

Influence of Histamine on the Immunoregulation of HIV-Infected Patients

Akhmedjanova Z.I., Zalyalieva M. V, Begisheva R. R.

Institute of Immunology, Academy of Science, Tashkent, Uzbekistan

Emails: zulfiya.akhmedjanova@gmail.com,

doc.zulfiya@gmail.com

ABSTRACT

Introduction: Increased level of histamine plays an important role in various manifestations of immediate type hypersensitivity reactions which prevail in HIV infected patients. However, there are not many studies about histamine in HIV infection.

Objective: To study histamine level in HIV infected patients on different stages according to CD-4 cells level.

Method: Ninety patients were included in our study; 64 of them were HIV infected patients in the ages between 21 and 54 years old (45 women, 19 men), other 26 were healthy individuals. All patients were divided into 3 groups depending on the level of CD-4 lymphocytes. Histamine analysis was done by the method of Meshyarikova S.A. with the spectrofluorimeter -F96 (LTD China)

Result: All HIV infected patients, irrespective of CD-4 cells count had histamine level higher than in control group, on average 1.294 mcmol/L with individual variation between 0.675-2.21 mcmol/L. Comparison of histamine levels of various groups of HIV infected patients has shown the greatest increase in the group of patients with CD-4 cell count more than 500 cells/mm³. Level of the histamine was decreasing as CD-4 cell count was falling. The highest level of histamine 1.77±0.07 mcmol/L was found in patients aged 40 to 54. The level of histamine remains increased irrespective of ARV therapy.

Conclusion: The revealed increased histamine level in HIV infected patients allows us to conclude that histamine plays a certain part in pathogenesis of HIV infection. An application of histamine receptor blocking medications has its ground in the management of HIV infection and should be considered during the course of treatment.

Keywords: Histamine level, HIV infection, CD 4 count, immediate type hypersensitivity reactions

Introduction

HIV infection/AIDS has become a pandemic. It is one of the leading causes of mortality among the young active population. It carries physical, psychological and economical damage to all countries (1, 2, 3, 4, 5).

Histamine is the indigenous factor (mediator) that has an important role in regulation of essential function of an organism and in the pathogenesis of some pathological conditions. Histamine is a hydrophilic vasoactive amine, derived from the decarboxylation of the amino acid histidine (6, 7).

Free histamine level increases at various pathological processes, such as anaphylactic shock, burns, frost bites, hay fever and other allergic conditions and also under influence of some chemical substances (8, 9, 10). Numerous domestic and foreign researchers indicate the role of histamine in pathogenesis of allergic reactions.

In HIV infection certain role belongs to allergic reactions. These reactions, probably, can explain many, not yet sufficiently clear pathological manifestations of immunological processes in HIV Infection. The borders between allergic and immunological manifestation are become less definite. In reality, the reaction between antigen and antibody is the basis of the both immunological and allergic processes. However, if the immunological reactions cause a straightening of the physiological defence mechanisms of the body, the allergic reactions are characterized by the certain clinical and pathological symptoms (11, 12, 13). HIV infection is characterized by the activation of T-helpers type 2 and the damage of T-helpers type 1. As was shown earlier in our studies, immediate hypersensitivity reaction prevails in HIV infection (14, 15, 16). Increased level of histamine plays an important role in various manifestations of those reactions (17, 18). However, there are not many studies about histamine in HIV infection.

Aim of study

This research aimed to study histamine level in HIV infected patients at different stages according to CD-4 cells level.

Materials and Methods

Ninety patients were included in our study. Sixty four of them (45 women and 19 men) were HIV infected patients in the age between 21 and 54 years, other 26 were healthy individuals.

All patients were divided into 3 groups depending on the level of CD-4 lymphocytes. The first group included 16 patients with CD-4 cell count more than 500 cell/mm³, second group consisted of 27 patients with CD-4 cell count from 200 to 499 cell/mm³, and third group had 21 patients with CD-4 cell count less than 200 cell/mm³.

Histamine analysis was done by the method of Meshyarikova S.A. According to an author's technique, histamine was determined by the spectrofluorimeter -F96 (LTD China). The method is based on the formation of fluorescence condensation products with o-phthalic aldehyde.

All HIV infected patients were registered in the Republic Center of AIDS. The diagnosis of all patients was confirmed clinically and by the laboratory methods of ELISA and Western blot method. All patients had the following investigations: CBC, Urinalysis, Blood glucose, biochemistry including BUN, LFT.

Statistical Analysis

Statistical analysis of data was done on IBM computers using a Microsoft special set of programs and functions. The strength of correlation was described by normal distribution. Student t-test was used to analyze the data.

Results

The average level of histamine in healthy individuals was 0.33 ± 0.001 micromoles per litre (Mcmol/L). All HIV infected patients, regardless of CD-4 cells count had histamine level higher than in control group and the average level was 1.29 ± 0.04 Mcmol/L with individual variation between 0.675-2.21 Mcmol/L. The analysis of the results according to stage of the disease is presented in figures 1-3.

In group of patients with CD-4 cells count more than 500 cells/mm^3 histamine level was increased and average level was 1.41 ± 0.05 Mcmol/L ($p < 0.001$). Furthermore, level of histamine was increased in all patients of this group irrespective to their clinical conditions. The level of histamine in this group was between 0.93-2.01 Mcmol/L.

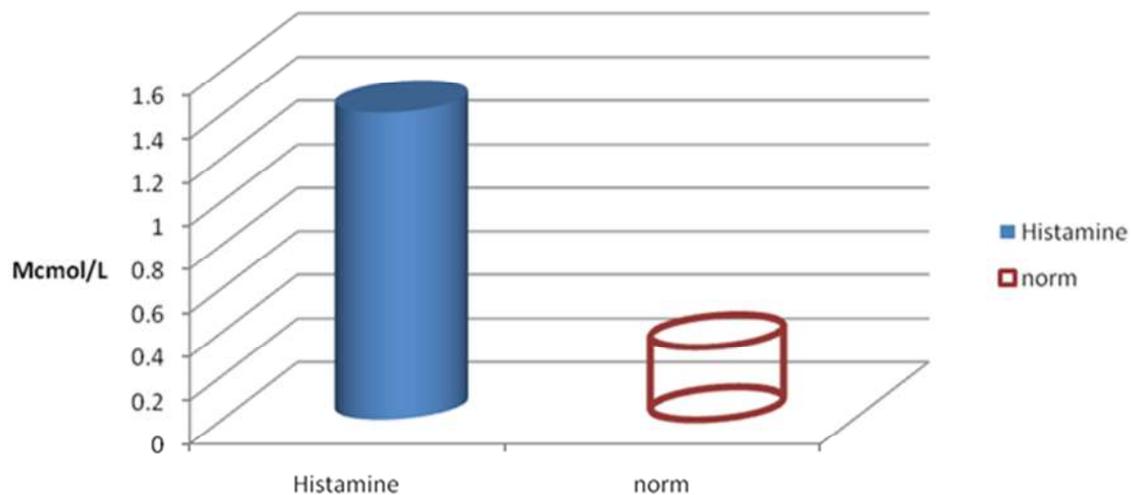


Figure 1: Histamine level when CD-4 higher than 500 Cell/mm^3

In group of patients with CD-4 cells count from 200 to 499 cells/mm^3 histamine level was reliably increased and average level was 1.24 ± 0.06 Mcmol/L ($p < 0.001$). In this group of patients histamine level was increased in all of them regardless to their clinical conditions and varied from 0.79 to 2.15 Mcmol/L.

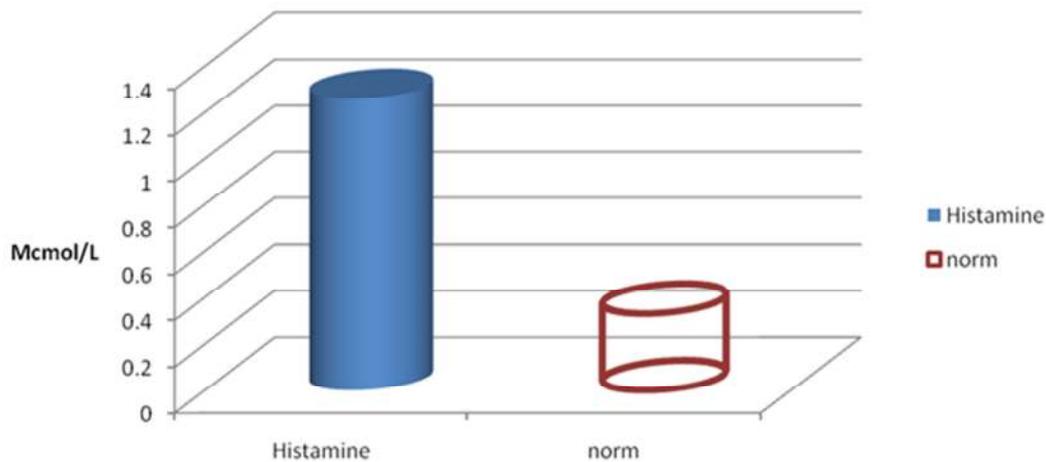


Figure 2: Histamine level when CD-4 between 200 - 499 Cell/mm³

Histamine level in HIV infected patients with CD 4 count between 200-499 cell/mm³. In patients with CD-4 cells count less than 200 cells/mm³, histamine level was also increased till 1,25±0,07 Mcmol/L (p<0.001) in average, with individual variation from 0.78 to 1.87 Mcmol/L. Figure 3.

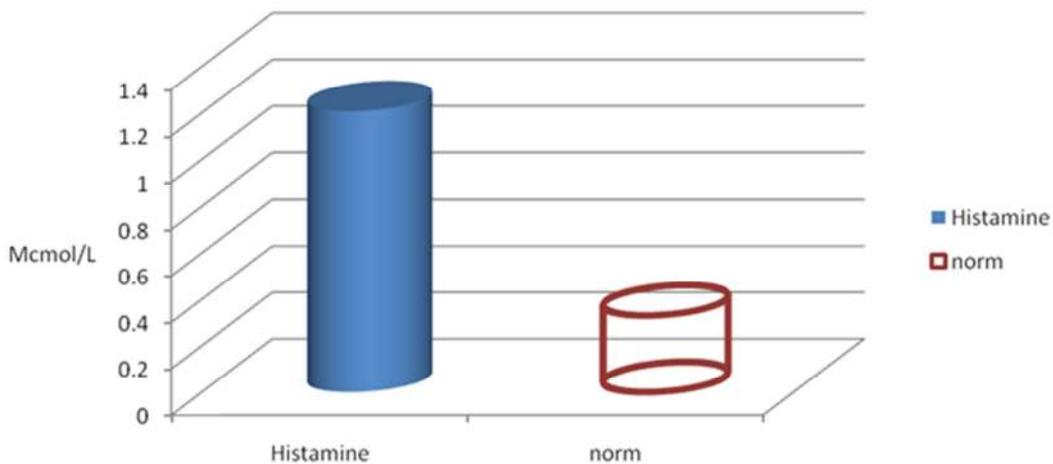


Figure 3: Histamine level when CD-4 lower than 200 Cell/mm³

Comparison of histamine level in different groups of HIV infected patients has shown the greatest increase of its level in the group of patients with CD-4 cells count more than 500 cells/mm³. The level of histamine was decreasing as CD-4 cells count was reducing. This data indicates the active role of T-helpers in immediate hypersensitivity reaction at the presence of HIV infection.

We also analyzed histamine level in patients according to their age. In patients from 21 to 29 years old histamine level was 1.4 ± 0.06 . In patients from 30 to 39 years old histamine level was 1.31 ± 0.05 . The highest level of histamine was found in patients aged from 40 to 54, it was 1.77 ± 0.07 .

The highest level of histamine (1.66-2.21 M μ mol/L) was registered in 11 HIV infected patients. 4 of them had histamine level between 1.93-2.21 M μ mol/L and 7 of them had histamine level between 1.66-1.87 M μ mol/L. 6 HIV infected patients had the lowest histamine level (0.78-0.86 M μ mol/L) compared to the rest of the patients.

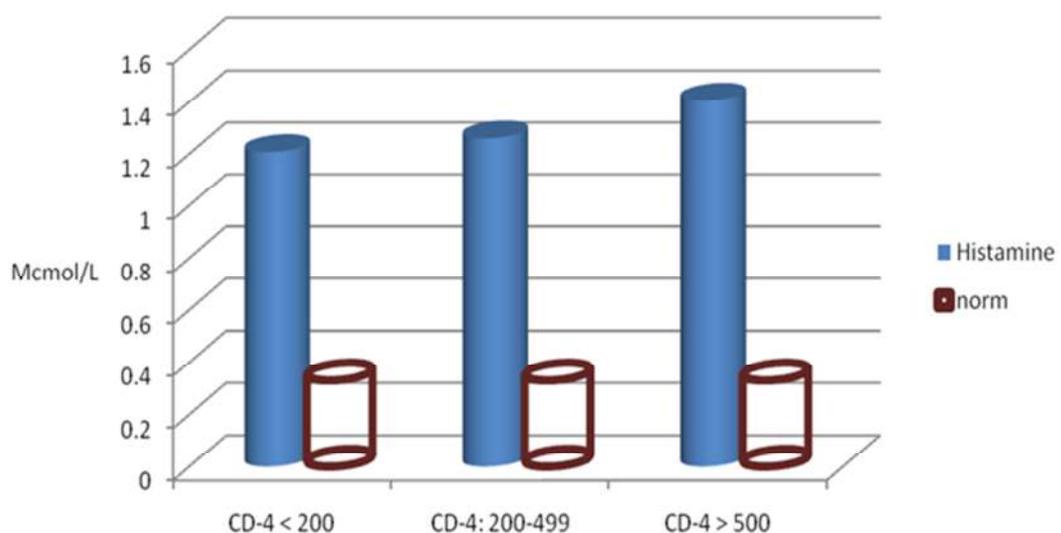


Figure 4

It is interesting to notice that most of the HIV infected patients with the highest histamine level had a viral load of zero on ARV therapy.

Discussion

The reactions caused by the histamine are diverse and wide spread (19, 20). Histamine exerts its actions by combining with specific cellular histamine receptors. Through H1 receptors histamine stimulates bronchial smooth muscle contraction, causes capillaries dilatation and increases capillary permeability. Through H2 receptors histamine reduces heart rate and stimulates gastric acid secretion. Histamine also acts as a neural mediator and has hormonal action. Nevertheless, no connections were found between the levels of IgE and histamine caused by anti IgE antibody in healthy people as well as in patients with pollinosis (21, 22).

It is known that histamine acts through H2 receptors of lymphocytes, activates adenylate cyclase, increases the intracellular level of cAMP. Through this system histamine acts as an immune-modulator. In particular, experiences in vitro have shown that increased level of intracellular cAMP caused by the histamine, blocks spontaneous rosettes formation. Basing on this, we can assume that histamine participates in suppression of receptors activity of immune competent cells.

According to our data the lowered and raised level of histamine in the blood correlates with the appreciable reduction of the total number of lymphocytes and, in particular, CD4 lymphocytes. It was considered in the literature that histamine acted only as a mediator of immediate type hypersensitivity reaction. But it has appeared that histamine can oppress the degranulation of mast cells and basophiles, and also suppress the production of proteins by the mononuclear phagocytes of the complement system. Histamine changes the phenotype of lymphocytes (CD4 + to CD8 +) and rises Fc-receptor activity, T-lymphocytes can strengthen biosynthesis of histamine and its secretion through interleukins.

All the above make it possible to assume that histamine takes a part in the regulation of immunologic reactivity, in the development of adaptive and compensatory reactions of immune system and in conservation of reserved abilities of the body. Rising concentration of histamine can indicate the specific adaptive reactions caused by adjusting to a series of factors, and a strain of various systems of an organism. The role of histamine in this case is dilation of capillaries and augmentation of their permeability to way out various metabolites from an organism. The increase in histamine level occurs due to the changes in permeability of ionic channels of the membranes of histamine contained cells as a response to intrusion of the virus of immunodeficiency

Discovered increased level of histamine in all HIV-infected patients suggests impaired tolerance to histamine which leads to various physiological reactions in the form of dilatation of blood vessels and disturbance of microcirculation. Those reactions are accompanied by various symptoms, typical for the developed picture of a HIV-infection: problem with the breathing, rhinorrhea, obstruction of respiratory tracts, extrasystoles, gastro-intestinal disturbances leading to loose stool and diarrhea. Many patients develop urticarial rash.

Histamine plays a certain role in immunoregulation, microcirculation and maintenance of homeostasis of an organism. Developed in the presence of HIV-infection complex antigen-antibody acts as a selective liberator and causes histamine release. This process is promoted by the disturbance of the levels of microelements in the body such as the reduction of Potassium and Calcium. Ions of those elements play role in the development of increased permeability of plasmatic membranes. Increased permeability leads to entrance ions of Sodium which forces histamine out of granular matrix. Previously conducted research on macro- and trace elements blood levels in HIV-infected persons (24, 25), have shown the decreased level of K, Ca, Cl, Fe, Cu, Co, Sb, As, Hg, Ag, Au, Se. Calcium metabolism and level are bound to a metabolism of other metals and anions: phosphorus, magnesium, zinc, cobalt, potassium, sodium, heavy metals. As a result it is possible to tell that disturbance of a biochemical condition of an organism initiate the mechanism of liberation of histamine which puts in action mechanisms of immunoregulation.

To maintain a histamine release from the leucocytes it is enough to add few micrograms of a specific antigen. This fact indicates the high immunospecificity of the reaction.

Conclusion

The conducted research has shown the increase of histamine level in HIV infected patients regardless to their CD-4 cells level. Histamine level was higher in older aged group of patients compared to younger ones. The level of histamine remained increased irrespective to ARV therapy.

We can assume that in the presence of HIV infection the ability of histamine receptors on lymphocytes to bind histamine is decreased. The revealed increased histamine level in HIV infected patients allows us to draw a conclusion that histamine plays a certain part in pathogenesis of allergic conditions in HIV infection. In wider aspect, regulation of release and activity of different inflammatory mediators are very important in the treatment of any other conditions caused by acute systemic inflammatory reactions. In these cases, scientifically grounded application of pathogenetic therapy has to be based on an adequate estimation of the role of inflammatory mediators, including histamine, on the development of inflammation process. Histamine plays the leading role in the development of inflammation processes and, in particular, in the development of acute inflammatory reactions. Due to this fact, an application of histamine receptor blocking medications has its ground in the pathogenetic management of HIV infection and we should consider prescribing these medications during the course of treatment.

Misbalance of macro and micro elements in HIV- infected patients (decrease K, Ca, Cl, Fe, Cu, Co, Sb, As, Hg, Ag, Au, Se) promotes liberation of a histamine by antigen – antibody complex, arising at a HIV-infection. It gives the chance to assume that normalization macro- and microelements level will affect histaminergic system of HIV-infected.

All the above gives us an opportunity to assume that increased histamine level in HIV infected patients unrelated to the stage of the disease and CD-4 cells level plays a certain role in pathological processes at the presence of HIV infection. Histamine most probably is the means of self-defense, warning signs of poor outcome. Our body sends signals to nervous system in the presence of impairment of physiological comfort, disturbances of homeostasis, disharmonic relations between cells, organs, tissues, and physiological systems.

The conducted research presents an important interest for physiology, immunology and biochemistry in the area of functional interaction of histamine with immunological regulation in HIV-infected of patients, and also shows the possibility of application of the given mediator for the directed influence on metabolic processes in HIV-infected organism.

Conflict of Interest: None declared

References

1. Bobkov A., Kazeinova E., Selimova L., A sudden epidemic of HIV type 1 among injecting drug users in the former Soviet Union: indification of subtype A, subtype B and novel gag A/env B recombinant. *Ibid.* 1998; 14(N8): 669-676.
 2. Kresina T. F., Mathieson B. Human immunodeficiency virus type 1 infection, mucosal immunity, and pathogenesis and extramural research program at the National Institutes of Health // *J. Immunol.* 1999; 161: 5127-5133.
 3. Mc Michael A. J., Phillips R. E. Escape of human immunodeficiency virus from immune control // *Ann. Rev. Immunol.* 1997; 15: 271-296.
 4. Morison L. The global epidemiology of HIV/AIDS // *Br. Med. Bull.* 2001; 58: 7-18.
 5. Pantaleo G., Fauci A.S. Immunopathogenesis of HIV infection // *Ann. Rev. Microbiol.* – 1996; 50: 825-254.
-

6. Greaves MW, Sabroe RA. ABC of allergies. Allergy and the skin. I—Urticaria.// *BMJ*. 1998 Apr 11;316(7138):1147–50. Review.
7. Lavrov O.V., “Direct and non direct action of biogenic amines on different sub population of lymphoid cells.” PhD thesis, Krasnodar, 1997.
8. Akhmedjanova Z.I., Zalyalieva M.V., Askarova L.I., Prohorova R.S., Akhmedjanov R.I., “Study of allergic aspects of pathogenesis of HIV infection. *Journal of theoretical and clinical medicine*.” 2009, #1: 84-86.
9. Merrill J.E., Mohlstrom C.// *Int. Arch. Allergy Appl. Immunol.* 1987; 82: 195-201.
10. Wendel T.D. An editorial for the HIV infected. Immunoregulation. The implications for treatment of HIV infection and the potential role of T cell suppressor pathways instead of apoptosis, energy or direct CD4 T cell deletion in AIDS pathogenesis // *Med. Hypotheses*. 2003; 60(N3): 373-381.
11. Romagnani S. Development of type 2 T-helper cells in allergy // *Curr. Immunol.* 1994; 6: 838-845.
12. Romagnani S. “Th2 hypothesis” in allergy // *Progress in Allergy and Clinical Immunology*. – 1997: 12-16.
13. Stafford CT. Urticaria as a sign of systemic disease.// *Annals of allergy*, March, 1990; 64.
14. D’Elios M., Del Prete G. Th1/Th2 balance in human disease // *Transplantation Proceedings*. 1998; 30: 2373-2377.
15. Morel P., Oriss T. Cross regulation between Th1 and Th2 cells // *Critical Review in Immunology*. – 1998; 18: 275-503.
16. Romagnani S. Th1/Th2 cells // *Inflamm Bowel. Dis.* 1999; 5(N4): 285-294.
17. Akhmedjanova Z.I., “Indicators of immediate and delayed types hypersensitivity reactions in HIV infected patients.” Scientific practical conference on HIV and TB of Central Asia: challenges and lessons of epidemic. 24-26 August, 2009, Kirgizia, Pgs.77-80.
18. Greaves MW, Sabroe RA. Histamine: the quintessential mediator.//*J Dermatol.* 1996 Nov; 23(11): 735–40. Review
19. Akhmedjanova Z.I. «Histamine levels in HIV infected patients.» 14th International Congress of immunology Kobe, Japan 2010: 64.
20. Akhmedjanova Z.I., Zalyalieva M.V., Isaeva G.N., Ishmakova R.N., Abdullaeva M.A., “Correlation between viral load and histamine in HIV”. Scientific practical conference on HIV and TB of Central Asia: challenges and lessons of epidemic. 24-26 August, 2009, Kirgizia: 89-90.
21. Prescott S., Sly P., Holt I. Raised serum Ig E associated with reduced responsiveness to DPT vaccination during infancy // *Lancet*. – 1998; 351: 1489.
22. Vercelli D. Regulation of Ig E synthesis in humans // *J. Biol. Regulators Homeostatic Agents*. 1995; 9: 1-6.
23. Kassil G.N., Science about pain, 2nd ed., publisher “SCIENCE”, Moscow, 1975
24. Akhmedjanova Z.I. «Histamine levels in HIV infected patients» 14th International Congress of immunology Kobe, Japan. 2010: 64.
25. Akhmejanova Z.I. Disbalance of some of the macro and micro elements in HIV infected patients. *Review of Global Medicine and Healthcare Research*. 2011; 2(1): 7-16.