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Etiopathogenesis of Alopecia Areata

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Abstract

Alopecia areata (AA) is a recurrent, non-scarring type of hair loss affecting the hair follicles and sometimes the nails. Current evidence indicates that hair follicle inflammation in alopecia areata is caused by a T-cell mediated autoimmune mechanism occurring in genetically predisposed individuals. Environmental factors like infections, diet, vaccination and stress may be responsible for triggering the disease. The association between alopecia areata and other autoimmune diseases suggests that alopecia areata is itself an autoimmune disease. Recently many cytokines have been implicated in the pathogenesis of AA and these are focused upon in this article.

Keywords: Alopecia areata; Hair loss; Autoimmune diseases

Introduction

Alopecia areata is a chronic inflammatory disease which affects the hair follicles and sometimes the nails. It was first described by Cornelius Celsus, and the term alopecia areata was coined by Sauvages in 1760. The onset may be at any age and there is no known race or sex preponderance. Alopecia areata usually presents as patches of hair loss on the scalp but any hair-bearing skin can be involved. The affected skin is usually normal but may be slightly reddened [1-3]. The exact incidence and prevalence of the disease is not available. In the only formal population study of alopecia areata, from Minnesota, USA, the incidence rate was 0.1-0.2% with a projected lifetime risk of 1.7%. About 20% of people with alopecia areata have a family history of the disease, indicating a genetic predisposition4. Associations have been reported with a variety of genes, including major histocompatibility complex, cytokine and immunoglobulin genes, suggesting that the genetic predisposition is multifactorial in nature [5]. Current evidence indicates that hair follicle inflammation in alopecia areata is caused by a T-cell mediated autoimmune mechanism occurring in genetically predisposed individuals. Environmental factors may be responsible for triggering the disease [6]. The association between alopecia areata and other autoimmune diseases suggests that alopecia areata is itself an autoimmune disease, although this is unproven [7,8].

Epidemiology

Alopecia areata (AA) is a common form of non-scarring alopecia involving the scalp and/or body, characterized by hair loss without any clinical inflammatory signs. It is one of the most common form of hair loss seen by dermatologists and accounts for 25% of all the alopecia cases [9]. The exact incidence and prevalence of the disease is not available. It accounts for 2-3% of the new dermatology cases in UK and USA, 3.8% in China, and 0.7% in India. In general population, the prevalence was estimated at 0.1-0.2% with a lifetime risk of 1.7%. Both males and females are equally affected, but some studies reported male preponderance. It can occur at any age. The youngest case reported in literature is 4-months-old and the oldest in late seventies [10]. Approximately twenty percent of cases are encountered in children, and in 50-60% of AA patients the first patch usually develops before 20 years of age. Highest prevalence is seen in the third and fourth decade. Family history is seen in approximately 8.7-20% of cases [11]. Nail changes consist of geometric pitting (fine regular pitting), punctuate leukonycia, trachyonychia, onychomadesis and red lunulae [12]. Dermoscopy shows yellow dots, black dots, broken hair and tapering hair [13].

Clinical features

Alopecia areata usually presents as well defined patches of hair loss on the scalp but any hair-bearing skin can be involved. Typically, the surface of patches is smooth and of normal skin colour without any secondary changes like scaling and follicular changes. Rarely, it can be erythematous [14,15]. Characteristic 'exclamatory mark hairs' are seen either within or at the border of the patches. These are short hairs with proximal tapering, close to scalp and distal thickening and widening [15,16]. The diagnosis is mostly clinical. Dermoscopy is useful in doubtful cases.

Types of alopecia areata

• Ikeda classified AA based on the associated conditions and on the course of the disease [16]:

Atopic type: It begins early in life and mostly (30-75%) progresses to alopecia totalis.

Autoimmune type: It is seen in middle-aged groups and is associated with autoimmune diseases, and progresses to alopecia totalis in 10-50%.

Prehypertensive type: It is seen in young adults whose parents are hypertensive and progress rapidly to alopecia totalis in 40% of cases.

Common type: It affects adults aged 20-40 years and alopecia totalis develops in 5-15% of cases.

• Based on the pattern of hair loss, alopecia areata is classified into [17]:

Reticular: Small distinct patches may merge and form larger patches.

Ophiasis: is a band-like AA along the posterior occipital and temporal margins.

Sisaipho: also called as ophiasisinversus, presents with alopecia involving the frontal, temporal, and parietal scalp but spares hair along the scalp periphery, mimicking androgenetic alopecia.

• Based on the extent of hair loss [18]:

Patchy alopecia areata: It may present as single or multiple patches.

Alopecia totalis: Involving the entire scalp hair.

Alopecia universalis: If the total body hair is involved.

• New variants:

Acute and diffuse total alopecia: It is characterized by female preponderance, generalized hair thinning, rapid progression, tissue eosinophilia, extensive involvement, brief clinical course, and favorable prognosis [19].

• Unusual patterns:

Perinaevoid and linear alopecia areata: Alopecia patches around the nevi,reported by Yesudian et al and unusual presentations may occur in linear distribution [20].

Pathology: In acute cases, peribulbar and intrabulbar lymphocytic inflammatory infiltrate around anagen follicles, resembling 'swarm of bees,' is characteristic [21]. The lymphocytes are mainly present around the hair matrix and dermal papilla and spare the bulge area, causing follicular edema, cellular necrosis, microvesiculation, and pigment incontinence. In subacute lesions, a high proportion of catagen/telogen hair follicles are seen. In chronic cases, follicular miniaturization with variable inflammatory infiltrate is seen in papillary dermis. The terminal to vellus hair ratio is decreased to 1:1 in contrast to 7:1 in normal population.

Etiopathogenesis

AA is a disorder of hair cycling and is considered to be a state of kenogen. Following are the various etiological factors which are postulated to play a role in the causation of alopecia areata:

Genetic factors

The role of genetic factors is supported by the occurrence of disease in families, which in most studies has been reported to occur in 10-20% of the cases and in twins (concordance rate of 55% in monozygotic twins with no concordance in dizygotic twins).The lifetime risk of alopecia areata in the children of a proband is approximately 6%. The genetic basis of the disease is polygenic and is probably modified by environmental factors. Alopecia areata has been strongly associated with major histocompatibility complex genes on chromosome-6, especially the class II alleles (HLA-DQB1*0301 and HLA-DRB1*1104). Susceptibility loci have also been noted on chromosomes 10, 16 and 18.Recently, genome wide association studies (GWAS) have identified specific genetic markers for AA, which may increase the risk for AA. Petukhova et al. surveyed the entire genome and identified 139 single nucleotide polymorphisms (SNPs) for AA, clustered in 8 regions of the genome [22]. GWAS studies have found key genes in AA related to T-cells (IL2/IL21, IL2RA, CTLA4, IKZF4, HLA) and hair follicle (NK-activating ligands-ULBP3, ULBP6, STX17, PRDX5) [23]. All these are suggestive of genetic predisposition in the development of AA.

Atopy

Several uncontrolled studies have reported an association between alopecia areata and atopic state, and the disease is more severe and earlier in onset in those with atopic diathesis. Moreover the prognosis is reported to be bad in these patients [24].

Autoimmunity

The association of alopecia areata with autoimmune diseases was first suggested by Rothman. The frequency of myxoedema, pernicious anemia and type 1 diabetes mellitus is increased in the relatives of patients with alopecia areata than in those without the disease. The patients with alopecia areata have an increased frequency of circulating organ and non-organ-specific auto antibodies compared with control subjects. Hair follicle-specific antibodies are increased in peripheral blood of AA patients, especially to keratin 16 and trichohyalin [25]. It is believed that hair follicle is an immune-privileged site [26]. In healthy hair follicle epithelium, major histocompatibility complex (MHC) class I and II molecules are not expressed and TGF- β, IGF-1, and α-MSH are more expressed [27]. This immune privilege is collapsed in AA by the presence of increased MHC I and II complexes, decreased immunosuppressive molecules, and higher expression of adhesion molecules (ICAM-2 and ELAM-1) in the perivascular and peribulbar hair follicular epithelium, leading to perifollicular inflammation [28]. This peribulbar inflammation adversely affects hair follicle activity, resulting in thin dystrophic hair with miniaturization. Thus, AA is considered as hair follicle-specific autoimmune disease, triggered by environmental factors in genetically susceptible individuals [29].

Stress

Stress is considered as one of the triggers, but controlled studies have failed to confirm this. Emotional trauma of a related death or an accident have been reported as precipitating factors in individual cases, but there are no controlled studies proving this [30].

Diet

Iron deficiency was noted in 24-71% of females with AA in one study [31]. AA has been observed less frequently in people, taking diet rich in soy. Some studies have found decreased levels of zinc in the blood of AA patients and others have reported conflicting results [32,33].

Vaccination

Hepatitis B vaccination has been implicated, but larger studies have failed to confirm any such association [34].

Infectious etiology

Epidemics of AA which were reported from orphanages and schools initially pointed towards an infectious etiology. Viral etiology was proposed. Cytomegalovirus infection has been implicated but studies have failed to confirm it [35].

Recent concepts in the pathogenesis of alopecia areata:

• According to the National Alopecia Areata Foundation, alopecia areata is a common autoimmune skin disease resulting in the loss of hair on the scalp and elsewhere. It affects approximately two percent of

the population overall. While it affects both men and women equally, it is diagnosed more often in women, since they are more likely to seek treatment. Among the eight genes found on GWAS, one stands out for its potential role in the onset of alopecia areata. The gene, called ULBP3, is known to act as a homing beacon for cytotoxic cells that can invade and quickly destroy an organ. Normally, ULBP3 is not present in hair follicles, but the ULBP3 proteins are abundant in hair follicles affected by alopecia areata. The proteins attract cells marked by a killer cell receptor, known as NKG2D. In addition to ULBP3, two other genes are expressed in the hair follicle, while the five remaining genes are involved in the immune response [36].

• A recently proposed hypothesis is the faulty upregulation of an immune signal that mistakes the hair follicle for an infected or dying cell, and therefore launches the release of cytotoxic T cells that attack the end organ. A key source for fuelling those particular killer T cells in an autoimmune response is IL-15, and therefore, therapies could be aimed at blocking the IL-15 signal that sustains those killer T cells. Two FDA-approved small molecule drugs that interfere downstream in these signalling pathways include ruxolitimib, a JAK1/2 inhibitor, approved to treat myelofibrosis, and tofacitinib, a JAK3 inhibitor approved for the treatment of rheumatoid arthritis (Annual Meeting news), Denver Colo, March 21-25, 2014, Annual meeting of American Academy of Dermatology.

• In recent studies, psychologic and psychopathologic factors have been analyzed as modulators of neuroendocrinologic, vascular, and immunologic variables; this is far from the initial concept of stress being the causal agent in the illness. In fact, stress may cause its effect by making alterations in immune responses related to neuropeptides, such as the migration of the macrophages, vasodilator or vasoconstrictor responses, phagocytosis, lymphocytic cellular immunity, and expression of some factors of leukocytic adhesion to the microvascular endothelium. In addition, the adaptation to the illness is regarded as an important factor with regard to prognosis. However the exact cause of AA is not known and such events are very common, making it difficult for the investigator to prove that they are in fact involved in causing or precipitating the disease [37].

• Macrophage migration inhibitory factor (MIF) seems to have an essential role in the etiopathogenesis of AA. It is located at an upstream position in the events leading to the possible dysregulatedimmuno-inflammatory responses, and the high level of this cytokine in AA may suggest a role of MIF in the pathogenesis of AA. There is also a positive correlation between MIF levels and clinical severity and disease duration. So, it is considered to be a promising target in the therapy of autoimmune diseases and as a future predictor of alopecia activity. Anti-MIF therapy might be added as one of the new biological treatments for AA [38].

Differential diagnosis of alopecia areata

The diagnosis of alopecia areata is usually straightforward although the following may cause diagnostic difficulties: Trichotillomania, tineacapitis, cicatricial alopecia, androgenetic alopecia, telogen effluvium, secondary syphilis, congenital triangular alopecia, pressure alopecia, traction alopecia and SLE.

Investigations

Investigations are unnecessary in most cases of alopecia areata. When the diagnosis is in doubt, following investigations may be ordered: KOH smear, fungal culture, scalp biopsy, serology for lupus erythematosus, serology for syphilis and thyroid screening. Hair pull test, hair pluck test, dermoscopy, SALT score (Severity of Alopecia Tool Score) are useful in assessing the activity and severity of the disease. Optical Coherence Tomography (OCT) is a recently evaluated non-invasive technique to detect the hair shaft abnormalities in AA [39]. The increased frequency of autoimmune disease in patients with alopecia areata is probably insufficient to justify routine thyroid screening.

Scoring system in alopecia areata

SALT score is useful to find out the quantitative assessment of scalp hair loss [40]. In SALT score the entire scalp in divided into 4 parts based on the surface area, Vertex (top) (40%-0.4), posterior (24%-0.24), right side (18%-0.18), and left side of scalp (18%-0.18). Percentage of hair loss in each area is determined independently and is multiplied by the percentage of scalp covered in that area of the scalp, and summing the products of each area gives the SALT score. For example, the hair loss is 40%, 30%, 20% and 10% in top, back and right and left side respectively, then the SALT score can be calculated as- $(40\times0.4)+(30\times0.24)+(20\times0.18)+(10\times0.18)=16+7.2+3.6+1.8=28.6$.
SALT score is easily reproducible and validated. However, it does not include hair pigmentation, body hair, and nail involvement.

Course and Prognosis

Spontaneous regrowth occurs in many patients. Most will have more than one episode. 50-80% of patchy AA patients have spontaneous regrowth in 6months to 1 year. In few it may persist for longer time, and some may never recover hair. The disease may progress and worsen in children, even with milder initial presentation [41].

Poor prognostic factors

Younger age of onset, family history, history of atopy, pattern (ophiasis, alopecia totalis, alopecia universalis), duration greater than 1 year and presence of nail disease and other autoimmune diseases [42].

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