ALOPECIA AREATA: SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

BACKGROUND
Alopecia areata is a common autoimmune disease that encountered worldwide. Many modalities have been used but no one was universally effective. Zinc sulphate has been used in the treatment of many skin diseases. Zinc supplement is popular trace element gave for hair loss.

OBJECTIVE
To estimate the efficacy of oral zinc sulfate in patients of patchy alopecia areata presenting in a tertiary care hospital

STUDY DESIGN
Randomized controlled trail

SETTINGS
Study was conducted at Dermatology Department Unit-II, Mayo Hospital, Lahore.

DATA COLLECTION PROCEDURE
Total 60 clinically diagnosed cases of patchy alopecia areata of scalp as non scarring alopecia for less than one year duration were included in the study. Patients were divided into two groups A & B by draw box methods, 30 patients in each group. In group A, oral zinc was given in the form of zinc sulfate capsules in a dose of 5 mg/kg/day in a single or two divided doses according to weight of the patient. In group B, patients received placebo in the form of brown sugar capsules once a day. Patients were followed on monthly basis till recovery or maximum upto four months. The response was assessed according to SALT score (annexure 1). Photographs were taken on each visit. All the above information was collected through a predesigned proforma. The data was entered and analyzed by using SPSS version 12.0.

RESULTS
Mean of patients in Group-A and in Group-B was 33.23±7.03 and 33.00±7.55 years. In Group-A mean Salt score before and after treatment was 7.53±4.79 and 3.26±4.32. While in Group-B mean Salt score before and after treatment was 6.05±4.34 and 5.46±4.98. Improvement was defined as 50% or more reduction in SALT score. As per this criteria in Group-A there were 20(66.7%) patients who had improvement while in Group-B only 2(6.7%) patients had improvement. According to p-value improvement was significantly associated with treatment groups. i.e. (p-value=0.000) Improvement rate of Group-A was high as compared to that of Group-B. Among male and female patients significant improvement was seen in Group-A patients. i.e. [p-value (male)=0.000 & p-value (female)=0.013]

CONCLUSION
Based on these results it can be said that oral Zinc therapy had a positive and significant role in treating patients with patchy alopecia areata. In terms of SALT scoring system improvement (>50% reduction in SALT score.) was seen in 66.7% patients who were treated with oral zinc.

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1. INTRODUCTION

Alopecia areata is an autoimmune disorder of hair characterized by rapid and complete or partial loss of hair in one or more, round or oval, nonscarring patches that can affect any hairbearing area. In 10% cases of alopecia areata pitting and sandpaper changes are seen in the nails. At any given time 0.2% of the world population suffer from alopecia areata with an estimated lifetime risk of 1.7%. Usual age of onset for alopecia areata is less than 25 years with an equal incidence in males and females. Various genetic and environmental factors are suggested in etiology of alopecia areata. About 20% have family history. Association with other autoimmune disorders such as Hashimoto’s thyroiditis, pernicious anaemia, diabetes, rheumatoid arthritis, vitiligo and myasthenia gravis suggest its autoimmune basis. Data shows that 34-50% of patients will recover within one year, 14-25% may progress to alopecia totalis or universals from which recovery is less than 10%.
2. REVIEW OF LITERATURE

2.1 Historical aspects

The first clinical description of alopecia areata is attributed to Celsus (14 to 37 B.C.), and the designation alopecia areata is by Sauvages. Hebra demonstrated the incorrectness of the hypothesis of fungal etiology as proposed by Willan and Gruby (1843). Later, Von Baresprung proposed the neurotrophic theory, and Jacquet elaborated the dystrophic theory, considering the disease to be caused by infectious focuses, particularly dental, a hypothesis today that has been totally discarded. Nowadays, alopecia areata is interpreted as an autoimmune disease with a genetic substrate.11, 12

2.2 Dynamic of hair loss

Hair follicle growth occurs in cycles. Each cycle consists of a long growing phase (anagen), a short transitional phase (catagen) and a short resting phase (telegen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle beginning the cycle again. There are considerable variations in the length of the three phases, with the duration of the anagen determining the type of hair produced, particularly its length. Normally about 100 strands of hair reach the end of their resting phase each day and fallout.13

2.3 Epidemiology & demography

AA is a relatively frequent disease with a prevalence of 0.1%-0.2% worldwide.16, 17 Among different races and ethnic groups, the prevalence can range, from 0.9% to 6.9% 18. Notably, individuals with Down’s syndrome seem to have a slightly higher incidence 19. In the United States, one study reported that about 14.5 million patients suffer from AA, constituting about 2% of the national population 18, while another study suggested that only about 5.3 million in the U.S. are clinically affected 20. Overall, AA seems to account for about 0.7%-3% of all patients in the United States 21, and about 2% in the United Kingdom 19.

2.4 Pathophysiology

The exact pathophysiology of alopecia areata remains unknown. The most widely accepted hypothesis is that alopecia areata is a T-cell–mediated autoimmune condition that is most likely to occur in genetically predisposed individuals.25

2.5 Autoimmunity

Much evidence supports the hypothesis that alopecia areata is an autoimmune condition. The process appears to be T-cell mediated, but antibodies directed to hair follicle structures also have been found with increased frequency in alopecia areata patients compared with control subjects. Using immune fluorescence, antibodies to anagen-phase hair follicles were found in as many as 90% of patients with alopecia areata compared with less than 37% of control subjects. The autoantibody response is heterogeneous and targets multiple structures of the anagen-phase hair follicle. The outer root sheath is the structure targeted most frequently, followed by the inner root sheath, the matrix, and the hair shaft. Whether these antibodies play a direct role in the pathogenesis or whether they are an epiphenomenon is not known. Histologically, lesional biopsy findings of alopecia areata show a perifollicular lymphocytic infiltrate around anagen-phase hair follicles. The infiltrate consists mostly of T-helper cells and, to a lesser extent, T-suppressor cells. CD4+ and CD8+ lymphocytes likely play a prominent role because the depletion of these T-cell subtypes results in complete or partial re-growth of hair in the Dundee experimental bald rat (DEBR) model of alopecia areata. The animals subsequently lose hair again once the T-cell population is replete. The fact that not all animals experience complete re-growth suggests that other mechanisms likely are involved. Total numbers of circulating T lymphocytes have been reported at both decreased and normal levels.26

2.5.1 Genetics

Many factors favor a genetic predisposition for alopecia areata. The frequency of positive family history for alopecia areata in affected patients has been estimated to be 10-20% compared with 1.7% in control subjects.27 The incidence is higher in patients with more severe disease (16-18%) compared with patients with localized alopecia areata (7-13%). Reports of alopecia areata occurring in twins also are of interest. No correlation has been found between the degree of involvement of alopecia...
areata and the type of alopecia areata seen in relatives. Several genes have been studied and a large amount of research has focused on human leukocyte antigen. Two studies demonstrated that human leukocyte antigen DQ3 (DOB1*03) was found in more than 80% of patients with alopecia areata, which suggests that it can be a marker for general susceptibility to alopecia areata. The studies also found that human leukocyte antigen DQ7 (DOB1*0301) and human leukocyte antigen DR4 (DRB1*0401) were present significantly more in patients with alopecia totalis and alopecia universalis.28

2.5.2 Cytokines

Interleukin 1 and tumor necrosis factor were shown to be potent inhibitors of hair growth in vitro. Subsequent microscopic examination of these cultured hair follicles showed morphologic changes similar to those seen in alopecia areata.29

2.5.3 Innervation and vasculature

Another area of interest concerns the modification of perifollicular nerves. The fact that patients with alopecia areata occasionally report itching or pain on affected areas raises the possibility of alterations in the peripheral nervous system. Circulating levels of the neuropeptide calcitonin gene-related peptide (CGRP) were decreased in 3 patients with alopecia areata compared with control subjects. CGRP has multiple effects on the immune system, including chemotaxis and inhibition of Langerhans cell antigen presentation and inhibition of mitogen-stimulated T-lymphocyte proliferation. 29

2.5.4 Viral etiology

Other hypotheses have been proposed to explain the pathophysiology of alopecia areata, but more evidence is needed to support them. Alopecia areata was believed to possibly have an infectious origin, but no microbial agent has been isolated consistently in patients. Many efforts have been made to isolate cytomegalovirus, but most studies have been negative.30

2.6 Stress

One of the most commonly cited causes of AA is psychological stress. However, in controlled clinical studies, no correlations between reported stress levels and AA have been observed 39, 40. Studies on specific stressful events experienced by AA patients have revealed contradicting results on whether it is causal 41, 42 or unrelated (89–91) to the development of AA. As such, the clinical data in support of the claim that stress can trigger AA onset is not strong. However, some studies have linked aberrant psychosocial traits with the development of AA and these include depression, anxiety, and aggression.43

In a mouse model, AA was found to be associated with altered hypothalamic-pituitary adrenal (HPA) activity in a recent study 44. When AA was induced, affected mice were shown to have significantly higher active central and peripheral HPA tone compared to unaffected controls. The mice displayed a blunted systemic HPA response to acute physiological stress and also a decreased habituation response to chronic psychological stress 44.

2.7 Diet

AA might also be modulated by dietary intake. In cross-sectional studies, it is reported that iron deficiency is associated with various forms of hair loss including AA 51. As revealed in these studies, iron deficiency is mainly observed in females such that 24–71% of the females presenting with AA were iron deficient 52. The mechanism by which iron deficiency could lead to AA is not known. One possible explanation is that iron deficiency hinders the rate-limiting enzyme for DNA synthesis and hence diminishes the proliferative capacity of hair follicle matrix cells 51.

3. OTHER FACTORS

Cytomegalovirus (CMV) has been suggested as a potential promoter of AA 56, but several subsequent studies were not able to confirm the potential association 57. Yet intriguingly, latest genetic research suggests a possible role for a CMV binding protein in natural killer cell activation 59. Vaccinations have also been implicated in the development of AA 58. However, a large scale study using the AA mouse model was unable to demonstrate a significant correlation between hepatitis B vaccination and AA 59. Hormones, while not directly environment derived, can be modified by other environmental factors. One small study with AA-affected mice suggested estrogens may accelerate AA progression while testosterone might reduce AA susceptibility 31.

3.1 Classic forms

- Alopecia areata in single or unifocal plaques
- In this form there is a single, round or oval, smooth alopecic plaque, in which the skin coloration is normal, with hair of a normal appearance in the periphery of the plaque that is easily plucked by traction (demonstrating activity of the process) typical exclamation mark hair can be present.
- Alopecia areata in multiple or multifocal plaques in this form typical alopecic plaques occur that affect the scalp or other pilar areas.
- Ophiasic alopecia areata
- In this presentation, the hair loss occurs along the line of temporoparietal implantation, giving rise to an extensive alopecic area, in a band that reaches the superior margins of the scalp.
- Alopecia totalis

3.2 Clinical presentation

The diagnosis of AA is essentially made on clinical grounds. Age at onset, duration and progression of disease, personal and family history of atopy, family history of similar disease with special reference to autoimmune disease and other systemic complaints are noted in detail. Routine investigations like complete hemogram, anemia panel, erythrocyte sedimentation rate, thyroid function tests, serum calcium, serum proteins, etc. should be carried out to arrive at a specific diagnosis. Skin biopsy and autoimmun epanel may be performed in selected cases. Alopecia areata most commonly manifests as a sudden loss of hair in localized areas. The lesion is usually a round or oval patch of alopecia and may be solitary (Alopecia Areata...
monolocularis) or numerous (Alopecia Areata multilocularis). The patch of alopecia usually has a distinct border where normal hair demarcates the periphery of the lesion. The scalp is the most common site affected by AA (90%)\(^61\),\(^62\).

### 3.3 Quantitating hair loss

Hair pull tests conducted at the periphery of the lesion may be correlated with disease activity and also assist in determining the etiology of alopecia. A few clinical tests are presented below:\(^67\)

- **The pull test:** This test helps to evaluate diffuse scalp hair loss. Gentle traction is exerted on a group of hair (about 40–60) on three different areas of the scalp. The number of extracted hairs is counted and examined under a microscope. Normally, <3 hairs per area should come out with each pull. If >10 hairs are obtained, the pull test is considered positive.

- **The pluck test:** In this test, the individual pulls hair out “by the roots.” The root of the plucked hair is examined under a microscope to determine the phase of growth and used to diagnose a defect of telogen, anagen, or systemic disease. Telogen hairs are hairs that have tiny bulbs without sheaths at their roots. Telogen effluvium shows an increased percentage of hairs upon examination. Anagen hairs have sheaths attached to their roots. Anagen effluvium shows a decrease in telogen-phase hairs and an increased number of broken hairs.

### 3.4 Gauging severity of disease

Researchers have devised a clinical scale in order to assess the severity of AA\(^68\), presented as follows:

1. **Mild:** Three or less patches of alopecia with a widest diameter of <3 cm or disease limited to eyelashes and eyebrows.
2. **Moderate:** Existence of more than three patches of alopecia or a patch greater than 3 cm at the widest diameter without alopecia totalis or universalis.

### 4. INVESTIGATIONS

Most of the AA cases are typical and obvious; therefore, laboratory tests are not necessary. Thyroid screening is not mandatory as thyroid disease and AA are not correlated clinically or causally.\(^73\) Thyroid screening may be of use in long-standing cases, females with persistent patches, patients with suggestive symptoms of thyroid disease and severe AA (AT/AU). Potassium hydroxide smear, fungal culture, serology for syphilis, and scalp biopsy may help in doubtful cases.\(^74\)

### 5. TREATMENT

Treatment is not mandatory because the condition is benign, and spontaneous remissions and recurrences are common. Treatments used are believed to stimulate hair growth, but no evidence indicates they can influence the ultimate natural course of alopecia areata. Treatment modalities usually are considered first according to the extent of hair loss and the patient's age. Assessment of the efficacy of a treatment must be considered with care because the condition is highly unpredictable in presentation, evolution, and response to treatment. Little data exist regarding the natural evolution of the condition. For example, in patients with less than 40% scalp involvement, a study showed no benefit with treatment (minoxidil 1% and topical immunotherapy) over placebo.\(^80\)

### 6. REFERENCES

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