in the same time CD4 T cell response is the main protective mechanism against HIV proteins. CD4 T helpers stimulate the production of B lymphocytes and cytotoxic CD8 T cells.

A constant decrease of the CD4 lymphocytes level was observed from the beginning of the first clinical stage of HIV infection. At the second clinical stage both relative and absolute number of CD4 T lymphocytes in all groups of patients were lower than in control group.

The third clinical stage of HIV infection was characterized by further reduction of relative and absolute number of CD4 lymphocytes.

To sum up, starting from the latent stage of HIV/AIDS a gradual decrease of CD4 T helper lymphocytes was observed.

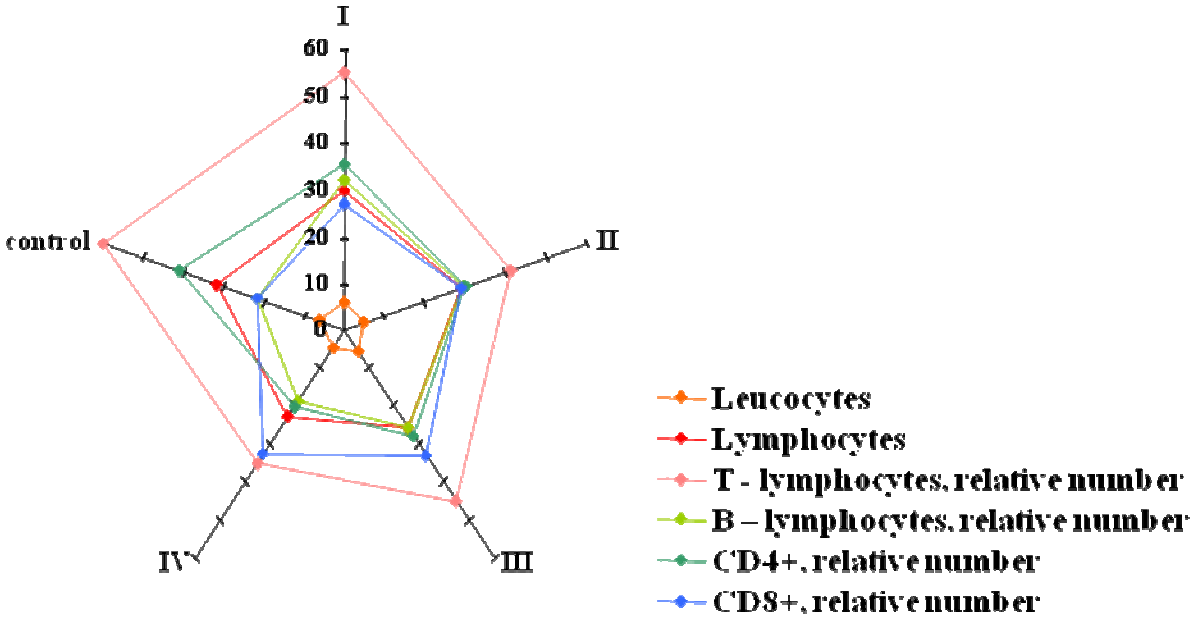

Table 1: CD4 T lymphocytes on different stages of HIV/AIDS (M±m)

Stages of HIV/AIDS	n	Groups of patients			
		CD3	CD4	CD8	CD16
First clinical stage: asymptomatic PLA		52,19±1,12** 938±51* 51,3±1,05***	29,19±0,3* 537±29 25,96±1,01**	26,74±0,96*** 487±29* 26,11±0,89***	14,52±1,01 263±20 14,3±0,91

		840±48**	425±31**	423±22	236±20*
Second clinical stage		51,92±2,42* 814±70**	27,44±1,12* 419±30**	28,74±1,31*** 453±34	14,38±1,08 231±23*
Third clinical stage		49,34±1,58*** 653±46**	23,88±1,36* 309±26***	29,61±1,22*** 390±32	13,49±1,44 182±28**
Fourth clinical stage		39,58±3,34*** 361±61***	15,91±1,35*** 146±22***	24,02±1,52* 237±43*	12,37±2,01 120±27***
Control group		62,07±1,27*** 1236±70	31,04±0,61 607±32	19,8±0,56 386±20	14,5±0,78 286±15

Numerator shows relative number in %
Denominator shows absolute number in cell/μl.
* – P<0,05; ** – P<0,01; *** – P<0,001

Cytotoxic CD8 T lymphocytes are responsible for elimination of different intracellular infections. They exert anti-viral pressure and suppress the infection by destroying the infected cells (5).

Analysis of cytotoxic T lymphocytes level.

According to our data an increase of relative number of CD8 T lymphocytes in HIV infected patients at all stages of the infection was observed. Absolute number of CD8 was increased only in asymptomatic stage. At the second and third stages absolute number of CD8 was comparable to normal and at the fourth stage it was decreased. (P<0,05).

Allergic skin test results to different herbs allergens were characterized by wide variability at all clinical stages: from absence of immediate hypersensitivity reaction to a strong positive reaction. 33.3% of patients had a negative reaction, 44.4% had a moderate reaction, 22.2% had a strong positive reaction. 22.2% of patients had a moderate reaction to the dandelion skin test; other patients had a weak or negative reaction. We didn't register a strong positive reaction to the food allergens. One patient had a positive reaction to beef meat, 3 patients to milk, 2 patients to eggs, 2 patients to rice, 1 patient to lemon. Test to flour caused a strong positive skin reaction in 22.2% of patients.

While testing the reaction to household allergens, moderate positive immediate hypersensitivity reaction was caused by the dog fur in 66.6% of patients. One patient had a moderate positive skin reaction to cat fur, three patients to the dust of book. Strong reaction in two patients was caused by dust of house and feathers of pillow. One patient had a moderate positive reaction to human hair and one to the allergen of cockroach.

Skin test to histamine caused a strong positive reaction in 33.3% of the patients, moderate positive in 33.3% and negative reaction in 33.4% of the patients. The strongest reactions developed to the Candida: 33.3% of patients had a strong reaction, 22.2% a weak reaction and a moderate reaction was only in one patient. Knowing that candidiasis indicate the progression of HIV/AIDS infection, we could expect a rapid progression of the disease in these patients.

Patients at the 4th stage of the disease despite the high level of IgE had immediate hypersensitivity reaction of less intense compared to HIV patients at the 2nd stage of the disease. It links to the reduced level of CD4 and reduced cell immunity response to antigens and allergens. Only one patient at this stage had a moderate allergic skin reaction to different herbs.
Skin test results to the food allergens were slightly positive to beef meat in two patients. Moderate and strong reactions to milk developed in two patients. Two patients had a weak positive reaction to eggs; and one patient had a positive reaction to grains. We didn't observe a positive reaction to flour and lemon.
Skin test reaction to household allergens revealed quite low sensitivity: two patients had a weak positive reaction to dog and cat fur, two patients – to the dust of books, one patient to house dust. One patient had a weak positive reaction to pillow feathers and human hair. Test results to Candida showed a positive reaction in patients with a rapid progression of HIV/AIDS.
Research has shown that measurement of relative and absolute numbers of lymphocytes plays an important role. Lymphopenia in HIV/AIDS indicates the decrease of CD4 lymphocytes numbers and deterioration of the course of the disease. Furthermore, lymphopenia can signal the transformation HIV infection to the next stage. Level of humoral immunity which has been measured by the level of immunoglobulins in HIV patients , has shown hyperproduction of IgG and IgE, (18,19, 20, 21) Hyperproduction of immunoglobulins is related to HIV infection and illustrates activity of T-helpers type 2.. (22, 23)

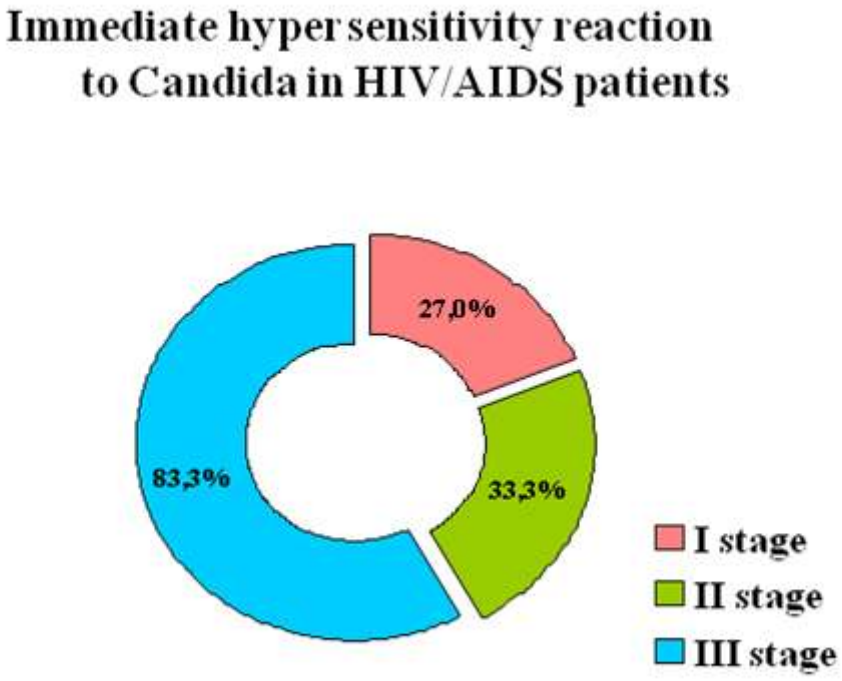

Figure 1: Immediate hypersensitivity reaction to Candida allergen on different stages of HIV

DISCUSSION

The study has shown that the measurement of relative and absolute number of lymphocytes plays an important role. Lymphopenia in HIV/AIDS is the evidence of decreased amount of CD-4 lymphocytes and worsening of the course of the disease. Moreover, lymphopenia can reveal the transformation of HIV/AIDS into the next stage. Level of humoral immunity that was estimated by the level of immunoglobulins in HIV patients at different stages of the disease revealed the hyperproduction of IgG and IgE, and increased level of IgM. (18,19, 20, 21) Hyperproduction of immunoglobulins relates to HIV infection and illustrates the activity of T helpers of the second type.(22, 23)

CONCLUSION

Development and extent of the immediate hypersensitivity reaction changes with the progression of HIV/AIDS despite the high level of IgE in infected patients compared to the control group. Study of the allegro reactivity in HIV infected patients revealed that some patients had paradoxical reactions which manifested by the absence of correlation of clinical condition, skin reaction and laboratory tests. Some patients had strong immediate hypersensitivity reaction without any allergic symptoms. Interestingly, skin test to Candida antigen was positive long time before the clinical appearance of Candidiasis in HIV infected patients. This fact in our opinion has an importance in diagnosis and management of such patients. Presence of the positive immediate hypersensitivity reaction to Candida allergen, growth of IgE and antibodies to Candida depend on the duration of HIV infection. Analysis of the immediate hypersensitivity reaction to Candida allergen may be used as an indicator of the development and progression of candidiasis in HIV infection. Further investigations of immediate and delayed hypersensitivity reactions in HIV infected patients will complement the present data. Results of immediate hypersensitivity reaction may be used as an indicator of the development and progression of different forms of candidiasis in HIV infected patients. Conduction of the allergic skin test plays an important role in the management of HIV infected patients. The results should be taken into consideration before initiating antiretroviral therapy to avoid the development of allergic drug reactions to this class of medications. Skin test results to Candida antigen are important as a simple prognostic tool to predict the progression of HIV infection.

Conflict of Interest: None declared.

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