ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 10 | October - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

IS THERE A GENDER BIAS IN ORAL MUCOSAL LESIONS?

Dental Science

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ABSTRACT

Gender equity is a worldwide motto in the current scenario and is the need of the century. But there are certain natural factors that may seem to show gender inequality. It is interesting to study those aspects of gender bias related to human diseases. This helps in better diagnosis and early treatment plan for diseases that show gender inequality. This article aims to discuss about the various factors that contributes to the 'gender bias' by nature.

KEYWORDS

Autoimmune diseases, Gender, Oral mucosal lesions

INTRODUCTION

Autoimmune diseases are conditions in which host immune system attack its own cells.

There are over 100 types of autoimmune diseases that predominantly affect women. Approximately 80% of all patients diagnosed with autoimmune diseases are women.[1] It is interesting to understand the reason behind this as it can lead to development of better treatment modalities, thereby providing better quality of life and reduced morbidity rate in patients affected by autoimmune diseases.

Immune System

Immunological response is different in males and females. Females have stronger immune reactivity, but it acts as a double edged sword. On one side it decreases the chance of development of infectious disease and on the other side it increases the susceptibility of developing autoimmune diseases. [2] It was hypothesised that B cell activation and antibody production is more in females compared to males.[3] CD4+ T-cell counts is found to be higher in females compared to males. Females also show elevated plasma IgM and T-helper 1 (Th1) cytokine production.[4]The gender bias in autoimmunity could be due to the difference in immune system in males and females. There are certain factors which are responsible for the difference in immune reactivity in males and females. Role of these factors are discussed below.

Role Of Hormones

Female hormones play a major role in creating a gender bias in development of autoimmune diseases. Females undergo major endocrine transitions in their life time compared to males. There are major fluctuations in hormone levels during puberty, pregnancy, lactation and menopause.[5, 6] Difference in severity of autoimmune disease during these endocrine transitions clearly indicates the role of hormones in development and progression of these autoimmune diseases. Many sex hormone receptors are found to be present on immune cells; also there are cytokine receptors on hormone producing tissues. Sex hormones affect autoimmunity by their effect of gene transcription.[7] Studies had shown that estrogen makes females more susceptible to autoimmune diseases while androgen plays protective mechanism against autoimmune diseases.[8] Estrogen affects the expression of intracellular Toll like receptors (TLRs). Studies have shown that the production of proinflammatory cytokines increases significantly in presence of estrogen.[7]

Estrogen increase B-cell activation and enhances antibody production while testosterone and progesterone have immunosuppressive effect. Androgen helps in CD8 + cell activation. Androgen causes increase in anti-inflammatory cytokines and decrease in proinflammatory cytokines. It also decreases NK cell activation.[9]

Pregnancy

Pregnancy involves many physiological changes. Change in various hormone levels are seen in pregnancy.[10] Change in severity of autoimmune disease is seen during pregnancy when level of estrogen and progesterone reaches its peak.[11] Hormones may not have same impact on different autoimmune diseases. Effect of pregnancy is contrasting in inflammatory autoimmune diseases and antibody mediated autoimmune diseases. For example, remission is seen in case of inflammatory autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA) and increase in severity seen in antibody mediated autoimmune diseases such as systemic lupus erythematosis (SLE).[12]There is a shift in activity of type 1 helper T cells (Th1) to type 2 helper T (Th2) cells during pregnancy. There is increased Th2-related and reduced Th1-related activities. Therefore during pregnancy the severity of Th1-mediated diseases decreases while severity of Th2-mediated diseases increases. This may be the cause of remission seen in case of rheumatoid arthritis during pregnancy.[13,14]Microchimerism is another factor associated with pregnancy which contributes to susceptibility to autoimmune diseases.[10] Microchimerism is the phenomenon of persistence of fetal cells in maternal circulation even after pregnancy.[15] Studies had shown microchimerism to be associated with autoimmune thyroid disease and systemic sclerosis. Various studies regarding the effect of microchimerism in development of autoimmunity had shown conflicting results.[1]

Lactation

Level of pregnancy hormone decreases after pregnancy but the increased level of prolactin and oxytocin is present during lactation period. Main action of prolactin is on mammary gland. Prolactin receptors are seen in T lymphocytes and monocytes.[10]Prolactin favours antibody production.[9]

Menopause

During menopause level of estrogen and progesterone reduces and FSH level increases. Also many immunological changes happens during menopause which include increased production and response to pro-inflammatory cytokines, decreased secretion of anti-inflammatory cytokines, decreased lymphocyte levels, and decreased activity of NK cells.[16,17]

All these factors together may contribute to increased incidence of autoimmune diseases during menopause. There are conflicting reports about the effects of menopause on various autoimmune diseases. Reduction in frequency of flare-ups is reported in case of SLE. In contrast physical disability score is found to be higher in postmenopausal women with RA.[10]

Chromosomes

The major differentiating factor between the two genders is the sex chromosome. Males have XY chromosome while females have XX chromosome.[18] X chromosome is larger than Y chromosome which means there is more number of genes on X chromosomes. There are 800-900 genes on X chromosome and 50-60 genes on Y chromosome. Also greater number of immune related genes is present on X chromosomes. Since females have two X chromosome this obviously puts females at greater risk of developing autoimmune diseases.[18]

X Chromosome Inactivation

Since there are two X chromosomes in females, one of the X chromosomes gets silenced during embryogenesis to prevent over expression of X chromosome-derived proteins. During this process some of the genes escape the inactivation. This leads to overexpression of certain genes.[9] Inactivation of X chromosome is usually random in all cells. Either the X chromosome from mother gets inactivated or X chromosome from father can get inactivated. There is equal chance of both. But in certain cases X chromosome inactivation gets skewed and

can favour one of the two X chromosomes. Studies have shown that skewed X chromosomes are more prevalent in patients with autoimmune diseases compared to healthy individuals.[19] Skewed X chromosome inactivation has been reported in scleroderma, rheumatoid arthritis and systemic sclerosis[21] but not seen in primary Sjögren's syndrome, systemic lupus erythematosus or multiple sclerosis.[21]

MicroRNAs (miRNA)

Difference in expression of miRNA is noted in males and females. Higher number of miRNA are seen in X chromosomes compared to Y chromosomes. Studies have shown disregulation of miRNA in SLE. Overexpression of miRNA is seen in females with SLE but this is not seen in males. Presence of two X chromosomes may be the reason for this overexpression.[22]

Any of these factors or synergic action of these factors can be considered as the reason behind the gender bias seen in autoimmune diseases. Below discussed are various common autoimmune disorders showing oral manifestations and the factors responsible for gender bias in each disease.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a severe and chronic autoimmune inflammatory disease. SLE has a female to male ratio of 8:1.[23] Lack of X inactivation and overexpression of CD40LG and CXCR3 genes is seen in SLE patients.[24] In SLE presence of antinuclear antibodies are seen. Estrogen enhances the production of these antibodies.[25] Studies have shown that transitional states in women favour development of SLE. A decline in incidence rate is seen after the age of 60 years.[26] Female to male ratio in SLE is lesser before puberty and after menopause which suggest the effect of hormones in development of SLE.[27]

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is characterized by chronic inflammation of joints. Rheumatoid Arthritis shows female to male ratio of 4:1. Incidence of rheumatoid arthritis is found to be higher in perimenopausal women.[27] Estrogen by its effect on interleukin-10 (IL-10) and transforming growth factor-β (TGFB), has the ability to decrease inflammation. Level of estrogen decreases during menopause which may be the reason behind increased incidence of rheumatoid arthritis in perimenopausal women.[18] Therefore hormonal changes can be considered as the contributing factor for the female predilection in case of rheumatoid arthritis.

Sjögren Syndrome

Sjögren Syndrome is an autoimmune disease showing oral and ocular manifestations. Sjögren Syndrome shows a female: male ratio of 9:1. Flare ups are seen during menarche and menopause which point towards influence of hormones.[28] Similar to rheumatoid arthritis estrogen plays a major role in development of Sjögren syndrome. There is decrease in estrogen level during menopause. Also females have increased level of antibody production which can contribute to development of Sjögren syndrome.[18]

Pemphigus

Pemphigus is an autoimmune disease characterized by bullae and erosions of the skin and mucous membranes. Studies had showed a female predominance in pemphigus. Prognosis is also found to be poor in females compared to male. Exact reason behind female predilection in pemphigus is not known, but presence of HLA alleles which are indicators of severe pemphigus is seen more commonly in females.[29]

Systemic Sclerosis

Systemic sclerosis is an autoimmune disease affecting multiple systems including skin, joints, lungs and heart. Systemic sclerosis shows female predilection with 4:1 ratio.[18] Defect in X chromosome inactivation is considered to be the reason behind this.[30] Studies had showed increased level of estrogen causing skin disease in patients with systemic sclerosis. Correlating this fact systemic sclerosis shows an increased incidence during child bearing age.[18]

Psoriasis

Psoriasis is an autoimmune disorder characterized by hyperkeratosis Hormonal changes play an important role on development of psoriasis in females. Flare ups are also found to be seen in response to hormonal changes. Development of psoriasis is found to be associated with changes in sex hormones, prolactin, glucocorticoids, epinephrine, thyroid hormone, and insulin.[18]

Lichen Planus

Oral lichen planus is a mucocutaneous disorder affecting both skin and mucous membrane including oral cavity. Though the exact etiology is not known, a T cell mediated immune response is considered to be associated with the development of lichen planus.[31] It shows a female predilection. It is mostly seen in age group of 30-60 years, which is the reproductive age which suggest role of hormone in development of lichen planus.[31]

Effect Of Gender On The Severity Of Autoimmune Diseases

Severity of autoimmune disease may also vary with gender. Gender biases in severity of autoimmune diseases are not very evident as the prevalence.[32] Further research is required in this area.

Effect Of Gender On Mortality Rate

In autoimmune diseases reduced life expectancy is seen compared to general population. Studies suggest that gender can have influence on mortality rate of autoimmune diseases. Some studies have shown greater mortality rate associated with female gender in case of SLE.[33]

Effect Of Gender On Treatment Response

Certain studies had shown gender bias in treatment response to various autoimmune diseases. Studies in different countries have shown that TNF inhibitor therapy for rheumatoid arthritis showed better remission rates in males compared to females.[34] Also females have shown greater adverse effect for biological therapies.[35]

Gender Bias In Infectious Diseases

Though increased immune response makes females more susceptible to development of autoimmune diseases, it is an advantage in case of infectious diseases. There are various studies showing increased incidence of infectious disease in males, for example tuberculosis shows male to female ration of 2:1.[36]

Another important finding is increased incidence and mortality rate in males in COVID 19 (SARS-CoV-2) infection. [37] According to the studies done so far ACE 2 are considered to be the receptors for SARS-CoV-2.[38, 39] Expression of ACE 2 is found to be higher in males compared to females.[39] this may be one of the reason for the male predominance in case of SARS-CoV-2 infection. Since there are limited number of studies done related to SARS-CoV-2 infection there may be many other factors which might influence this gender bias which is yet to be studied.

CONCLUSION

The gender bias in autoimmune diseases must be because of complex interaction between the factors like pregnancy, lactation, menopause, chromosomal factors and presence of micro RNA. Further studies are required to prove these, and to develop new treatment modalities considering the influence of these factors in development, severity and treatment response in various autoimmune diseases.

REFERENCES

1. Invernizzi P, Pasini S, Selmi C, Gershwin ME, Podda M: Female predominance and X chromosome defects in autoimmune diseases. J Autoimmun. 2009;33:12-16
2. Kira Rubtsova, Philippa Marrack, Anatoly V. Rubtsov. Sexual dimorphism in autoimmunity . J Clin Invest. 2015;125(6):2187–2193.
3. Kronzer VL, Bridges SL Jr, Davis JM III. Why women have more autoimmune diseases than men: An evolutionary perspective. Evol Appl. 2021;14:629–633.
4. Lleo A, Battezzati PM, Selmi C, Gershwin ME, Podda M. Is autoimmunity a matter of sex? Autoimmun Rev 2008;7:626-30.
5. Silverthorn DU, Ober WC, Garrison CW, Silverthorn AC, Johnson BR. Human Physiology: An Integrated Approach. San Francisco, CA: Pearson/Benjamin Cummings (2004).
6. Sherwood L. Human Physiology: From Cells to Systems. Cengage Learning (2015).
7. Emerging Infectious Diseases www.cdc.gov/eid Vol. 10, No. 11, November 2004
8. Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. Nat Rev Immunol 2010; 10: 594 - 604.
9. Cincinelli G, Generali E, Dudam R, Ravindran V, Selmi C. Why women or why not men? sex and autoimmune diseases. Indian J Rheumatol 2018;13:44-50
10. S.T. Ngo et al. Frontiers in Neuroendocrinology. 2014; 35:347–369
11. Borchers AT, Naguwa SM, Keen CL, Gershwin ME. The implications of autoimmunity and pregnancy. J Autoimmun 2010;34:287-99
12. Hantai D, Richard, P, Koenig J, Eymard B. Congenital myasthenic syndromes. Curr. Opin. Neurol. 2004;17:539–551.
13. Doria A, Cutolo M., Ghirardello A, Zampieri S, Vescovi F, Sulli A, Giusti M, Piccoli A, Grella P, Gambari P.F,. Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. Arth. Rheum. 2002;47:202–209.
14. Doria A, Ghirardello A, Iaccarino L, Zampieri S, Punzi L, Tarricone E, Ruffatti A, Sulli, A, Sarzi-Puttini P C, Gambari P F, Cutolo M. Pregnancy, cytokines, and disease activity in systemic lupus erythematosus. Arth. Rheum. 2004;51:989–995.
15. Bianchi D.W, Zickwolf G.K, Weil G J, Sylvester S, DeMaria M.A. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc. Nat. Acad. Sci.

1996;93:705–708
16. Gameiro C, Romao F. Changes in the immune system during menopause and aging. Front. Biosci. 2010;2:1299–1303
17. Gameiro CM. Romao F, Castelo Branco C. Menopause and aging: changes in the immune system – a review. 2010;67:316–320
18. Angum F, Khan T, Kaler J, et al. (May 13, 2020) The Prevalence of Autoimmune Disorders in Women: A Narrative Review. Cureus 12(5): e8094. DOI 10.7759/cureus.8094
19. Ozcelik T, Uz E, Akyerli CB, Bagislar S, Mustafa CA, Gursoy A, et al. Evidence from autoimmune thyroiditis of skewed X-chromosome inactivation in female predisposition to autoimmunity. Eur J Hum Genet. 2006;14:791-7.
20. Ozcelik, T., 2008. X chromosome inactivation and female predisposition to autoimmunity. Clin. Rev. Allergy Immunol. 34, 348–351.
21. Invernizzi P, Pasini S, Selmi C et al. Female predominance and X chromosome defects in autoimmune diseases. J Autoimmun 2009; 33: 12 - 6.
22. Hewagama A, et al. Overexpression of X-linked genes in T cells from women with lupus. J Autoimmun. 2013;41:60–71.
23. JB Albilia, D. K. Lam, CM. Clokie, GK Sándor, Systemic lupus erythematosus: a review for dentists. J. Can. Dent. Assoc..2007; 73(9):823–828
24. Stewart JJ: The female X-inactivation mosaic in systemic lupus erythematosus . Immunol Today. 1998;19:352-357.
25. SV Lourenço.et al. Lupus erythematosus: clinical and histopathological study of oral manifestations and immunohistochemical profile of the inflammatory infiltrate . J. Cutan. Pathol. 2007;34(7);558–564
26. Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. Ann Rheum Dis. 2016;75:136–41.
27. Desai MK, Brinton RD. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. Front. Endocrinol. 2019;10:265.
28. A Bascones Martínez, V García-García, JH Meurman, L Requena Caballero. Immune-mediated diseases: what can be found in the oral cavity?, Int. J. Dermatol. 2015;54(3):258–270
29. Cathy Y Zhao, Dédée F.Murrell. Autoimmune blistering diseases in females: a review Int. J. Women's Dermatology. 2015;1:4–12
30. Peoples C, Medsger TA Jr, Lucas M, Rosario BL, Feghali-Bostwick CA: Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. J Scleroderma Relat Disord. 2016;1:204-212.
31. Naresh Gangeshetty, B Praveen Kumar. Oral lichenplanus: Etiology, pathogenesis, diagnosis, and management. World J Stomatol. 2015;4(1): 12-21
32. Sakai R, Matsui S, Fukushima M, Yasuda H, Miyauchi H, Miyachi Y. Prognostic factor analysis for plaque psoriasis. Dermatology. 2005;211:103–106
33. Grytten Torkildsen N, Lie SA, Aarseth JH, Nyland H, Myhr KM. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. Multip. Scl. 2008;14:1191–1198
34. Jawaheer D, Messing S, Reed G, Ranganath VK, Kremer JM, Louie JS, Khanna D, Greenberg JD, Furst DE. Significance of sex in achieving sustained remission in the consortium of rheumatology researchers of North America cohort of rheumatoid arthritis patients. Arthritis Care Res. 2012;64(12):1811–8.
35. Kristensen LE, Karlsson JA, Englund M, Petersson IF, Saxne T, Geborek P. Presence of peripheral arthritis and male sex predicting continuation of anti-tumor necrosis factor therapy in ankylosing spondylitis: an observational prospective cohort study from the South Swedish Arthritis Treatment Group Register. Arthritis Care Res. 2010;62 (10):1362–9.
36. Sukesh Rao. Tuberculosis and patient gender: An analysis and its implications in tuberculosis control. Lung India. 2009;26(2): 46–47.
37. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;1–13.
38. Li W, Sui J, Huang IC, Kuhn JH, Radoshitzky SR, Marasco WA, et al. The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. Virology. 2007;367(2):367–74
39. George M. Bwire .Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN Compr. Clin. Med.2020