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Role of histamine as a toxic mediator in the pathogenesis of vitiligo

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Abstract

Background: The precise cause of vitiligo is still unclear. Multiple theories have been proposed, including genetic, autoimmune, neural, and biochemical mechanisms. An immune mediated pathogenesis is indeed the most popular theory. The autoimmune hypothesis considers the role of toxic mediator that might cause an injury to the melanocytes with the release of an antigenic substance and subsequent autoimmunization. **Aims:** This study performed over a period of 10 years (February 1975 to June 1985) aims at exploring the role that histamine might play in the pathogenesis of vitiligo. **Materials and Methods:** Fifty patients with a particular type of vitiligo characterized by faint white patches occurring with significant pruritus and a history of atopy were selected and blood histamine levels were determined by Bio-Assay method. **Results:** Blood histamine values of patients with vitiligo of short duration and with pruritus were significantly increased in comparison with values of matched controls. **Conclusion:** Histamine appears to play a significant role in the pathogenesis of a particular type of vitiligo characterized by faint hypopigmented patches with significant itching.

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Full Text

Introduction

Vitiligo is an acquired, idiopathic disorder of the skin characterized clinically by circumscribed depigmented macules and histologically by the absence of identifiable melanocytes. Functional melanocytes disappear from the involved skin by a mechanism(s) that has not been identified.[1] The main mechanism of melanocyte destruction in vitiligo is thought to be due to an autoimmune lymphocytic attack on melanocytes.[2] There are several hypotheses concerning the pathogenesis of vitiligo. Of the many hypotheses suggested by various investigators from time to time the following three have received general acceptance: (1) Autoimmune hypothesis: Suggests that depigmentation is due to formation of autoantibodies directed against body's own melanin or some other part of melanocyte. This may arise as a primary aberration of the immune surveillance, or the primary event could be an injury to the melanocyte with release of antigenic substance(s) and subsequent autoimmunization. Autoimmune etiology is favored by its association with known autoimmune diseases such as Addison's disease, Hashimoto's thyrioditis, pernicious anemia,[3] and the fact that patients with vitiligo have increased organ-specific autoantibodies including antibodies to adrenal cytoplasm, thyroglobulin, gastric parietal cells, and pancreatic islet cells. Antibodies directed against melanocyte cell surface antigens are often demonstrated in the sera of vitiligo patients.[4] Also antibodies against tyrosinase have been reported in patients of localized as well as generalized vitiligo.[5] (2) Self-destruction hypothesis: Suggests that in the process of synthesis of melanin within the melanocytes some toxic metabolic intermediates form. The normal melanocytes have inherent mechanisms by which these metabolites are successfully eliminated. Defects in, or absence of, of this inherent mechanism results in accumulation of toxic melanin precursors causing melanocyte dysfunction or death.[6] (3) Neuro-chemical hypothesis: suggests that release of a neuro-humoral or chemical factor destroys the melanocyte or inhibits melanin formation giving rise to depigmentation. Nature of this toxic mediator remains speculative. For a long time neurotransmitters from peripheral nerve-endings (acetylcholine and catecholamines) have been incriminated. A reduced acetylcholinesterase activity in vitiliginous skin has been reported.[7] Also dysfunction of sympathetic nerves in vitiliginous skin has been reported showing abnormalities in catecholamines and related enzymes (catechol-o-methyl transferase and monoamine oxidase).[8],[9] The neural hypothesis is based in the first place on the presence of segmental vitiligo. Segmental vitiligo is often described as following a dermatomal pattern and unilateral. But actually it does not follow a specific cutaneous sensory nerve distribution pattern.[10]

It has now been realized that all the various clinical types of vitiligo cannot be explained by a single hypothesis. Koga has shown that there are two distinct types of vitiligo, each having a different pathogenesis.[11] According to his view, the pathogenesis of dermatomally distributed vitiligo involves some disturbance in some sympathetic nerves of the affected area, which influences the melanocyte causing their functional inhibition or destruction. In contrast, nondermatomal vitiligo has a different pathogenesis in which primary disturbance lies in the melanocyte itself, where an autoimmune mechanism is suspect. This clinical distinction of segmental vitiligo and nonsegmental vitiligo done by Koga has not been challenged until recently. The Vitiligo European Task Force (VETF) in its consensus paper has followed this classification of Koga.[12] The VETF concluded that there was no significant evidence that the various sub-types of nonsegmental vitiligo were clearly distinct. Only recently it has been reported that in certain vitiligo patients, a characteristic segmental involvement become associated usually in a second-step with bilateral vitiligo patches and the term “mixed vitiligo” has been proposed by Mulekar et al., to designate this particular form of the disease.[13] The sequence of early segmental vitiligo leading to late onset nonsegmental vitiligo as found in the study of Ezzedine et al.,[14] may reflect the role of a cutaneous gene defect causing segmental vitiligo and later triggering a generalized immune response against cutaneous melanocytes driven by another immune-related gene defect.[15]

The idea that histamine might act as a toxic mediator in the pathogenesis of vitiligo arose from the observation that a good number of vitiligo patients attending the Pigment Clinic gave a

history of significant pruritus over vitiligo patches. More significantly, many patients gave a history of spread of vitiligo lesions just preceded by itching in the new areas. Such patients differed from the general pool of vitiligo patients in that they presented with hypo-pigmented patches scattered diffusely and were of short duration. Many of them gave history of sudden onset of such lesions with itching while several of them associated their lesions with photosensitivity and complained of flare-up of lesions after administration of melanizing agents. Histamine is particularly relevant in this context since histamine, which is also liberated along with other chemicals when cells are damaged, is one of the chemical mediators of itch. Moreover, there is evidence that in frog both histamine and histamine releaser produce skin color blanching and melanophor contraction. Also a significant number of vitiligo patients gave a history of atopy along with pruritus. The term atopy, or as presently used, atopic allergy implies a familial tendency to manifest alone or in combination such conditions as asthma, allergic rhinitis, and urticaria. Asthma is associated with increased IgE levels and high levels of IgE are found in patients with atopic dermatitis.[16] It has now been reported that histamine promotes the differentiation of dendritic cells toward a TH2 profile.[17] It is known that several hormones regulate melanogenesis through the action of ubiquitous cyclic adenosine monophosphate (AMP). High levels of cyclic AMP causes reduced secretion of histamine.

Based on the above facts and observations, it was hypothesized that histamine might act as a toxic mediator in the pathogenesis of a particular type of vitiligo.

Materials and Methods

The present study is a retrospective analysis of data of a select group of patients attending the Pigment Clinic of the Department of Dermatology, SSKM Hospital and IPGME and R, Kolkata between February 1, 1975 and June 30, 1985.

Design of study

All new vitiligo patients attending the Pigment Clinic were closely scrutinized by carefully taken histories and thorough clinical examination. Only those patients satisfying one or more of the following criteria were selected for the study: (1) Presence of pruritus in the lesions; (2) Faintly defined hypopigmented guttate type lesions that are distributed in a diffuse manner and are of recent origin; (3) A positive history of atopy in the patient or in the family; and (4) Association of halo nevus, Koebner's phenomenon, or photosensitivity.

Patients studied

In the period under review, a total of 50 patients were studied. Detailed histories and clinical features were recorded systematically in charts. Important clinical data of the patients are summarized in [Table 1].{Table 1}

Histopathological examination

From a small lesion of recent origin in a suitable area a thin slice of skin was taken with the help of a punch under local anesthesia. The tissue obtained by punch biopsy was subjected to conventional sectioning through the stages of fixation, dehydration, clearing, impregnation and embedding. Sections from each tissue are stained by haemtoxylin-eosin stain and by toluidine blue stain (for mast cells).

Blood histamine assay

Before giving any treatment to the patients, blood samples were taken for estimation of histamine levels in the blood. Five (5) ml of blood was dissolved in 10 ml of 10% trichloroacetic acid solution in a test-tube, and after vigorous shaking; the mixture was kept in a refrigerator. Estimation of blood histamine level was done by Bio-Assay method (H.O. Schild, 1942)[18] using a strip of terminal guinea pig ileum in an organ bath.

Dose-related contraction in the presence of atropine (to exclude acetylcholine activity) followed by inhibition of this activity by antihistamine mepyramine maleate confirms the presence of histamine. This method reliably detects concentrations in the range of 1-2.5 ng/ml.

Results

Analysis of clinical data

Of the 50 patients studied, pruritus was a significant finding in 28 patients and atopy in 12 patients. Regarding distribution of lesions, symmetry was observed in 27 patients while only 4 patients revealed dermatomal pattern. Nine patients gave family history of vitiligo. And five patients had association with halo nevus.

Histopathological findings

The histology of lesions of recent origin revealed flattening of epidermis, homogenization (a ground glass appearance) of collagen in the upper dermis and mild increase of vascularity with slight perivascular infiltrate and edema. Melanocytes are decreased in number with scanty or absent pigment granules. Except three cases, infiltrate (which is chiefly lymphocytic) was patchy, scanty, and perivascular. In three specimens the infiltrates are slightly heavy in the border of the active lesions and in one the infiltrate invaded the epidermis. Mast cells are significantly increased in number and are loaded with numerous granules. No degeneration of nerve fibrils seen and the sweat glands and other appendages are normal.

Analysis of blood histamine values

The blood histamine values of vitiligo patients were significantly increased in comparison with values of matched controls (normal human volunteers) as shown by the overall mean values in [Table 2].{Table 2}

When the blood histamine values of the vitiligo patients were further analyzed forming groups in terms of presence of or absence of pruritus, and length of duration, it was found that the blood histamine values were higher in all cases except those of long duration where the values are significantly lower than the general trend ($P < 0.05$). The overall mean values of different groups are compared in [Table 3]. Blood histaminase levels were also determined (expressed in provisional units/ml) and were found to be significantly high in vitiligo patients compared with normal group [Table 4]. High plasma histaminase values along with high blood histamine levels indicate even higher value of histamine in vitiligo than what has been found in the patients. The values are statistically significant. Significantly higher values of histamine in short duration cases is shown in a histogram [Figure 1].{Table 3}{Table 4}{Figure 1}

Discussion

The precise cause of vitiligo is still unclear. However, multiple theories have been proposed, including genetic, autoimmune, neural, and biochemical mechanisms. Reviews addressing the etiology of vitiligo, viewed in totality suggest that vitiligo is probably a heterogeneous disease encompassing multiple etiologies.[19]

This study, performed in earlier times when modern immunological techniques were not available, showed that a considerable number of patients presented with pruritus and atopy and it seems reasonable that histamine might be acting as a toxic mediator in these cases. Histopathological study revealed slight perivascular infiltrate and moderately increased vascularity with some vasodilation and significantly increased number of mast cells. Also upper dermis showed some edema and homogenization of collagen. These vascular changes might be produced by histamine released in the tissue. Another consistent histopathological finding is the flattening of the epidermis. This flattening of the epidermis and vacuolization of some epithelial cells reflect an involvement of histamine since it has now been reported that histamine acts as an inhibitor of human keratinocytes and suppressor of epidermopoiesis in humans and animals. Blood histamine values of vitiligo patients are significantly higher than the values found in normal persons ($P < 0.05$). Also blood histaminase levels were determined and were found to be significantly elevated in vitiligo cases of short duration compared with normal control group. High plasma histaminases along with high blood histamine indicate even higher value of histamine in vitiligo. These observations support the hypothesis that histamine has a role in the pathogenesis of a particular type of vitiligo, characterized by faint white patches, pruritus, occasional intolerance to melanizing agents, and an association of atopy. Histamine might also be operative in the pathogenesis of other types of vitiligo but the present study has been restricted to a group of patients having vitiligo of a particular type specified.

Now it has been established that histamine regulates T-cell and B-cell function by differential expressions of H1 and H2 receptors.[20] Histamine enhances Th1 responses by triggering the H1 receptor, whereas both Th1 and Th2 responses are negatively regulated by H2 receptor via the activation of different intracellular signaling pathways. These findings indicate an important regulatory mechanism in the control of immune functions through release of histamine.

An immune-mediated pathogenesis is indeed the most popular theory. This theory is based on increased number of immune phenomena and immunological disorders seen in vitiligo patients. An increased frequency of hypothyroidism (e.g., Hashimoto thyroiditis, Graves' disease), diabetes mellitus, and alopecia areata are commonly seen in vitiligo patients. Humoral and cell-mediated immunological defects are common phenomena in vitiligo.[21]

Several investigators have also addressed the role of peripheral blood and lesional cytokine expression in the pathogenesis of vitiligo. Elevated levels of serum soluble IL-2 receptor, IL-6, and IL-8 and elevated lesional tissue levels of IL-2 have been reported in vitiligo patients.[22] Histamine activity regulates the formation of cytokines. Histamine, through the H2 receptor, reduces the production of IL-1, IL-6, and TNF-α from endotoxin-stimulated monocytes.[23] Thus, it has now been clear that histamine mediates some actions through various interleukin pathways and thus this finding can be taken to correlate with this study, which was performed much earlier, showing role of histamine in the pathogenesis of vitiligo of a particular kind.

Conclusion

From our findings of high blood histamine level as well as high blood histaminases level in cases of a particular type of vitiligo of short duration and characterized by faint hypopigmented patches with significant itching, we hypothesize that histamine has a definite role in the pathogenesis of vitiligo. This study, which was performed much earlier, highlighted that some allergic phenomena were operative in the pathogenesis of vitiligo as evidenced by high levels of blood histamine and histaminases. The idea raised by this study that some allergic phenomena were suspect in the causation of vitiligo has been corroborated by subsequent workers showing autoimmune nature of the disease.

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