A CLINICAL STUDY OF COMORBIDITIES AMONG PATIENTS WITH ALOPECIA AREATA

By

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Dissertation submitted to

Sri Devaraj Urs Academy of Higher Education and Research,

Tamaka, Kolar, Karnataka

DOCTOR OF MEDICINE
IN
DERMATOLOGY, VENEREOLOGY AND LEPROSY

Under the guidance of

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A C K N O W L E D G E M E N T

One of the joys of completion of this dissertation is to look over the journey past and remember and thank all the people who have helped and supported me along this long but fulfilling road. First and foremost, I thank the Almighty for giving me the strength and ability to carry out this study.

I am deeply indebted and grateful to my guide ***Dr. Rajashekar T S****, MD, Professor and Head, Department of Dermatology, Venereology and Leprosy, Sri Devaraj Urs Medical College, Tamaka, Kolar, for his able guidance, support, timely advice and constant encouragement throughout the period of the study.*

I am thankful to ***Dr. Raghavendra B N****, MD, Associate professor Department of Dermatology, Venereology and Leprosy****, for his helpful guidance during my postgraduate career.*

I thank ***Dr. Rajesh G****, MD, and* ***Dr. Satish S****, MD, Dr.* ***Suresh Kumar K****, MD, Department of Dermatology, Venereology and Leprosy, for their constant encouragement and support.*

I thank ***Dr. Mona Nomgmeikapam****, MD, Associate professor, Department of Psychiatry for her guidance in the study.*

No words can express the deepest gratitude I feel towards my beloved parents, ***Mr. T K Ramachandra*** *and* ***Mrs. B S Rama****, whose countless sacrifices and cherished blessings have made me who I am today in my life.*

I thank my aunt ***Mrs. B S Lakshmi*** *for all her time, help and tireless effort without which, it would not have been possible for me to complete this 3 year postgraduate period.*

*I thank my best friend and dear husband **Mr. Kishore Ramegowda** for his unending faith, unconditional love and support throughout this endeavor.*

I am also thankful to my postgraduate colleagues, my seniors and dear juniors for their constant motivation and co-operation.

Last but not the least, I thank all my patients involved in this study, without whose co-operation, this study would not have been possible.

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LIST OF ABBREVIATIONS USED

AA - Alopecia Areata

AT - Alopecia Totalis

AU - Alopecia Univeralis

AD – Atopic Dermatitis

AR – Allergic Rhinitis

ANA - Antinuclear Antibody

C3 - Complement Component 3

CMV - Cytomegalovirus

HLA - Human Leukocyte Antigen

ICAM - Intercellular Adhesion Molecule

Ig - Immunoglobin

IL - Interleukin

MHC - Major Histocompatibility Complex

MSH – Melanocyte Stimulating Hormone

TGF - Transforming Growth Factor

TH - T Helper

TNF - Tumour Necrosis Factor

TSH - Thyroid Stimulating Hormone

TD – Thyroid Disease

ABSTRACT

BACKGROUND: Alopecia areata (AA) is a common inflammatory disease presenting with sudden onset, nonscarring hair loss with huge cosmetic impact. Among patients with AA, there are significant associated comorbid conditions like autoimmune thyroid disease, atopic dermatitis, psychiatric disorders, vitiligo, psoriasis, allergic rhinitis and lupus erythematosus. Different ages of onset is associated with different comorbidities. As there is a paucity of studies in Indian population there is a need to study such comorbid conditions in relation with the clinical profile of Alopecia areata patients, so that the outcome can be predicted and suitable therapeutic measures can be instituted.

AIMS AND OBJECTIVES: To document the comorbid cutaneous and extra cutaneous conditions and the age of their onset in patients with AA. To correlate the comorbid conditions with the severity of AA.

MATERIALS AND METHODS: This study was done in the Dermatology Department of R L JALAPPA HOSPITAL from December 2013 to January 2015. An informed written consent was taken. All clinically diagnosed patients with Alopecia areata were included in the study. Patients on immunosuppressive therapy, radiotherapy and chemotherapy were excluded from the study. Diagnosis was made clinically and based on the history of abrupt patchy hair loss with or without progression and absolutely normal looking scalp without any secondary changes on examination. Psychiatric diagnosis will be made based on ICD-10 criteria. Physical examination includes site of involvement, evaluation of pattern, disease extent, associated nail changes and whole body examination for associated diseases, which are recorded in a proforma. Laboratory tests will be done in diagnosing comorbid conditions whenever required.

RESULTS: In the present study most patients belonged to the age group of 21- 30 (30%) closely followed by 31-40 years (26.6%). A slight preponderance of males (56.6%) was seen compared to females (43.3%). Age of onset varied between 21-40 years (46.6%) followed by age group less than 20years (38.3%). 2 patients had onset at the age of 1 year, one of which had alopecia universalis. Patchy type of AA was mostly seen constituting 80% followed by reticular type constituting 6.6%. 66% of the cases had size of total number of lesions in each case less than 5cms.76.6% presented with multiple patches and 23.3% had solitary patch. Nail changes were noted in 20% of patients. The commonest nail change being pitting seen in 11 patients (18.3%). longitudinal ridging was present in 16.6% and onychodystrophy, melanonychia and beaus lines were noted in 1.6% of patients. It was interesting to note that 36.5% of the lesions were present in occipital region and vertex was a distant second with 25% in this study. Mild form of the disease was seen in 52 patients (86.6%) and severe disease was noted in 8 patients (13.3%). Recurrence was present in 55% of patients. In the present study, atopic dermatitis was associated with increased frequency in patients with alopecia areata, i.e., 23.3% cases. In the present study vitiligo was seen in 3.3% patients In the present study we did not find a single case of comorbid psoriasis. 70% of patients presented with psychiatric comorbidity of which 51.6% (31patients) had social phobia disorder, 33.3% (20patients) had depressive episodes and 26% (16patients) had anxiety disorder with most of them falling into the age group 11 to 30years. In the present study the prevalence of thyroid disease was 21.7% (13 patients), strikingly all these patients had hypothyroidism which is in contrast with other studies. In the present study we found 13.3% allergic rhinitis cases. Diabetes mellitus was seen in 15% of the patients. In the present study where only 10% of the patients presented with hypertension. ANA was negative in all patients.

CONCLUSION: AA is related to atopic and autoimmune diseases and there is a high psychiatric comorbidity. Age of onset varied between 21-40 years followed by the age group less than 20years. Since ANA is not specific for autoimmunity the presence of other autoimmune diseases in these patients can be a coexistent finding or an association due to autoimmunity etiology. Also there was no significant association between severity and duration of the disease.

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INTRODUCTION

Hair performs no vital function whatsoever in man whose body can be perpetually depilated or shaved without any physiological disadvantages. But, the psychological function of hair seems almost immeasurable. Scalp hair is major social and sexual display feature of the human body: For women, the crowning glory of a decently exposable femininity; for men, a traditional symbol of masculinity. If lack of scalp hair is almost a disaster for women, excess body hair beyond the cultural norms can be distressing. Hair cannot, therefore, be scientifically neglected.[1]

Alopecia may be interpreted as a loss, miniaturization, involution, or increased fragility of the hair at all hair bearing sites, such as scalp, face, eyebrows, eyelashes, and body.

Cornelius Celsus who flourished in Rome has also described Alopecia Areata which even now is sometimes referred to as *'area celsi*'. Sauvages (1706-67) first used the term Alopecia Areata (AA).[2]

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. 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 show male preponderance and some female preponderance. It can occur at any age. [3]

The etiology of AA has eluded investigators for years and therefore a multitude of associations have been proposed by researchers in the field of trichology. One of the strongest associations is

with autoimmunity. This view has been supported by the occurrence of AA in association with other autoimmune disorders like vitiligo, lichen planus, morphea, atopic dermatitis, Hashimoto's thyroiditis, pernicious anemia and diabetes mellitus. More recently, it has been reported that there is a high prevalence of mood adjustment, depressive and anxiety disorders in patients with AA. This element of psychiatric morbidity has widely been purported to be both, a cause and effect of AA.[4]

AA is hypothesized to be an organ specific autoimmune disease mediated by T lymphocytes directed to the hair follicles. Although genetic predispositions and environmental factors may trigger the initiation of the disease, the exact cause is still unknown. Other proposed origins reported include infectious agents, cytokines, emotional stress, intrinsically abnormal melanocytes or keratinocytes, and neurologic factors.

The histopathologic changes in Alopecia Areata can be divided as four distinct stages: acute hair loss, persistent alopecia, partial telogen to anagen conversion and recovery. A peribulbar and at the lower one third of the follicle, a lymphocytic infiltrate ('swarm of bees') with no scarring is characteristic in all stages. In addition, miniaturization of hairs with numerous fibrous tracts along with pigment incontinence is appreciable. A decrease in anagen to telogen ratio resulting in marked increase in telogen and catagen hairs can be observed in scalp biopsy specimens. In long standing cases there is an increase in Langerhans cell numbers. Electron microscopy shows ultrastructural abnormalities in the dermal papillae of both lesional and clinically normal hair follicles.

Although hair loss is usually asymptomatic in majority cases, but few patients describe paresthesias with mild to moderate pruritus, tenderness, burning sensation, or pain before the appearance of the patches.

Clinical presentation of Alopecia Areata is subcategorized according to the pattern or extend of hair loss. Based on the pattern the following forms are seen: patchy AA, round or oval patches of hair loss (most common), reticular AA, reticulated pattern of hair loss, ophiasic band like AA, hair loss in parieto-temporo-occipital scalp; ophiasis inversus, a rare band like pattern of hair loss in fronto-parieto-temporal scalp; and diffuse Alopecia Areata, a diffuse decrease in hair density. If categorized according to the extent of involvement following forms may be seen: Alopecia Areata, partial loss of scalp hair; Alopecia totalis, 100% loss of scalp hair; and Alopecia universalis, 100% loss of all body hair. [5]

The hairs when examined under the microscope are telogen hairs, fractured hairs can also been seen at the active margins of Alopecia commonly described as 'exclamation-mark' hairs because the distal segment is broader than the proximal end. In the earliest classification of AA, Ikeda (1965) divided AA into 4 categories: the 'common' type with generally a good prognosis, the 'atopic' type often an onset in childhood, the 'pre-hypertensive' type showing a high rate of progression to Alopecia totalis and the 'endocrine-autonomic' type or the 'auto immune' type.

AA is mainly a cosmetic concern, causing more emotional problems, especially in children and women. Spontaneous remissions can occur in up to 80% of limited AA within one year.[34] Counseling and informing the possible true expectations of the available treatments are important.

Although some AA features are known poor prognostic signs, the course of the disease is unpredictable and the response to treatment can be variable. A multipronged approach is therefore warranted in the management of such patients. Though corticosteroids have been the mainstay in therapy, a wide array of evidence based therapies have come into fore for management of AA. Corticosteroids: topical, intralesional and systemic, topical irritants, topical

immunotherapy, photochemotherapy, systemic immunotherapy, minoxidil, cyclosporine, isoprinosine, azathioprine and combination therapies which takes up the best of each modality are used to treat Alopecia areata. In extensive cases hair replacement options or tattooing have been suggested. It is also imperative for the physician to address the psychological impact of the condition.

AIMS AND OBJECTIVES

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1. **To document the comorbid cutaneous and extra cutaneous conditions and the age of their onset in patients with AA.**
2. **To correlate the comorbid conditions with the severity of AA.**

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ANATOMY OF HAIR

Hair is the keratinized product of the hair follicle, a tube-like structure continuous with the epidermis at its upper end. The follicles are sloped in the dermis, and longer follicles extend into the subcutaneous layer. An oblique muscle, the erector pili, runs from the mid-region of the follicle wall to a point in the papillary dermis close to the dermo–epidermal junction. Above the muscle, one or more sebaceous glands, and in some regions of the body an apocrine gland also, open into the follicle.

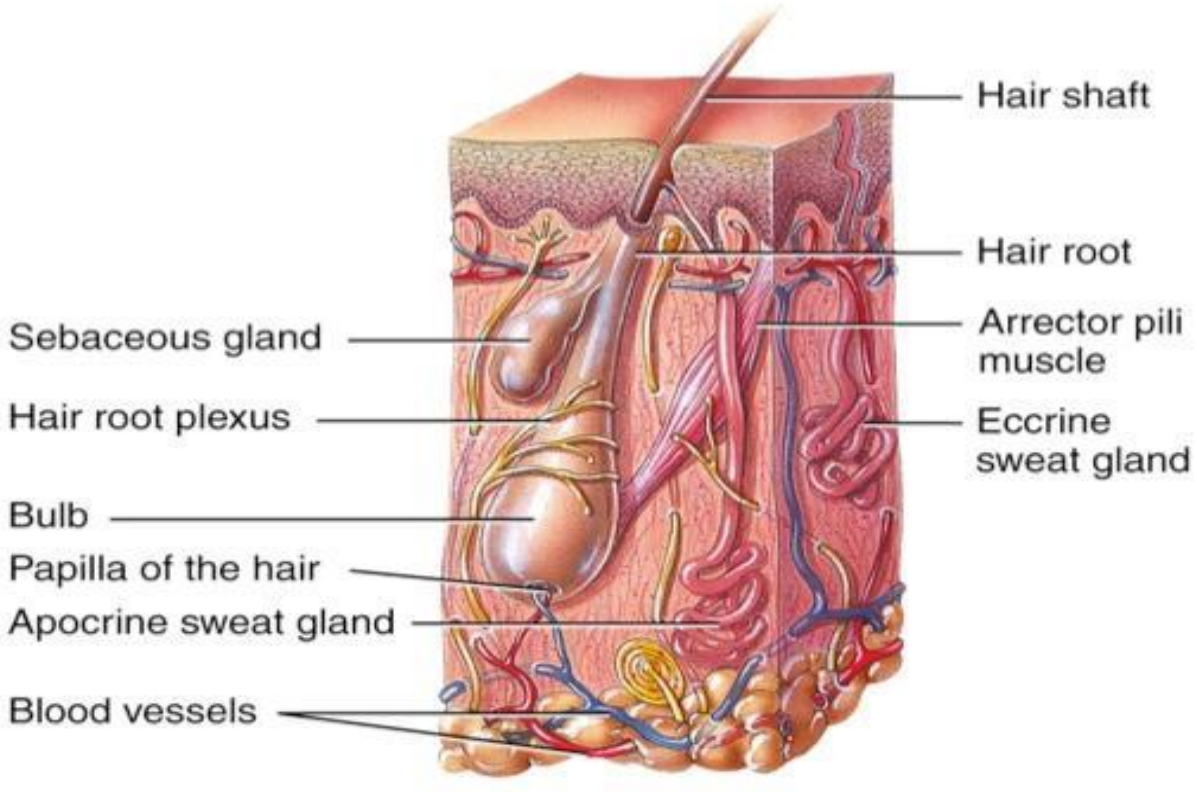


FIGURE 1: ANATOMY OF SKIN

The hair fibre is made up of three cell layers: an outer cuticle, the cortex (which forms the bulk of the fibre in most hair types) and a variable central medulla, all of which derive from highly proliferative cells in the hair bulb at the base of the follicle. Cells in the hair bulb also give rise to the inner root sheath which surrounds the hair fibre and which disintegrates before the hair emerges from the skin. The inner root sheath is itself enclosed by the outer root sheath, which forms a continuous structure extending from the hair bulb to the epidermis, although the functions and microscopic structure of the outer root sheath vary along the length of the follicle. The hair follicle also has a specialized dermal component, which includes the dermal or connective tissue sheath surrounding the follicle, and the dermal papilla which invaginates the hair bulb.

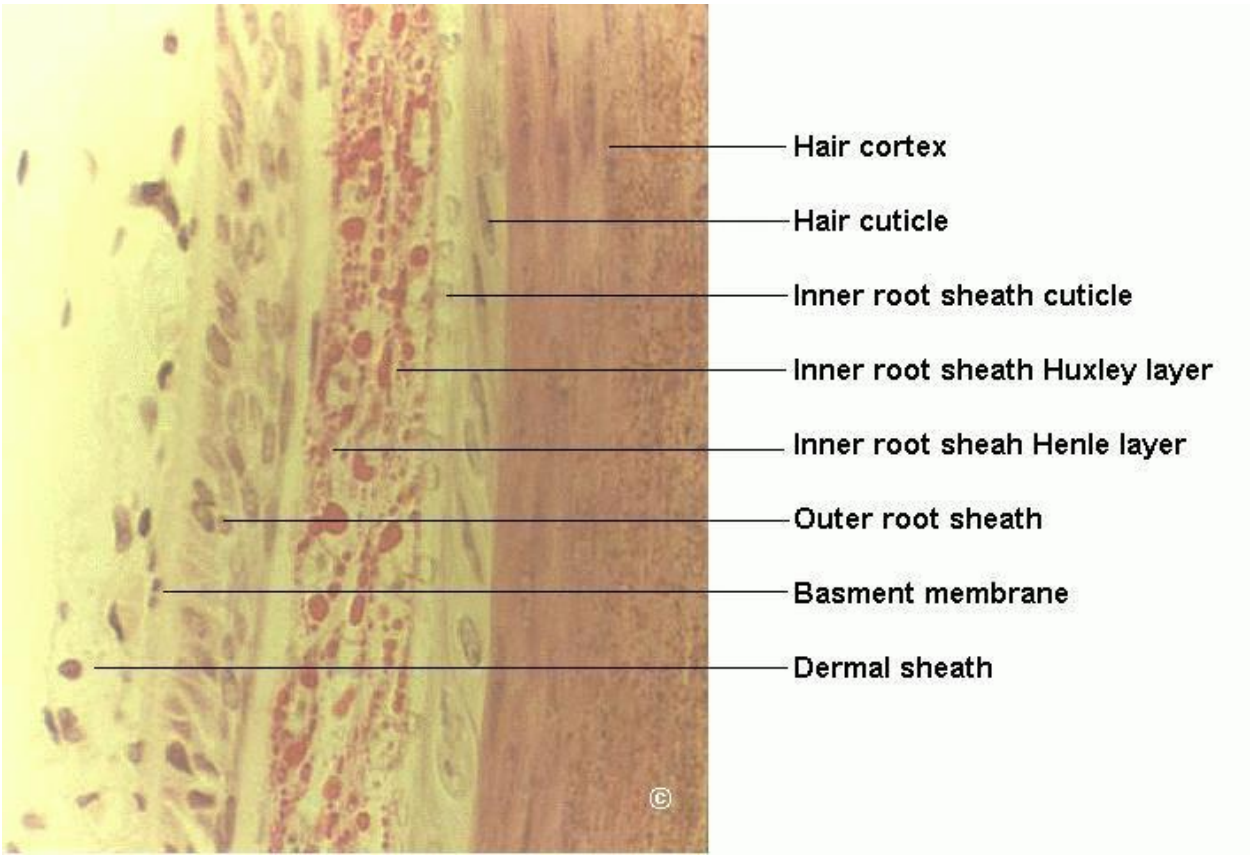


FIGURE 2: STRUCTURE OF HAIR

The hair follicle is conventionally divided into two regions: the upper part consisting of the infundibulum and isthmus and the lower part comprising the hair bulb and suprabulbar region. The upper follicle is a relatively constant structure, whereas the lower follicle undergoes repeated episodes of regression and regeneration during the hair cycle. On the scalp, and some other regions of the skin, hair follicles are arranged in groups of three or more follicles known as follicular units.[6]

MORPHOGENESIS

Hair morphogenesis is the development of the entire hair apparatus/pilo-sebaceous unit from the primitive epithelium. It is essential to understand the embryology of the hair as some of the steps in the development are reenacted during the normal hair cycle. In the embryo, the skin begins as a single layer of epidermal stem cells. Soon after, as mesenchymal cells populate the skin to form the underlying collagenous dermis, morphogenesis of the hair follicle begins. Specialized dermal cells organize, stimulating the overlying epithelial stem cells to grow downward and produce a hair follicle. As the follicle grows down, it assumes the shape of a rod several cell diameters wide. The primary hair germ starts developing in the third month of fetal life with crowding of basal keratinocytes (pregerm stage). This epidermal thickening then grows downward toward the dermis (hair germ stage) with the underlying mesenchymal cells showing signs of activity. It gradually elongates into a column pushing the underlying dermal cells with it (hair peg stage). As the column elongates, its tip forms a cup (the future bulb) that comes to enclose the group of dermal cells underneath (bulbous peg stage).[6]

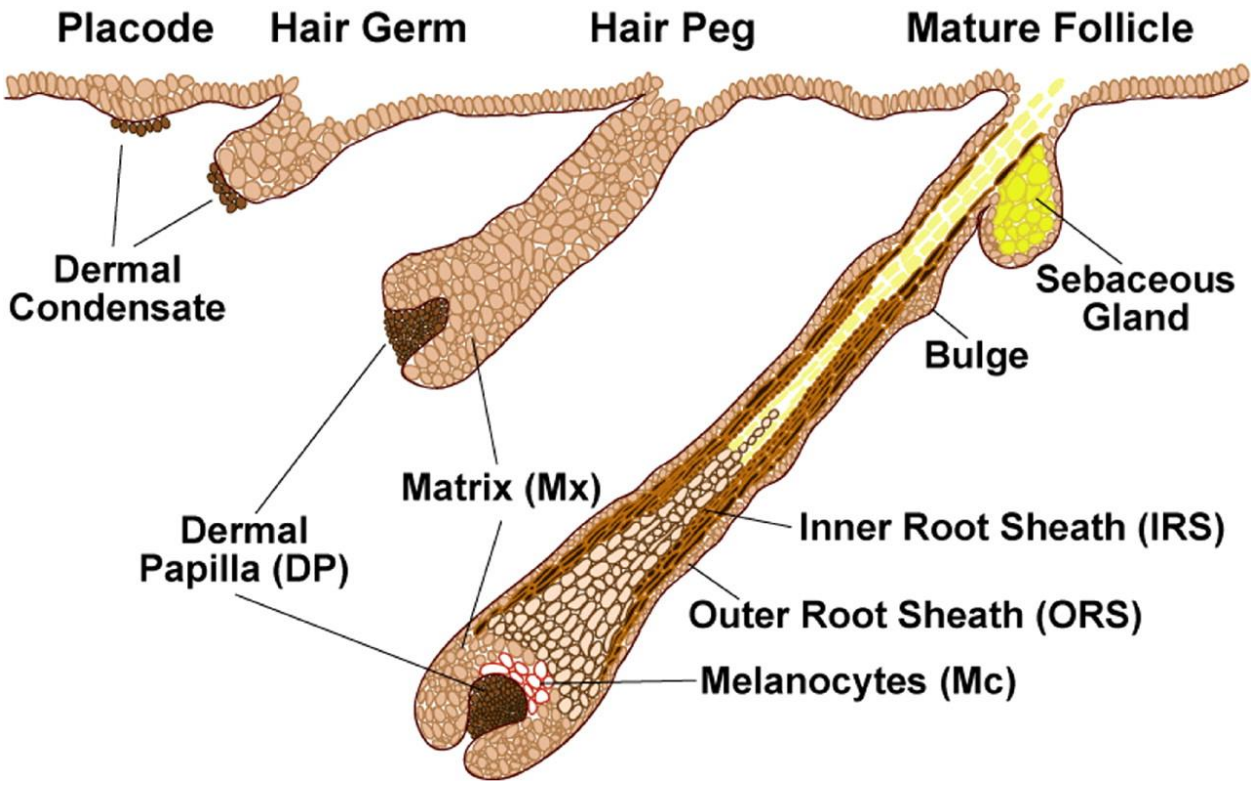


FIGURE 3: MORPHOGENESIS OF HAIR

At about 12 weeks, the cells of the base of the bulb start differentiating on various lines; the outermost forming the IRS and the inner cells, the future hair shaft. This differentiated hair "cone" covered by the IRS penetrates the hair column forming a hair canal. As the skin expands, the hair germs get separated and new secondary germs develop between them.[8]

HAIR CYCLE

Hair follicles undergo a repetitive sequence of growth and rest known as the hair cycle. The timing of the phases of the hair cycle and its overall duration varies between species, between follicles in different regions of the skin in the same species and, in some animals, between different follicle types, in the same region of the skin. This hair cycle starts with the growth phase (anagen), which lasts for 2–10 years for the scalp hair. This is followed by the transitional

phase of catagen, which takes 1–3 weeks, and leads to the resting phase of about three months, termed as telogen. The period of active hair growth is known as anagen and the duration of this phase is responsible for determining the final length of the hair.

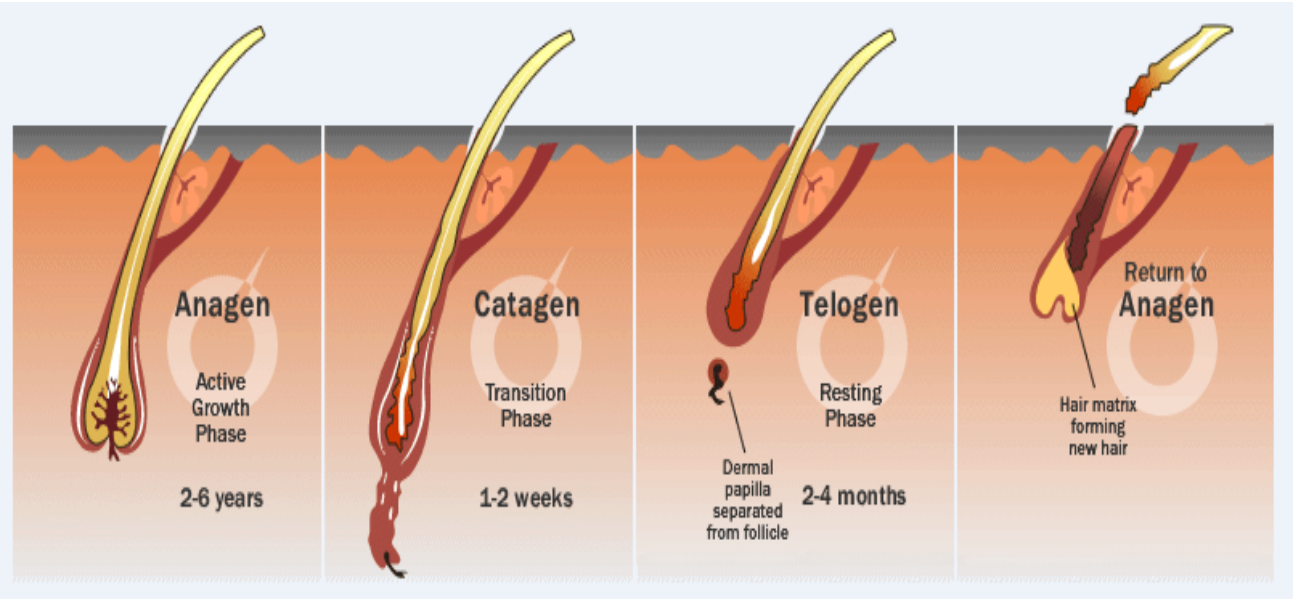


FIGURE 4: THE HAIR CYCLE

Under normal circumstances, 80–90% of hair follicles on the human scalp are in anagen at any one time. The entry of a resting hair follicle into anagen is heralded by the onset of mitotic activity in epithelial cells overlying the dermal papilla at the base of the follicle. The developing hair bulb partly envelops the dermal papilla, and epithelial cells start to differentiate to form the inner root sheath and the hair shaft. The dermal papilla expands from a tightly packed ball of cells into a flask shaped structure where the cells become separated by an extracellular matrix rich in proteoglycans and basement membrane proteins. A network of capillary blood vessels develops around the lengthening follicle, extending into the dermal papilla in larger follicles. In the fully developed anagen follicle, epithelial cells in the hair bulb undergo vigorous proliferative activity. Their progeny move distally and differentiate in an ordered fashion to form the layers of

the inner root sheath and the hair shaft. At the end of anagen, epithelial cell division declines and ceases, and the follicle enters an involutionary phase known as catagen. During catagen, the proximal end of the hair shaft keratinizes to form a club-shaped structure and the lower part of the follicle involutes by apoptosis. The basement membrane surrounding the follicle becomes thickened and corrugated to form the ‘glassy membrane’. The base of the follicle, together with its dermal papilla, moves upwards, eventually to lie just below the level of the arrector insertion. The period between the completion of follicular regression and the onset of the next anagen phase is termed telogen. The club hair is eventually shed through an active process termed exogen. In human scalp, hair follicles may remain in a state of latency, also known as kenogen, for a prolonged period after the club hair is shed.[6]

The normal human scalp has about 100,000 hairs. With the approximate durations of anagen, telogen, and catagen being 1000, 100, and 10 days and their approximate proportions of about 90%, 10% and 1%, respectively, it is expected to shed about 100 hairs per day. However, since all the lost hairs are rarely recovered, the actual number of hairs lost that can be noticed is between 50 and 100.

NOMENCLATURE AND HISTORICAL ASPECTS

The word Alopecia is derived from the Greek word 'Alopex' meaning 'Fox mange' (baldness). Cornelius Celsus, landowner and encyclopaedist, who flourished in Rome in AD 14-37 has been credited with the first description of Alopecia Areata (AA) said, “alopecia spreads out in a pattern where is pleases; but ophiasis begins at the back of the head”. Celsus called the disease *'alopecia areata*' and Pare named it as *'pelade'* in France. The term 'Alopecia Areata' was first used by Sauvages (1706-67) in his Nosologia medica, published in Lyons in 1760. Robert Willan gave a fuller description of the condition but named it 'porrigo decalvans'. Willan's rival as a

classifier of the dermatoses regarded what he called 'porrigo tonsurans' as the same. In 1843, Gruby as expected found a fungus in 'porrigo decalvans' the parasitic theory of AA was firmly launched misleading course. In 1851, Hebra clearly separated AA from 'herpes tonsurans' but at first still accepted that AA was of fungal origin, which he later revised. The earlier protagonists of AA believed that a fungus was the organism concerned, later bacteria were suspected. In the late 19th century an association with thyroid hormone was made. [9] By the 1920's most dermatologist had abandoned the parasitic theory of AA and put forward hypothesis which blended the trophoneurotic and the endocrine aspect.

DEFINITION

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.[3]

INCIDENCE AND EPIDEMIOLOGY

AA is one of the most common form of hair loss seen by dermatologists and accounts for 25% of all the alopecia cases.[10] AA accounts for 2-3% of all new outpatient attendance in dermatology in UK and USA, 3.8% in China and 0.7% in India.[11-13] It is common throughout the world and has been estimated to effect between 0.1% and 0.2% of the US population, with a life time risk of 1.7%.[3] AA effects males and females equally,[14] but some studies have reported female preponderance,[15] and few have reported male preponderance.[16,17] It can occur at any age but onset before first year is unusual, but reportedly it has occurred at 4th month of life up to late seventies.[3] Highest prevalence was between 30-59years of age.[10] Family members are affected in 8.7-20% of cases.[3]

ETIOLOGY

The pathogenesis of AA and the molecular mechanisms that lead to hair loss are poorly understood. In the past, AA was believed to be of infectious or neurotrophic origin.[18] Recent research studies have indicated that AA is an inflammation driven disease and is likely an autoimmune disorder.[5, 19] There are other proposed origins reported including infectious agents, cytokines, emotional stress and intrinsically abnormal melanocytes or keratinocytes.

MODULATION OF THE HAIR FOLLICLE GROWTH CYCLE

AA causes significant disruption in the dynamics of hair growth cycle clearly, but different perturbations in hair growth occur depending on the pattern, severity, and duration of AA in each patient. There are several possible presentations of AA. First, the anagen phase of a hair follicle can become inflamed and maintained in a dystrophic anagen state, unable to produce hair fiber of significant size or integrity. When there is a greater intensity of inflammation, the hair follicles may be forced into a telogen phase and then cycle through multiple anagen–telogen phases of brief duration. Also the telogen hairs are abnormal indicating a defective catagen. Correspondingly, inflammatory cell infiltration occurs in early anagen follicles without migration to draining lymph nodes as follicles capitulate and return to telogen.[21-23] Finally, when AA is chronic, the hair follicles tend to persist in a prolonged telogen phase without an apparent attempt to return to an anagen growth phase.[5] The end result based on the severity of inflammatory insult is a malformed telogen hair or a dystrophic anagen hair.

GENETIC FACTORS

Genetic factors have an important role in the origin of AA. Autosomal dominant inheritance with variable penetrance has been suggested for AA. Inheritance of AA is based on observations on

monozygotic twins; AA in twins can have similar times of onset and patterns of hair loss.[5] Some patients with AA have a strong family history suggesting that AA can be inherited. Between 4% and 28% of patients who have AA will have at least one other affected family member.[20]

Gene association studies have indicated that human leukocyte antigen (HLA) genes play a role in AA. MHC (HLA) class I (A, B, and C) molecules are present on almost all nucleated cells and they present antigens to $CD8^+$ T cells. There is an aberrant expression of HLA antigens found within the follicles of AA affected patients.[5] However, the evidence in support of an association of HLA class I with AA is inconsistent with different susceptibility alleles identified in different cohorts.[24]

A much more consistent and stronger association between HLA class II alleles and AA development has been observed. HLA class II antigens are constitutively expressed on specific immune cells and may be upgregulated on nonimmune cells in response to injury. They are responsible for presenting antigenic peptides to $CD4^+$ T cells. HLA class II antigens are aberrantly highly expressed on AA affected hair follicles. Specific alleles, such as DQB1∗03 and DRB1∗1104, have been reported as markers for susceptibility to AA.[25] These findings suggest the importance of specific HLA class II alleles in the onset and progression of AA and imply that antigen presentation to $CD4^+$ cells plays a significant role in AA development.[5]

Histologic and ultrastructural evidence of cellular damage and increased expression of class I and class II HLA antigens, led to the suggestion that cells undergoing early cortical differentiation form the primary disease target within the hair follicle. Increased HLA antigen expression by hair matrix keratinocytes, however, appears to be a late event in alopecia areata and may result from cytokine release by infiltrating immune although this remains unconfirmed.[26]

Several association studies have investigated non-HLA gene alleles, indicating that multiple genes may contribute to AA susceptibility.[18]

In conclusion many studies reveal the possibility that AA is a polygenic disease, with certain genes correlated with susceptibility and others with severity. Most likely there is an interaction between genetic an environmental factors that trigger the disease.

IMMUNOLOGY

AA has been considered as an autoimmune disease due to aberrant T cell response against hair follicle self antigens.[27] Circumstantial evidence in support of an autoimmune mechanism underlying AA comes from several sources. The presence of inflammatory lymphocytes around and within affected hair follicles and the ability to promote hair regrowth with the use of immunosuppressive agents is consistent with an autoimmune hypothesis.[5] The infiltration of antigen presenting cells (APCs) such as macrophages and Langerhans cells both around and within the dystrophic hair follicles has also been observed.[19] This is potentially consistent with a response to autoantigens within the hair follicles and attraction of these APCs.[5]

There is also an increase in proinflammatory markers such as intercellular adhesion molecule and endothelial cell selectin in the blood vessels around the hair follicles. The presence of hair follicle specific IgG autoantibodies in the peripheral blood of AA patients also further reinforces the hypothesis that the development of AA could be autoimmune related.[19]

This evidence of an autoimmune etiology derives from three sources: the association of AA with other autoimmune disorders, studies of humoral immune function in AA and studies of cellular immune function in AA.[27]

AA AND ASSOCIATED DISEASES: There are reported associations between AA and classic autoimmune disorders although most part circumstantial; the main associations are with thyroid disease, atopy and vitiligo.[28] The prevalence of thyroid disease in patients with AA varied from 0 to 28% when compared with only 2% of the normal population.These thyroid diseases include Hashimoto's thyroiditis, Graves' disease, simple goitre and others.[29] This evidence has been further confirmed by documentation of an increased prevalence of antithyroid antibodies and thyroid microsomal antibodies in patients with AA.[30] Also studies have revealed an increased prevalence of gastric parietal antibodies as well as antinuclear and antismooth muscle antibodies in sera of patients with AA.[31] Several studies have reported the occurrence of vitiligo with AA.[32-34] Also an association with the Vogt-Koyanagi-Harada syndrome has been reported. In classification of AA suggested by Ikeda, atopic cases were placed in a separate category which included 10% of the study group.[26] AA and atopy share a Th2 cytokine pattern and increased levels of IgE antibodies, mast cells, and eosinophils. In addition, a biphasic pattern of T- helper response in both AA and atopic dermatitis has been observed. There is a Th2 (interleukin [IL]-4) response in localized AA versus a Th1 (interferon [IFN]-ɤ) response in generalized AA. Similarly, there is a Th2 response in acute phase atopic dermatitis (IL-4) versus a Th1 response (IFN- ɤ) in chronic phase. It has been reported that histamine, which is secreted by mast cells, up-regulates Th1 cytokine and down-regulates Th2 cytokine responses by increasing IFN- ɤ and decreasing IL-4 and IL-13.43 Th2 cytokines (IL-4 and IL-13) also influence epidermal barrier

function by down regulating the filaggrin gene expression, encoding a protein of the keratin cytoskeleton. These findings support a common pathway between atopy and AA.[35]

There are also numerous case reports of AA in patients with other known or probable autoimmune diseases. This include pernicious anemia, diabetes mellitus, systemic lupus erythematosus, discoid lupus erythematosus, rheumatoid arthritis, scleroderma, ulcerative colitis, lichen planus, hypogammaglobulinemia, autoimmune hemolytic anemia, lichen sclerosus et atrophicus, polymyalgia rheumatica, myasthenia gravis, and the candida endocrinopathy syndrome. Down's syndrome patients have an increased frequency of AA, with upto 8.8% of patients affected.[2, 6]

HUMORAL IMMUNITY AND ALOPECIA AREATA: Circulating antibodies have been found in humans to follicular structures. Highly divergent results have been obtained and no consistent association has been found. The conflicting immunological evidence and histological changes and the regrowth of hair in many cases on treatment with induced contact allergy has been suggested that AA results from a defect in immunoregulation.[6] Indirect immunoflourescence compared AA patients with controls, high levels of auto antibodies to multiple structures of anagen hair follicles in AA patients were recorded. The antibody response was heterogeneous because different patients developed different patterns of antibodies to different follicle structures. The most common target structures were the outer root sheath, followed by the matrix, inner root sheath and the hair shaft.[31]

CELL-MEDIATED IMMUNITY: The conflicting results of numerous immunologic studies in AA can be understood better in the light of the heterogeneity of AA.[2] The propensity of most autoimmune diseases to manifest themselves in the skin depends on whether T cells learn what is 'self in thymus or until later peripherally which would probably explain the range of severity of

the diseases.[36] Using monoclonal antibody techniques suppressor cell activity in AA has been shown to be increased significantly in patients showing spontaneous hair regrowth. The current hypothesis is that both CD4þ and CD8þ T cells have a role in the pathogenesis of AA, the CD8þ cells acting as the ejector cells with help from the CD4þ Tcells. The autoantigen(s) in AA remains to be identified, but results of current studies suggest that it may be melanocyte derived. Support for this hypothesis comes from clinical observations that pigmented hair fibers are preferentially lost and that vitiligo is commonly associated with AA. In addition, hair bulb melanocytes in AA demonstrate both histologic and ultrastructural abnormalties.[37] A recent theory for AA proposed in a study involves the upregulation of MHC antigens and/or downregulation of locally produced immunosuppressants (melanocyte-stimulating hormone, adrenocorticotropic and transforming growth factor), allowing the immune system to recognize the immune privileged hair follicle antigens leading to onset of AA. No specific marker have yet been identified which would support an autoimmune etiology of AA.[31]

To sum up the features that would suggest an autoimmune etiology are a shared hereditary susceptibility, on histopathology accumulation of lymphoid cells around the hair bulbs during active phase of disease, antibodies to pigmented hair follicles, the clinical course is similar to other autoimmune diseases, association with organ specific autoimmune diseases, increased prevalence of autoantibodies, an increase in ratio of helper to suppressor T cells, response to anti-inflammatory drugs like steroids. Further research in this area is clearly required. Prospective long term studies and the relationship between lymphocytes and disease activity are worthy of further attention.[31]

ENVIRONMENTAL IMPACT

Stress, Trauma and Infection

Psychological trauma is often suggested as a factor involved in precipitating attacks of alopecia areata. The significance of such an association is difficult to establish formally because of the problems in performing a controlled investigation. Psychological stress is cited as a cause for AA onset, but controlled clinical studies have been inconclusive.[5] If psychological factors are involved in precipitating attacks of alopecia areata, it is likely that they are just one of several possible triggers that can operate in individuals with a genetic constitution associated with the disease predisposition. The role of organic nervous disease in AA is unknown. Acute psychotrauma before the onset of AA, higher number of stressful events in 6 months of preceding hair loss, higher prevalence of diagnosed psychiatric disorders, and psychological factors and family situations in patients with AA have been reported.[31] Major depression, generalized anxiety disorder, social phobia, and paranoid disorder are the most commonest psychiatric comorbidity associated with AA.[38] These studies therefore indicate that severe emotional stress could be a precipitating factor which is not totally contradictory to an immunological view of pathogenesis since severe psychological stress can alter immune function.

AA can result from environmental factors. Even though specific gene alleles provide an innate degree of susceptibility to AA for an individual, environmental factors determine the actual onset, hair loss pattern, and severity of the disease.[24] However, the exact environmental stimuli required for AA expression are yet to be determined. Hormonal fluctuation, iron deficiency, decreased levels of zinc and vaccinations have all been cited as possible triggers for AA.[3] Alopecia areata-like lesions have also been observed after tick bites. Another form of stress that

has many times been reported as a precipitant of alopecia areata is dental disease and treatment. Focal infection, particularly of the tonsils, has also had numerous advocates as a trigger factor for alopecia areata but has never been shown conclusively to be important. Also Cytomegalovirus (CMV) infection has been implicated in causing AA. There are many such reports describing the probable etiology for AA but these are unsatisfactory.[26]

INTRINSICALLY ABNORMAL MELANOCYTES OR KERATINOCYTES

Regressive changes in the hair bulbs of anagen hair follicles have been found in the morphological analysis of hair follicle. Abnormal melanogenesis and melanocytes are common findings. Also there is evidence suggestive of antibodies to pigmented hairs of AA which explains why some of the associated pigmentary anomalies are seen clinically in acute AA. Degeneration of precortical keratinocytes has been shown in follicles of active AA lesions. Abnormal melanosomes in clinically normal regions, along with degenerative changes including vacuolation in the outer root sheath of all hair follicles from non-balding lesions of AA, correspond well with the hypothesis of a subclinical condition of the disease in clinically normal areas of AA.[31]

NEUROLOGICAL FACTORS

The role of neurological disease in AA is unknown. It has been suggested that local changes in the peripheral nervous system at the bulge region may play a role in the evolution of AA because the peripheral nervous system can deliver neuropeptides that modulate a range of inflammatory and proliferative processes. Furthermore, increased Substance P in the stockade region and the vellus hair regrowth support the need for additional studies so as to understand the role of peripheral nervous system in causing AA.[37]

CYTOKINES

Cytokines seem to have a significant pathogenic role in AA. Cytokines are immunomodulators mediating inflammation and regulating cell proliferation. These are derived from epidermal keratinocytes, IL-lα and IL-1β and tumour necrosis factor alpha (TNF-α) are potent inhibitors of hair follicle growth and in vitro produce changes in hair follicle morphology similar to those in AA. T helper cells also produce cytokines. Type 1 T helper (TH 1) cells produce interferon gamma (IFN-γ) and IL-2. Type 2 T helper (TH 2) cells produce IL-4 and IL-5. There is an expression of cytokines of the TH 1 type and IL-1β in affected areas in scalp in patients with AA.[31]

DRUG INDUCED ALOPECIA AREATA

As per few studies drugs like rifampicin can induce AA.[40]

ENDOCRINE FACTORS

A case report of Alopecia totalis in a pregnant women has been recorded indicating a possible hormonal pathogenesis.[31]

To sum up, for many years now AA is considered an immune-mediated disease. Despite numerous studies, the nature of immune involvement in the pathology and whether immune disturbance is a primary event in causing the hair follicle lesion is still inconclusive. Because of the multiple associations and clinical presentations, it has been proposed that AA is a heterogeneous group of disease and not a single entity. The evidence is accumulating; however, to suggest that AA is a clinical reaction pattern that is the result of combinations of genetic and environmental factors.[31]

PATHOGENESIS OF ALOPECIA AREATA

The earliest clinical evidence of the disease is an increase in telogen shedding, which is usually focal and then spread in a centrifugal pattern.[41] These telogen hairs are often malformed, suggesting that catagen is abnormal, and the histologic counterpart of this has been termed nanogen.[42] Anagen/telogen ratios vary considerably with the stage and duration of the disease process. Some anagen hair bulbs are situated at a higher level in the dermis than normal; a peribulbar lymphocytic infiltrate is seen around follicles, this being more dense in early lesions; the infiltrate consists predominantly of T cells, with increased number of Langerhan cells.[43]AA affects the follicle in anagen but does not cause an abrupt cessation of mitotic activity in the matrix. Once in telogen the follicle is thought to be 'safe' but when reentry into anagen takes place the attack is resumed, and the follicle returns prematurely to telogen. Therefore there is a cyclical process, which may explain why follicles are not destroyed permanently.[43] A study suggested that in AA, an unidentified trigger stimulates an autoimmune lymphocytic attack on the hair bulb. This inflammation is specific for anagen hairs and causes anagen arrest. A disruption of the growing phase, that is anagen arrest, causes abnormal loss of anagen hairs (anagen effluvium), clinically recognized as dystrophic anagen hair with tapered proximal ends and

lack of root sheaths.

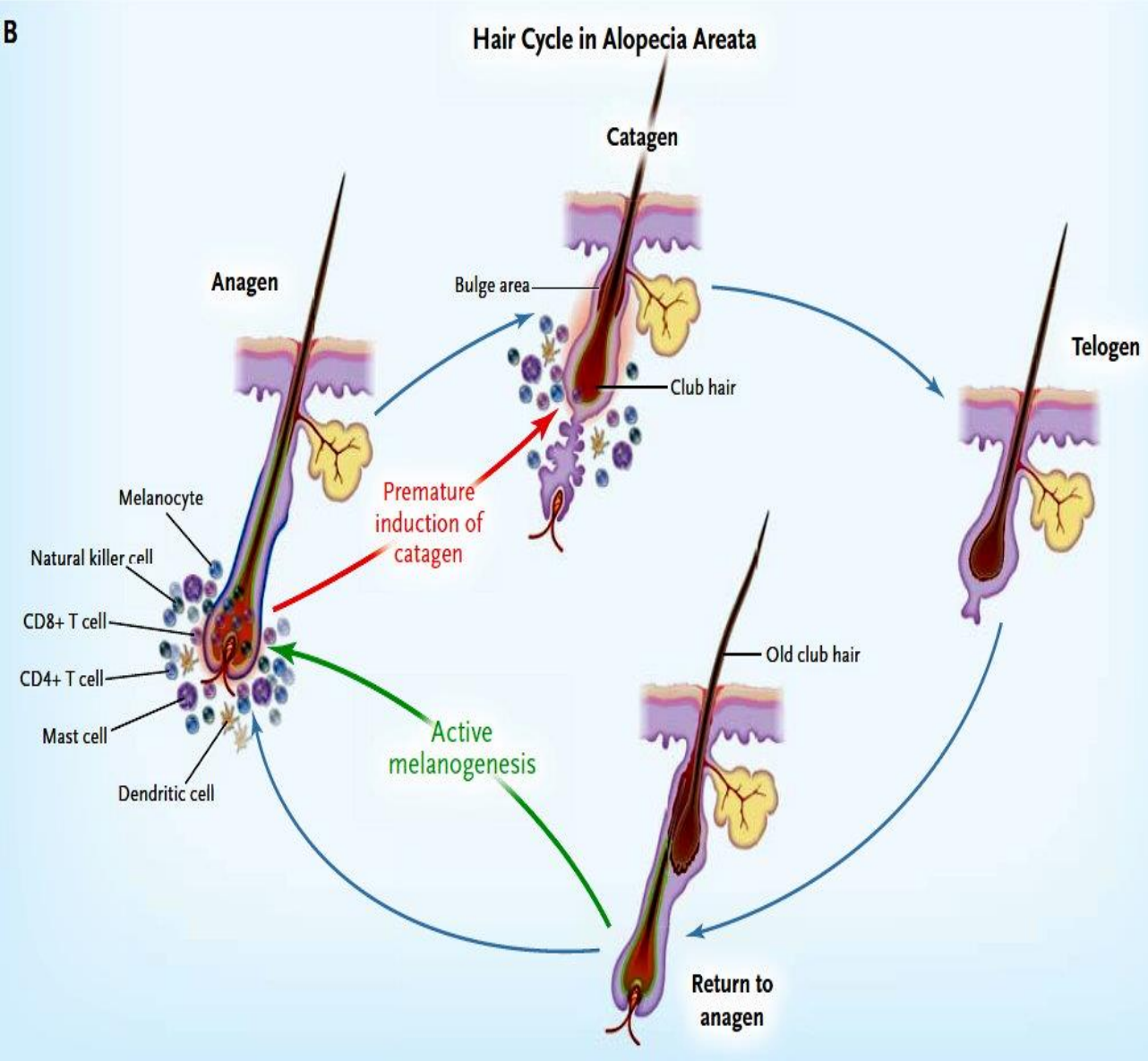


FIGURE 5: HAIR CYCLE IN ALOPECIA AREATA

This is an umbrella term inclusive of conditions wherein the affected hairs undergo an abrupt conversion from anagen to telogen (anagen release), clinically seen as localized shedding of hair in the telogen and morphologically identified as hair with a depigmented bulb. Exclamation mark hair is the main feature, although they are not invariably present. They are thought to be club

hairs of normal caliber and pigmentation, but the distal ends are ragged and frayed.[43] Injury to the hair follicle precorneal matrix cells and presumptive cortex cells results in defective hair shaft. Torsional stress on the shaft as it emerges above the skin produces the typical broken distal end in association with the tapered proximal shaft that terminates in a telogen (club) root.[44] After an initial extensive telogen shedding of terminal hairs, the newly formed anagen bulbs are arrested in the anagen stage. Consequently the new anagen hairs are either small intrafollicular keratinous structures or short thin and colourless hairs, resembling vellus hairs.[45] The simplest hypothesis to explain all these facts is that, a transitory failure near the matrix causes the anagen hair to shed and that shearing of hair from follicles moving into catagen produces the truncated protruding exclamation mark hairs. Since the follicles already in telogen remain unaffected, the only remaining hairs that can be plucked are club hairs. Morphological studies of plucked hairs from concentric zones of scalp lesions have suggested that a wave of follicle damage moves centrifugally to produce expanding patches of hair loss and that the follicles react to the damage in three ways: 1. Severe damage occurs to the keratogenous zone resulting in a focally weakened hair shaft which breaks when exposed to stress present at the level of epidermis. The hair roots have the typical club shape and the proximal portion of the shaft shows a dystrophic gradual taper, probably a reflection of the follicular insult. The arrested or hypoplastic anagen follicles produce inner root sheath tissues, imperfect rudimentary hair like keratin structures, or short (several mm long) thin non pigmented hair shafts with varied diameter, sometimes tapered towards the proximal end. Thus an exclamation mark hair is formed. 2. A less severe insult may precipitate a normal catagen and followed by telogen and produces loss of normal club hairs at the margins of the lesion. The subsequent follicular cycles also may be impaired and produce short, dystrophic anagen hairs. 3. Minimal follicular insult may result in anagen hairs, which are

found at the lesion margins. The possibilities of sparing of white hairs in AA; although similarly attacked white hairs in AA is more resistant to the diseased than the pigmented hair since white hair follicles spent longer time in telogen than pigmented hair follicles. The disease target is reduced or absent in white hair.[46]

HISTOLOGYAND IMMUNOCYTOCHEMICAL FINDINGS IN AA

Expanding lesions of AA on biopsy shows many follicles in various stages of catagen and early telogen.[47] The exact pattern of changes depends critically on the biopsy site. The histopathologic appearance of AA varies depending on disease duration.[48] Eosinophils are also detectable in all stages of AA, within both the peribulbar infiltrate and the fibrous tract. Although clinical correlation is necessary, this feature helps in diagnosis of AA in some biopsy specimens without peribulbar lymphocytic infiltrate.[47]

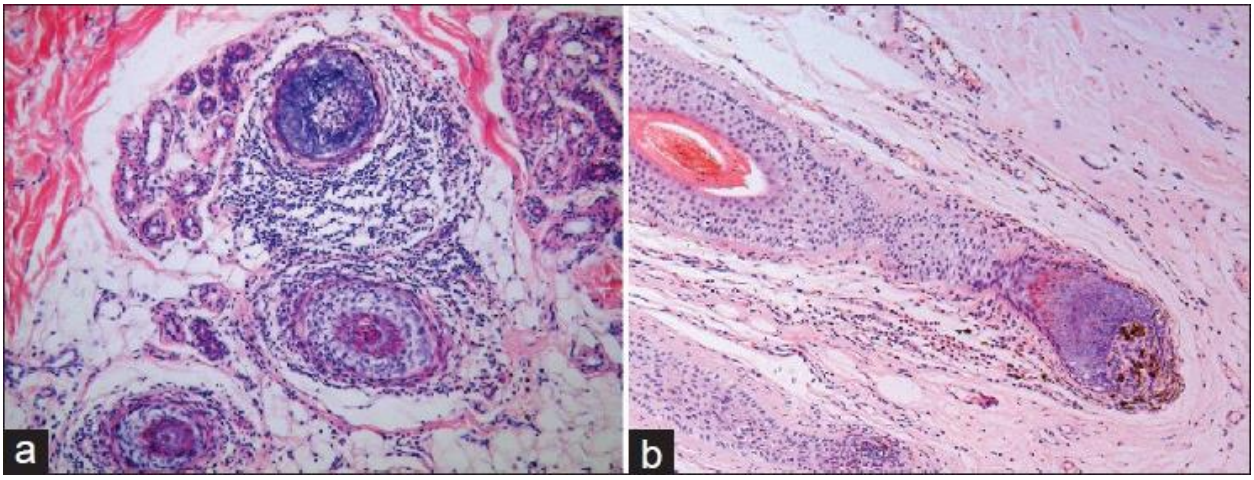


FIGURE 6: Histopathology of biopsied scalp tissue from diffuse alopecia areata patients (a) Intense inflammatory infiltration around and inside the hair bulb. Horizontal section. (b) Prominent eosinophilic infiltration around lower hair follicles.

In the acute stage, a peribulbar lymphocytic infiltrate "swarm of bees" preferentially targeting anagen stage follicles. The infiltrate is composed of both $CD4^+$ and $CD8^+$ cells with the $CD4^+/CD8^+$ ratio being higher in clinically active disease this results in edema, microvesiculation, apoptosis, necrosis, macrophages, and foreign body giant cells around the affected hair follicles.[21] The root sheaths and hair matrix are infiltrated by lymphocytes and there may be hair follicle pigment incontinence, keratinocyte cell necrosis, and vacuolar damage. Focal matrix cell vacuolization and necrosis, a relatively uncommon event, is claimed to be a characteristic feature of AA.[49] Anagen arrest, shortly followed by catagen, weakens the hair shaft and causes breakage at the surface of the skin. As the follicle goes into telogen, the fractured widened tip will further extrude, resulting in the typical exclamation mark hair.[21] Trichomalacia with marked narrowing of the hair shafts ("pencil point hair") results in fragile hairs that fall from the scalp in great numbers.[49]

In the subacute stage, large numbers of catagen hairs, followed by telogen hairs, can be observed.[21] The percentage of catagen/telogen is markedly increased and often exceeds 50% of the total follicles.[49]

In the chronic stage, there is marked hair follicle miniaturization. The terminal to vellus scalp hair follicle ratio is reduced and is likely to be 1:1. Chronic lesions are characterized by the presence of nanogen follicles. The inflammatory infiltrate, if present, is likely to be in the papillary dermis around miniaturized follicles.[21]

Immunohistochemical analysis of AA specimens reveals a prominent expression of ICAM-1 in the dermal papilla and keratinocytes of the matrix and outer root sheath.[31] Immunofluorescence shows deposits of C3, IgG and IgM in the basement membrane zone of hair follicles in some

studies while others contradict. In most lesional anagen follicles, lymphocytic infiltration of the dermal papilla and bulbar epithelium is accompanied by increased expression of HLA class I and class II antigen. In prolonged AA the "secretory activity of sebaceous glands declines with the duration of disease.[6]

CLINICAL FEATURES AND CLASSIFICATIONS

AA commonly manifests as localized, well-demarcated patches of hair loss. Often, they are suddenly noticed, and they may progress circumferentially. Scalp is the most common site (90%), but any part of the body may be affected. AA can be classified depending on extent and pattern of hair loss.

It can be patchy AA, alopecia totalis (AT) involving the entire scalp and body hair such as eyebrows, eyelashes, beard, axillary hair and pubic hair and alopecia universalis (AU) if the total body hair is involved. 5-10% of patchy AA may progress to AT/AU. If AA develops before puberty, the risk of AT is 50% and in older individuals, the risk is about 25%. The pattern of hair loss can be reticular, ophiasis, and sisaipho. Ophiasis (snake-like) is a band-like AA along the posterior occipital and temporal margins. Sisaipho, also called as ophiasis inversus, presents with alopecia involving the frontal, temporal, and parietal scalp but spares hair along the scalp periphery, mimicking androgenetic alopecia.[3]

Acute diffuse and total alopecia, a new variant, was recently described. It is characterized by female preponderance, generalized thinning, rapid progression, tissue eosinophilia, extensive involvement, brief clinical course, and favorable prognosis. Sometimes, unusual presentations may occur in linear distribution.[5]

BASED ON PATTERN	BASED ON EXTENT	NEW VARAINTS	UNUSUAL PATTERNS
RETICULAR	PATCHY	ACUTE TOTAL ALOPECIA	PERINEVOID
OPHIASIS	TOTALIS	DIFFUSE TOTAL ALOPECIA	LINEAR
SISAPHIO	UNIVERSALIS		

TABLE 1: CLASSIFICATION OF ALOPECIA AREATA

Ikeda classified AA based on the associated conditions and on the course of the disease.

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

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

Prehypertensive type: It is seen in young adults whose parents were hypertensive and progress fastly to AT in 40% of cases.

Common type: It affects adults aged 20-40 years and AT develops in 5-15% of cases.[3]

COMORBIDITIES ASSOCIATED WITH ALOPECIA AREATA

PSYCHIATRIC COMORBIDITY

Prevalence rates of psychiatric disorders associated with hair loss due to alopecia areata is higher than those of the general population. Adjustment disorders, generalized anxiety disorders, and depressive episodes are the most prevalent psychiatric diagnoses in patients with AA.[50]

It is possible that the pathologic anxiety associated with social contact is apparent with alopecia totalis or universalis, the cosmetic repercussions obviously being greater in these forms of the disease. Concerning personality, obsessive, anxious, and dependent traits are seen commonly. This ties up with the old concept of "alexithymia" (failure to find words for feelings); this characteristic is related to psychosomatic disease and manifests itself through the patient's operative way of thinking. This can result in a greater interiorization of stress, which may, in turn, alter immune responses related to neuropeptides, such as the migration of macrophages, vasodilator or vasoconstrictor responses, phagocytosis, lymphocytic cellular immunity, and expression of some factors of leukocytic adhesion to the microvascular endothelium, etc., thus helping us to understand the complex nature of the triggering factors involved in AA.[50]

A study demonstrated that in human beings, adults who experienced childhood maltreatment showed reduced ability to control the hypothalamic pituitary adrenal axis response to a psychologic stress. The consequence of this is a more limited inhibition on inflammation by glucocorticoids.[5] Also studies suggest that personality and social factors, such as avoidant attachment, alexithymia and poor social support might result in AA.[51] Generally, AA in patches interfered little with the patient's normal functioning. There was widespread concern about the disease and the medical care received, which might suggest that patients would benefit from

more complete information about the clinical characteristics of AA, possibilities for treatment, and prognosis. Extensive patches of AA, duration of AA, and gender of the patient were not related to worse adjustment to the illness; this was associated with psychiatric variables, such as personality and the presence of psychiatric comorbidity. Worst adjustment was found with dependent personalities, followed by antisocial personalities, generalized anxiety and depressive episode.[50]

This shows that an integral approach to the illness is necessary, given that treatment of a depressive or anxious state, or working with the personality traits of the patients, would improve their adaptation to the disease, and perhaps its dermatologic prognosis. Furthermore, because dermatologists act as the primary care physician for patients with alopecia areata, they are in a unique position to recognize psychiatric comorbidity and execute meaningful interventions.

ENDOCRINAL COMORBIDITY

THYROID DISEASE

Thyroid diseases were found to be associated with alopecia areata in 0-28% of the patients. Alopecia areata is found to be associated with various thyroid diseases (e.g., Hashimoto's thyroiditis. Graves' disease, simple goiter, hypothyroidism, etc.). The prevalence of auto-antibodies against thyroid constituents, gastric parietal cells and smooth muscle is increased in alopecia areata and there is an increased prevalence of thyroid disease in patients and their relatives. Diminished T cell numbers and responses are associated with the presence of auto-antibodies which indicates that auto-immune mechanisms are involved in the pathogenesis of alopecia areata.[29]

Among the thyroid disorders, hypothyroidism is the most frequent association. Although the effects of hypothyroidism on hair is known, the mechanism is still not clear.[27] Also studies have proved that a history of hypothyroidism increased the risk of AA by 3-fold.[35] Confirmation of an autoimmune mechanism requires the demonstration of reactivity against follicle constituents. A close association exists between decreased T cell reactivity autoantibodies and alopecia areata, the nature of the relationship between the immune abnormalities and the hair loss is still not clear.

DIABETES MELLITUS

Diabetes mellitus occurs more frequently in relatives than in patients with AA. A history of diabetes mellitus is significantly more common in family members of children with AA (18.4%) compared with controls (2%).[15]

ATOPIC COMORBIDITIES

Atopic dermatitis is a classic endogenous eczema, shown to involve different mechanisms: atopic dermatitis as predominantly T-helper (Th) 2- mediated and AA as predominantly Th1-mediated. It is characterized by pruritic, recurrent, flexural and symmetric eczematous dermatosis. The clinical manifestations depend on the age of the patient. Infants present with facial and body lesions, either focal or generalized. In adolescents and adults flexural areas and the hands are mainly involved.[27] There has been recent evidence, however, to suggest that these immune mechanisms may not be so clear cut in either disease, especially in their chronic forms. Recent genetic studies have shown that some susceptibility loci in atopic dermatitis correspond with known susceptibility loci in psoriasis (another predominantly Th1-mediated disease), but not with those linked to asthma.[52] AA and atopy share a Th2 cytokine pattern and increased

levels of IgE antibodies, mast cells and eosinophils. In addition, a biphasic pattern of T helper response in both AA and atopic dermatitis has been observed thereby suggesting a common pathway between these conditions.[35]

VITILIGO

Vitiligo has been associated with a number of autoimmune disorders. There is an association between alopecia areata and vitiligo.[2] As per a study the incidence of vitiligo in AA patients was found to be 4% as compared to an estimated frequency of less than 1% in the general practice.[53] Possibly related is the finding of another study of ocular pigmentary changes in nine patients with alopecia areata.[54] The interrelationship of these diseases is equally obscure. It is tempting to implicate an abnormality of hard keratin synthesis to explain the alopecia but difficult to reconcile such an abnormality with vitiligo. However, a study has measured increased urinary MSH excretion in alopecia areata and has postulated that vitiligo results from release of a melanocyte lightening substance at the peripheral nerve endings. These challenging and ingenious suggestions await definitive confirmation. The possibility that the diffusely lightened skin color represents an optical phenomenon secondary to the changes of alopecia rather than a true decrease in melanin content also remains to be determined. In addition, the apparent total vitiligo could result per se from the universal alopecia areata.[2]

DOWN'S SYNDROME

There is an increased incidence of alopecia areata in patients with Down's syndrome. A study found sixty cases of alopecia areata among 1,000 patients with Down's syndrome compared to one case of alopecia areata in a population of 1,000 mentally retarded controls.[55] Their findings were supported by another study who detected alopecia areata in 8.9% patients with trisomy 21.

Immunologic abnormalities in Down's syndrome may be somehow responsible for the development of alopecia areata in these patients.[2]

OTHER ASSOCIATED CONDITIONS WITH ALOPECIA AREATA

The following disorders with a possible immunological background have also been reported in association with alopecia areata: systemic lupus erythematosus, discoid lupus erythematosus, rheumatoid arthritis, scleroderma, ulcerative colitis, pernicious anemia, lichen planus, myasthenia gravis, thymoma, hypo- gammaglobulinemia, autoimmune hemolytic anemia, Candida-endocrinopathy syndrome, lichen sclerosus et atrophicus and polymyalgia rheumatica.[2]

CUTANEOUS AND EXTRACUTANEOUS MANIFESTATIONS IN ALOPECIA AREATA

NAIL CHANGES IN AA

Any comprehensive theory of pathogenesis of alopecia areata will have to explain the common occurrence of dystrophic nail changes in this disorder.

Nail dystrophy may be associated with AA. The reported incidence of onychodystrophy in AA ranges from 10%-66%.[31] A study reported an incidence of nail dystrophy upto 60% of the cases. A case of AU along with onychodystrophy and vitiligo has been reported.[56] The gross nail dystrophy is said to be proportional to the degree of hair loss. It seems that nails in AA initially becomes luster less, later rough and finally definite pitting becomes evident. Changes may be seen in one, multiple, or all of the nails. The dystrophy may precede or follow resolution of AA.[2, 3, 5]

Pits are larger and less deep than in psoriasis, longitudinal ridging and irregular thickening are more frequent findings. Characteristically nail plate is pitted and these pits are regularly arranged in horizontal and vertical rows or both. This may persist even after hair has regrown.[3, 5]

Pitting with irregular pattern or in organized transverse or longitudinal rows, trachyonychia (longitudinal striations resulting in sandpaper appearance), beau's lines (grooves through the nail matching that lunula margin), onychorrhexis (superficial splitting of the nail extending to the free edge), thinning or thickening (psuedomycotic), onychomadesis (onycholysis with nail loss), koilonychia (concave dorsal nail plate), punctate or transverse leukonychia and red spotted lunula may be associated with AA.[2,3,5]

TESTICULAR MANIFESTATIONS IN AA: A study reported testicular changes in 55% of AA patients. These included oligospermia, hypogonadism, testicular atrophy, spermatocele, varicocele which were seen both unilaterally and bilaterally.[54]

EYE CHANGES SEEN IN AA

Cataract is more common in elderly patients and is associated with alopecia totalis. In a study asymptomatic punctate lens opacities were found in 17% patients. 3 cases of cataracts were reported in a study of 5 alopecia universalis patients mainly of posterior subcapsular type.[31]

Posterior subcapsular cataract, retinal changes, decreased visual acquity, exophthalmos, uveitis, pigmentary hyperplasia of choroid and retinal epithelium, discrete depigmentation of choroid and retina, ectopia of pupil, optic atrophy, Horner's syndrome, tortuosity of fundal vessels, iris atrophy are the commonly noted eye changes.[54]

HAIR CHANGES IN AA

Depigmentation, easy pluckability, weakening, narrowing, easy breakability, exclamation hair, undulation, coudability, exclamation mark hairs, anagen atrophy, graying phenomenon, yellow dots, black dots and vellus hair are the commonly seen hair changes.

A frequent feature of AA patch is exclamation hairs that may be present at its margin. Exclamation mark hairs are broken, short hairs that taper proximally. It represents a response of anagen hair follicle to acute injury-namely transition state in the process of which imperfect keratin is synthesized and pigment is dumped into the hair fiber and external root sheath. This projects about 1cm above the scalp surface. Its distal tip is dark and frayed and rough, with magnification uneven ends of keratin fibrils can be seen. More proximally the shafts become depigmented and tapers to a small, poorly formed club root. Exclamation mark hair is pathognomonic of a new expanding patch of AA, which may not always be present and is not seen in any other alopecia/ nor in old static patches of AA.[56]

Coudability is a physical sign of AA since the kink in the hair gives the shape of a coude catheter.[57] In subacute condition of AA follicle which are affected partially or transiently, the hair can be seen to continue to grow. This result in a short length of poor shaft, partly depigmented and narrowed often with localized splaying where the hair has begun to split. A single hair may be affected several times but mostly there is a single area of weakness which corresponds to a single episode. This occurs 5- 10mm above the scalp, presumably because follicle is no longer active and the stationary shaft defect has not yet revealed. When irregularity of shape or vagueness of outline of a lesion causes diagnostic confusion, inward movement of the hair will produce a sharp kink which reveals the site of affection and on microscopy shows anagen atrophy. As the disease progresses, large bald spots are formed by the coalescence of several smaller patches, frequently these areas assume bizarre shapes.[58]

White Hairs in AA: AA may selectively attack pigmented hair and cause rapid whitening. If the patients has some white hairs at the time of onset of AA, these are usually spared by the disease process. If the white hairs are numerous the sudden diffuse onset of AA may result in the patient's shedding only his pigmented hairs, and they appear to 'go white' over the course of a few days.[6]

COMPLICATIONS:

Strictly medical implications of AA are minor. The loss of eyelashes could deprive the eye of protection from foreign bodies. The occurrence of cataracts in patients with AA as an association, or as a complication of treatment with systemic steroids can occur. But the most significant complication would be psychological with patient having a feeling of helplessness, emotional liability and of depression.[51]

NATURE AND COURSE OF THE DISEASE

The only predictable thing about AA is that it is unpredictable. Recurrence is the rule.[6] The progress is sometimes rapid with large number of hair being lost in a short time. It commonly starts on the scalp and most of the times restricted to the scalp only. In few cases it spreads to other areas or new patches may develop nearby with confluence causing total loss of hair AT and rarely generalized loss AU. The recovery from the hair loss may be complete, partial, or non-existent.[59]

Early age of onset	Nail changes: Pits, onychodystrophy, onycholysis, anonychia
Extensive scalp involvement (>50% scalp)	Associated systemic disorders: Atopy, hypertension, connective tissue disorders
Loss of eyebrows and eyelashes	Associated genetic disorder: Down syndrome
Alopecia totalis	Patchy regrowth of terminal hairs within the patch
Alopecia universalis	Family history of AA
Recurrent episode	*MIF-173*C* gene[108]
Patterns—ophiasis, sisaphio, reticular	

Note: MIF, Macrophage migration inhibitory factor.

TABLE 2: POOR PROGNOSTIC FACTORS IN ALOPECIA AREATA

Pregnancy is sometimes associated with regrowth in long standing severe AA, but the recovery is usually only temporary.[31] The initial patch may regrow within a few months, or further patches may appear after an interval of 3-6 weeks and then still more patches after a similar interval. There is no constant duration for these intervals. A succession of discrete patches may rapidly become confluent by the diffuse loss of the remaining hair. In some cases however, the initial hair loss is diffuse and total denudation of the scalp may occur within 48 hours. When regrowth takes place it is often nonpigmented, but the hairs gradually resume their normal caliber and color. Regrowth in one region may occur with simultaneous patches at other sites.[6]

DIFFERENTIAL DIAGNOSIS

1. Tinea capitis- it can be excluded by Wood's lamp and by microscopy and culture.
2. Traumatic alopecia or Trichotillomania- Alopecia is usually incomplete. Broken of hairs show black dot appearance, injured follicles may form soft, twisted hair. Hairs present

FIGURE 7: TRICHOTILLOMANIA IN A 14YEAR OLD FEMALE

retain normal reaction pattern to epilation. Cutting of the hairs very close to the scalp will temporarily prevent further epilation and aid in diagnosis.

3. Psuedopelade is a confusing entity clinically characterized by patches with irregular edges, often perifollicular erythema, and definite atrophy. The hairs from the border of a lesion can be removed without resistance but they retain the root sheaths unlike atrophic hairs in AA.
4. Syphilitic alopecia- the hair fall leaving multiple small scattered irregularly thinned 'moth eaten patches' of semi baldness, irregular borders, and incomplete loss of hair within the

patch, and predilection for the posterior scalp. History of exposure and other cutaneous manifestations of secondary Syphilis may be present along with serological evidence.

5. Telogen/Anagen effluvium- these have to be differentiated from diffuse pattern of AA. In telogen effluvium there is history of preceding high grade fever, pregnancy or certain drugs. The plucked hair show large proportion of normal and clubbed hair.
6. Systemic lupus erythematosus- can be confirmed by biopsy and immunoflourescence.
7. Congenital triangular alopecia- it is identified by early onset (5th or 6th year), typical site and shape.
8. Infantile occipital alopecia- presents as alopecia in occipital region.
9. Tinea capitis, pyoderma, dissecting cellulitis, lupus erythematosus, or scleroderma in which the peculiar linear form may involve the median line of the forehead and the scalp.
10. Male pattern baldness in females
11. Traction alopecia
12. Alopecia mucinosa- a chronic history with follicular papules with hair loss; a manifestation of cutaneous lymphoma when above 40 years age with characteristic histopathology of accumulation of mucin in the degenerating pilosebaceous units.[59]
13. Alopecia neoplastica- There are case reports of alopecia totalis as presenting manifestation of metastatic breast cancer.

DIAGNOSIS

The diagnosis of AA can be done on clinical grounds and microscopic aid. The typical circumscribed form usually presents no difficulties and can be confirmed microscopically by the presence of exclamatory mark hair and dystrophic anagen hair. History includes age, duration,

onset, progression and physical examination for clinical signs, pattern of diffuse or patchy loss; and hair pull test.

Routine testing is not indicated in AA. Routine screening for autoimmune disease (thyroid disease in particular) is not generally indicated because of insufficient clinical evidence.Older patients, patients with long disease duration, females, patients with persistent patchy AA (as compared to transient patchy AA), and patients with AT/AU have been found to more likely have thyroid abnormalities. However, because AA severity and thyroid disease are neither correlated nor causal, routine thyroid testing is not recommended.
Potassium hydroxide, fungal culture, lupus serology, syphilitic screening, and a scalp biopsy may be necessary in ambiguous or difficult to diagnose cases.

MICROSCOPIC DIAGNOSIS OF AA:

1. **Trichogram** -It is a composite measurement of several growth parameters of hair. Examination should be carried out at a standard time at least 4 days after hair loss. The hair is cut at about 0.5 cm above scalp surface, and approximately 50 hairs should be extracted briskly in the direction of their insertion. The hair is immediately examined under water under low power microscopy. Anagen hair plucked from the margin of the actively spreading lesion shows counts significantly reduced, size diminished, thin, unpigmented root broken off at the narrowest point and the absence of root sheath designated as dystrophic anagen hair. The telogen hairs have no keratogenous zone with the proximal tip club shaped keratinised and this predominates in slow growing patches. The catagen hairs are increased in ratio upto 50%. Exclamatory mark hairs are pathognomic of AA with an overall average of 3mm.[59]

2. **Dermatoscopy-** Yellow dots, black dots, broken hairs, coudability hairs, and clustered short vellus hairs (<10 mm) are the most common features found in dermatoscopy.[3] Black dots and yellow dots correlated with disease severity whereas black dots, tapering hairs, and broken hairs correlated with disease activity. Short vellus hairs correlated negatively both with disease severity and activity. Tapering hairs include exclamation mark hairs and coudability hairs and are a marker for disease activity and severity. Exclamation mark hairs are fractured hairs that present a frayed thicker tip; these are exclusively seen in AA, mostly along the edges of the patches. Coudability describes hairs of normal length with a narrowed proximal shaft.[57]
3. **Biopsy of lesions and histopathological examination**

FIGURE 8: EXCLAMATION MARK HAIR

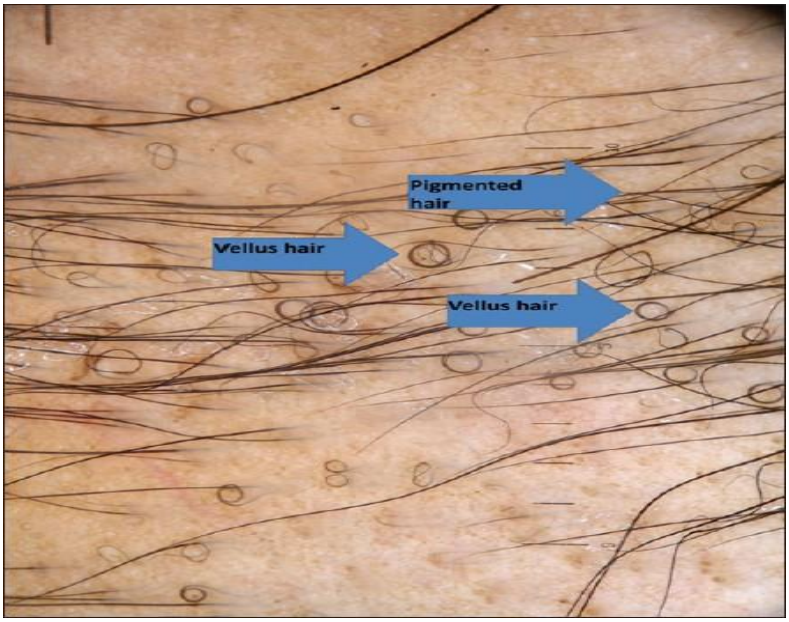


FIGURE 9: DERMATOSCOPIC FINDINGS IN ALOPECIA AREATA

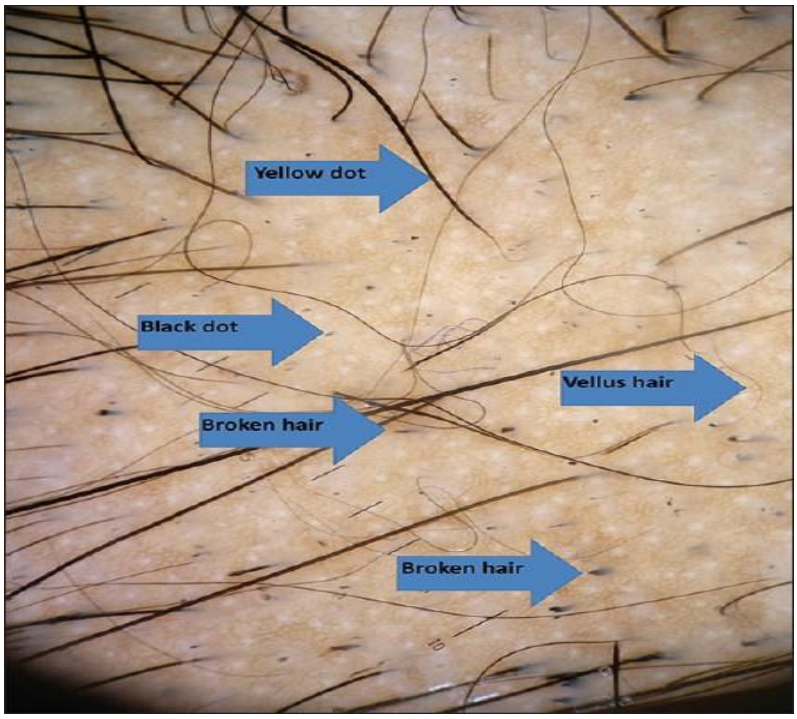


FIGURE 10: YELLOW DOTS AND BLACK DOTS ON DERMATOSCOPY

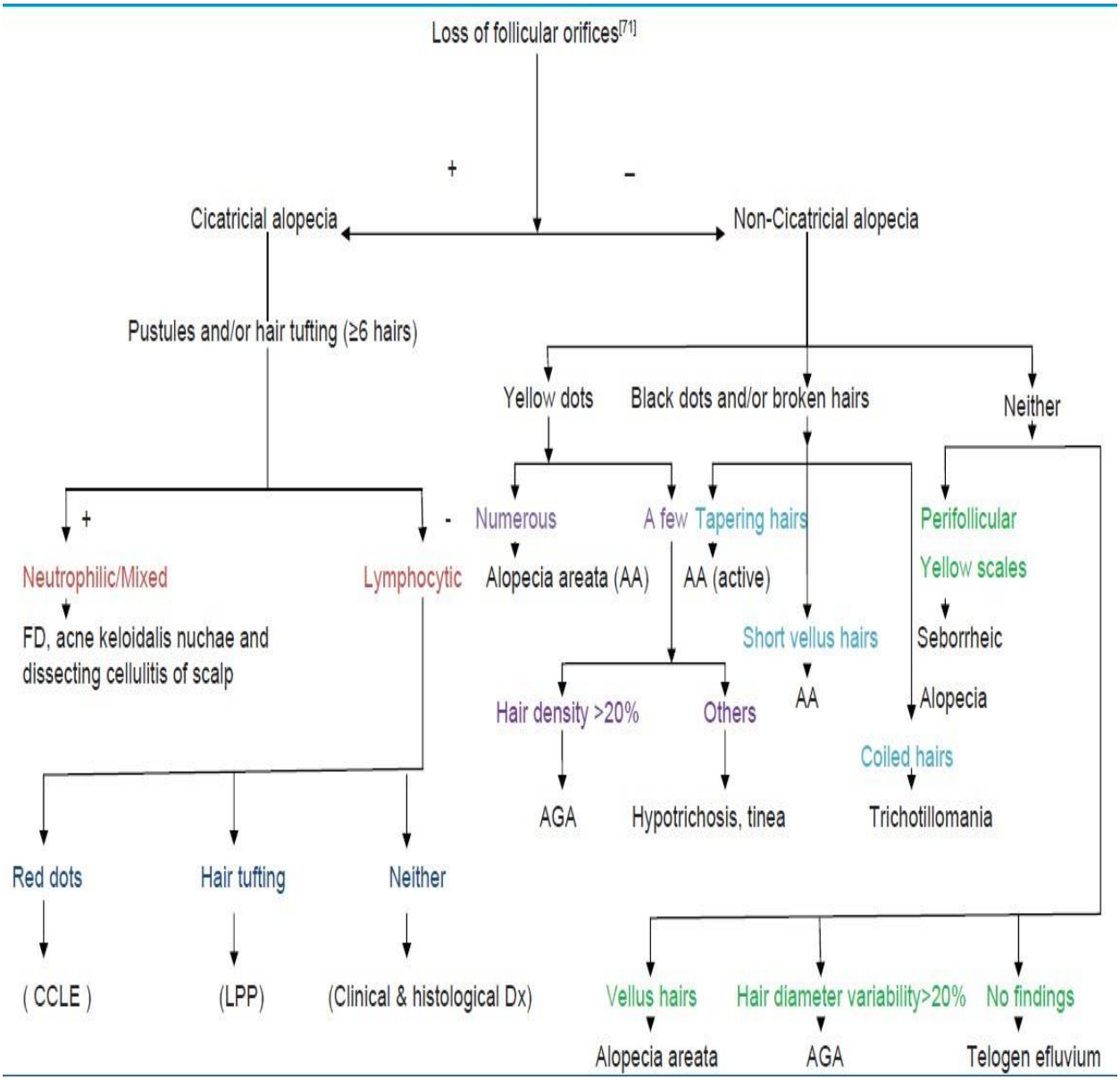


FIGURE 11: APPROACH TO ALOPECIA BASED ON DERMATOSCOPY

MANAGEMENT

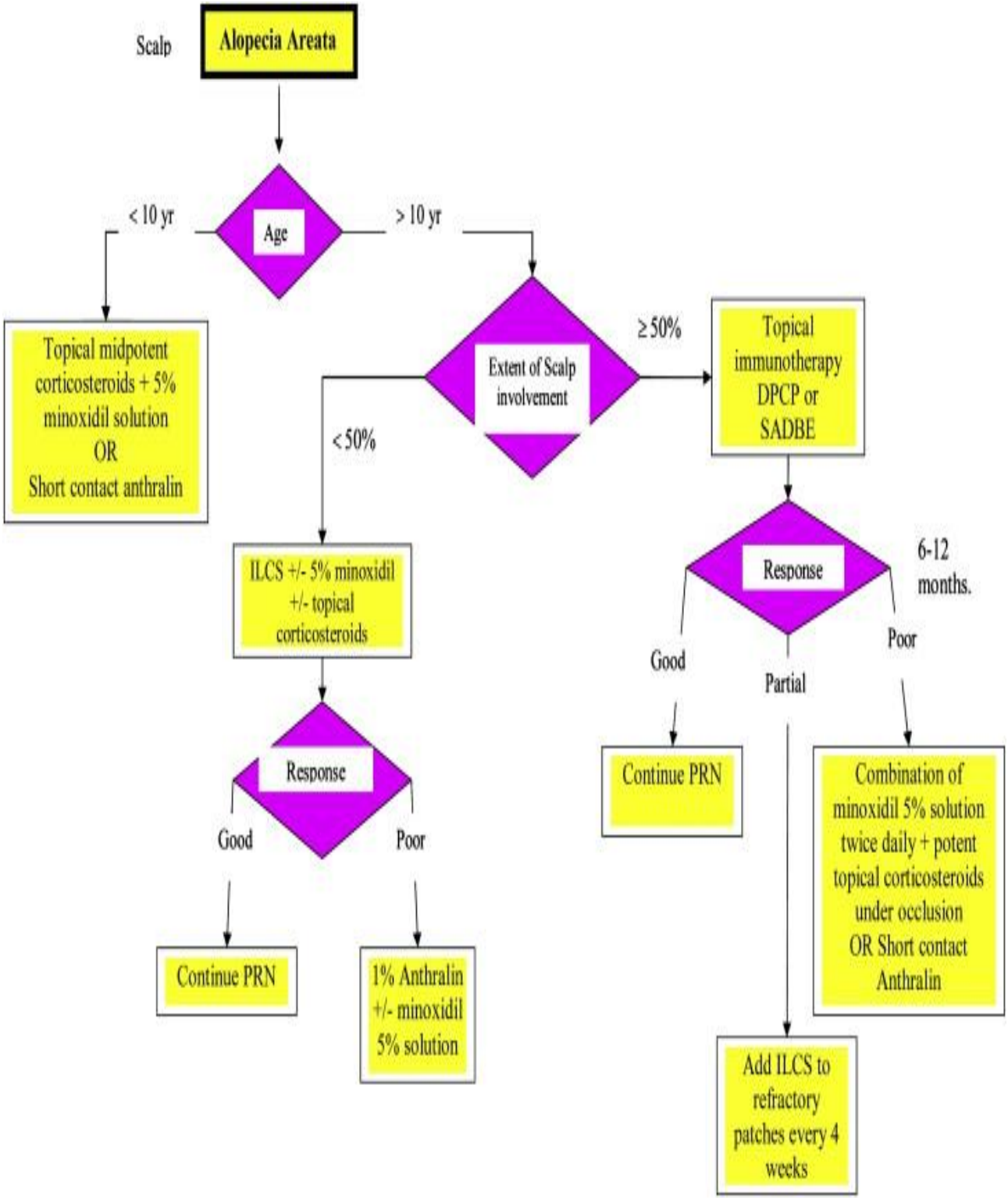


FIGURE 12: TREATMENT PROTOCOL IN ALOPECIA AREATA

TOPICAL THERAPY

TOPICAL CORTICOSTEROIDS- Potent topical corticosteroids are widely used to treat alopecia areata but there is little evidence that they promote hair regrowth. Several forms of topical corticosteroids have been reported to exhibit varying levels of efficacy in AA.[4] Some of the topical therapies have included fluocinolone acetonide cream, fluocinolone scalp gel, betamethasone valerate lotion and clobetasol propionate ointment.[60] They remain a very good option in children because of their painless application and wide safety margin.[4]

MINOXIDIL- First introduced as an antihypertensive agent, its side effect hypertrichosis led to its use as treatment for various forms of alopecia. Cosmetically acceptable regrowth was induced in 20%–60% of cases in various studies, higher concentrations being more effective.[8] Minoxidil directly affects follicles by stimulating proliferation at the base of the bulb and differentiation above the dermal papilla, independent of its vascular influences. Minoxidil has shown considerable results in the management of AA and it is believed that patients resistant to minoxidil treatment often suffer from severe AA, AT or AU. Combination therapy of minoxidil 5% lotion and anthralin have been documented to show better results by few authors.[4]

ANTHRALIN- Anthralin exerts its effect through its irritant contact properties. It also acts through its immunosuppressive and anti- inflammatory properties via the generation of free radicals. Patients are instructed to apply 0.5–1% anthralin cream to bare areas for 20–30 min daily over 2 weeks, gradually increasing daily exposure until low-grade erythema and pruritus develops, which when once achieved is continued for 3–6 months. It is believed to be a suitable agent for children under 10 years of age.[4] Other side effects include folliculitis and cervical lymphadenopathy. Regrowth of hair with anthralin without accompanying dermatitis has also been described.[8]

TACROLIMUS- Tacrolimus is a topical calcineurin inhibitor that inhibits transcription following T-cell activation of several cytokines including interleukin-2, interferon-and tumor necrosis factor.[4] The peculiarity of tacrolimus was that the induction of anagen and hence hair growth promotion was observed with the topical but not with the systemic route of administration. However, there has not been a positive result with tacrolimus 0.1% applied twice daily even after 24 weeks in patients with AA.[8]

TOPICAL IMMUNOTHERAPY-Topical immunotherapy relies on inciting an allergic contact dermatitis (ACD) by applying potent contact allergens to the affected skin. It is believed that contact sensitizers act through immunomodulation of the skin and its appendages at several different points. Dinitrochlorobenzene (DNCB) was the first sensitizer used for the treatment of AA.[4] Squaric acid dibutyl ester (SADBE) and diphenylcyclo- propenone (DCP) are the contact sensitizers in current use, the latter being more stable.[8]The only disadvantage of DNCB is its mutagenicity by Ames test.[4]

The method of use of DCP consists of inducing sensitivity by the application of 2% DCP and following up two weeks later with applications of lower concentrations (0.001%–0.25%) over the bald patch at weekly intervals. The concentration may be modified to maintain a mild erythema and pruritus for about 48 hrs. Regrowth starts after 4–8 weeks and needs to be maintained with less frequent applications.[8]

Contact sensitizers act by “antigenic competition”, nonspecific suppression of delayed hypersensitivity, and regularization of HLA expression in the lower portion of hair follicle epithelium. After successful treatment with a contact sensitizer the T helper–suppressor ratio (T4/T8) of the peribulbar infiltrate changes from 2–4:1 to 1:1.[8]

Side effects of contact sensitizers include contact urticaria, postinflammatory hyper and hypopigmentation, erythema mutliforme, facial or eyelid edema, fever, flulike symptoms, anaphylaxis and vitiligo.[4]

MESOTHERAPY- Mesotherapy employs multiple injections of pharmaceutical and homeopathic medications, plant extracts, vitamins, and other ingredients into the target tissue. However, this is expensive and not effective, thereby precluding its widespread use.[4]

PROSTAGLANDIN ANALOGUES- Latanoprost and bimatoprost are prostaglandin analogues, which are used in open angle glaucoma caused hypertrichosis of eyelashes and hair on the malar area as an adverse effect. Because of this effect, these were tried in eyelash AA and found ineffective. Though the earlier studies failed to induce hair growth, a recent trial showed a cosmetically acceptable hair growth in 45% of the latanoprost-treated group. Bimatoprost has also been beneficial in AU patients. Transient mild eye irritation or hyperemia may occur.[4]

CAPSIACIN-Capsaicin was previously shown to induce vellus hair regrowth in AA. More recently, a study showed that topical capsaicin and clobetasol 0.05% are comparable.[4] The idea of using capsaicin in AA emerged from the theory of nervous system and neuropeptide role in the development of the disease.[60] Capsaicin can release substance P (SP) and calcitonin gene–related peptide (CGRP), and after repeated application, it depletes neurons of SP. Capsaicin cream 0.075% resulted in vellus hair regrowth in two patients after 3 weeks of treatment.[27]

FRACTIONAL THERMOLYSIS LASER- A single case report who had complete regrowth after multiple sessions with fractional Er:Glass laser has been reported. The mechanism of action is thought to involve the induction of T-cell apoptosis and direct enhancement of hair growth.

This report sheds some light on, and stimulates the research of, the role of this fairly new technology in AA treatment.[61]

INTRALESIONAL CORTICOSTEROIDS- Depot corticosteroid injected intralesionally stimulates hair regrowth at the site of injection in some patients. Hydrocortisone acetate25 mg and triamcinolone acetonide5–10 mg are commonly used.[4] Triamcinolone acetonide in a concentration of 10 mg/ml is administered using a 0.5-inch long 30- gauge needle in multiple 0.1 mL injections approximately 1 cm apart. Corticosteroid is injected just beneath the dermis in the upper subcutis. Multiple injections may be given, the main limitation being patient discomfort. For circumscribed AA involving less than 50% of the scalp, intralesional corticosteroids are the first-line approach. Initial results of intralesional treatment are often seen in 1–2 months. Additional treatments are repeated every 4–6 weeks.[60]

PHOTOCHEMOTHERAPY- The use of PUVA (psoralen plus ultraviolet light A) is based on the concept that the mononuclear cells and Langerhans cells that surround the affected hair follicles may play a direct pathogenic role and that PUVA therapy can eradicate this inflammatory cell infiltrate. They proposed that PUVA acts through systemic immunomodulation rather than local stimulation. Side effects included slight erythema and painful burning.[8] Oral methoxsalen and whole body exposure to UVA much more useful than local PUVA therapy.[3] Turban-PUVA is a modification of topical PUVA in which a towel soaked in 8-methoxypsoralen (0.0001%, i.e. 1 mg/L) is wrapped around the scalp for 20 min and followed by UVA irradiation.[8] However, the long-term utility of PUVA therapy is doubtful.

SYSTEMIC THERAPY

SYSTEMIC CORTICOSTEROIDS - Systemic corticosteroids do not constitute the first line treatment for alopecia areata because of their extensive side effect profile. The dosages necessary to maintain hair regrowth in AA are between 30 and 150 mg daily. Treatment course can range from 1 to 6 months, but prolonged courses should be avoided secondary to the numerous side effects of these drugs especially when children are treated. Systemic steroids are thus not preferred in the treatment of alopecia areata except for some cases as a short course only. Its side effect profile in conjunction with the long-term treatment requirements and high relapse rates make systemic corticosteroids a more limited option.[4]

ORAL MINI PULSE STEROIDS- To avoid the side effects of daily steroids, pulse therapy was conceived. In a study conducted by Pasricha et al., betamethasone oral mini-pulse therapy is a convenient and fairly effective treatment modality for extensive alopecia areata. Oral mini-pulse therapy (OMP) with corticosteroids has been successfully used for the treatment of alopecia areata with minimal side effects. Persistent hiccups is a rare complication of oral and intravenous corticosteroid therapy.[4]

CYCLOSPORINE- Cyclosporine A is a common antimetabolite drug used in post-transplantation patients which exerts its effect via inhibition of T-cell activation. A common cutaneous side effect is hypertrichosis, which occurs in approximately 80% of patients, possibly as a result of prolongation of the anagen phase of the hair cycle. It also decreases the perifollicular lymphocytic infiltrates, particularly the mean number of helper T cells.[4] Cyclosporine has been used alone or in conjunction with coeticosteroids with a success rate upto 76.6%. Cyclosporine use is limited by its side effects and high relapse rate.[60]

SULFASALAZINE- Sulfasalazine is believed to be a good alternative treatment for alopecia areata because of its good efficacy, good adverse event profile and steroid sparing nature. The

drug has immunosuppressive and immunomodulatory effects, including the inhibition of inflammatory cell chemotaxis, and cytokine and antibody production and similar to cyclosporine, sulfasalazine has been shown to inhibit the release of interleukin 2.[4] It is started at 0.5g twice daily for 1month, 1g twice daily for 1month, and then 1.5g twice daily for 4months. Adverse effects include GIT distress, rash, headache and laboratory abnormalities.[60]

BIOLOGICAL THERAPY- These medications synthesized from recombinant proteins reduce the pathogenic T cells, inhibit T-cell activation and inhibit inflammatory cytokines, suggesting a potential role in the treatment of AA. Etanercept is a biological agent and a fusion protein receptor consisting of two human TNF receptors and Fc domain of human immunoglobulin G1.Studies with other biological agents in the treatment of AA are still underway.[4]

BEXAROTENE- In a single recently published study, bexarotene 1% gel resulted in a 26% hair regrowth rate. The mechanism of action is thought to be through immunomodulation and induction of T-cell apoptosis. Dermal irritation is a common side effect.[4]

PSYCHOSOCIAL SUPPORT-AA is associated with high psychiatric comorbidities (mainly adjustment disorder, generalized anxiety disorder, and depressive disorders). There is a need for larger randomized controlled trials to evaluate the use of antidepressants in AA. Support groups that involve regular meetings of AA patients and family members can be an invaluable resource. Patients can derive emotional support and information that can help them develop positive coping strategies, overall improved quality of life, and increased treatment compliance. The National Alopecia Areata Foundation provides patients and physicians with brochures, research updates, bimonthly newsletters, a pen pal program, sources for scalp prostheses, and many patient conferences.[60]

VITAMIN D

1, 25-dihydroxycholecalciferol [1, 25(OH)2D3] is the biologic active form of the vitamin D3.Vitamin D has a multitude of biologic effects interacting with the innate and adaptive immune system, mainly leading to its downregulation. It regulates the differentiation of B cells, T cells, dendritic cells, and the expression of Toll-like receptors. The relation between vitamin D levels and the development of AA and whether vitamin D supplementation helps in the treatment of AA represent an attractive area of research, the results of which may prove that vitamin D is a safe and helpful choice in AA treatment.[60]

WIGS

For many female patients with extensive alopecia areata a wig or hairpiece is the most effective solution. Some men also require wig although male wigs rarely appear natural. Acrylic wigs are much cheaper than real hair wigs and are easier to look after. However,real hair wigs are preferred mainly because the better fit allows a wider range of social activities.[4]

In cases where all the treatments fail, other options that have been reported for AA are hair transplant, but recently it has only been performed in eyebrows with good results. Another alternative is micropigmentation, also known as tattoo; it has been used esthetically to camouflage various medical conditions related to dermatology.[4]

To sum up although many treatments exist for AA, none alters the natural history of the disease, and assessment of each treatment is difficult because of a lack of controlled trials and the occurrence of spontaneous remission. Most studies are short term, lasting less than 6months, and those that last longer show poor long-term benefit from the interventions. Alopecia areata has a great impact on the appearance and psyche of the afflicted individual. Moreover, no uniformly dependable treatment is known. Corticosteroids have shown promising results and are time tested drugs in management over the years. Contact immunotherapy is the best documented treatment for severe AA, including extensive patchy loss, alopecia totalis and universalis. However, a relatively small proportion of patients achieve good long-term cosmetic results, and contact immunotherapy is not licensed or widely available. Potent topical steroids or intralesional steroids form the mainstay of treatment for limited disease but are of little value in rapidly progressive alopecia or alopecia totalis/universalis. Support mechanisms in the form of local support groups should be formed in order to provide counseling for the affected patients and allay their psychiatric comorbidities.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was done in the Dermatology Department of R L JALAPPA HOSPITAL from December 2013 to January 2015. An informed written consent was taken.

Criteria for selection of study group

Inclusion criteria:

- All clinically diagnosed patients with Alopecia areata.

Exclusion criteria:

- Patients on immunosuppressive therapy, radiotherapy and chemotherapy.
- Diagnosis will be made clinically and based on the history of abrupt patchy hair loss with or without progression and absolutely normal looking scalp without any secondary changes on examination.

METHODOLOGY

Clinical details including sex, age of onset, duration of disease, site of onset, sites affected, precipitating and aggravating factors, associated diseases with special reference to atopy, autoimmune conditions, psychiatric conditions, thyroid diseases and a significant family history will be recorded on a proforma.

Age of onset is defined as age when patient became aware of the disease for the first time, which at that time or later was diagnosed as AA.

Psychiatric diagnosis will be made based on ICD-10 criteria.[5]

Physical examination includes site of involvement, evaluation of pattern, disease extent, associated nail changes and whole body examination for associated diseases, which are recorded in a proforma.

Laboratory tests will be done in diagnosing comorbid conditions whenever required.

SAMPLE SIZE: To conduct a clinical study of comorbidities among patients with Alopecia areata, which has an estimated prevalence of 0.1- 0.2% in the general population.[6] At 95% confidence interval and 2% absolute error, 60 subjects have to be studied.

STATISTICAL ANALYSIS: The collected data will be analyzed using mean, standard deviation, proportions and confidence interval. The association between AA and comorbid conditions will be assessed by Chi- square test and Fischer exact test.

OSERVATION AND RESULTS

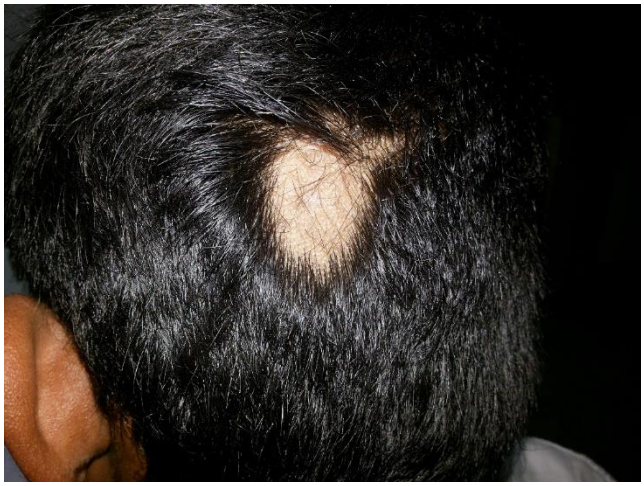


FIGURE 13: A 10YEAR OLD BOY WITH PATCHY ALOPECIA AREATA

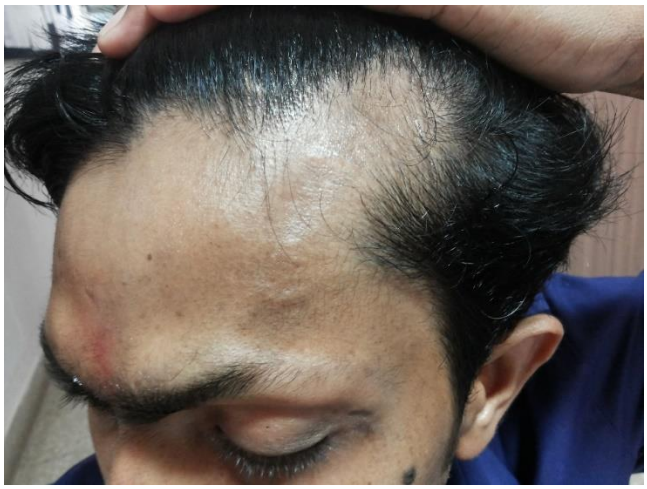


FIGURE 14: ALOPECIA ARETA ON THE FRONTAL REGION AND EYEBROWS

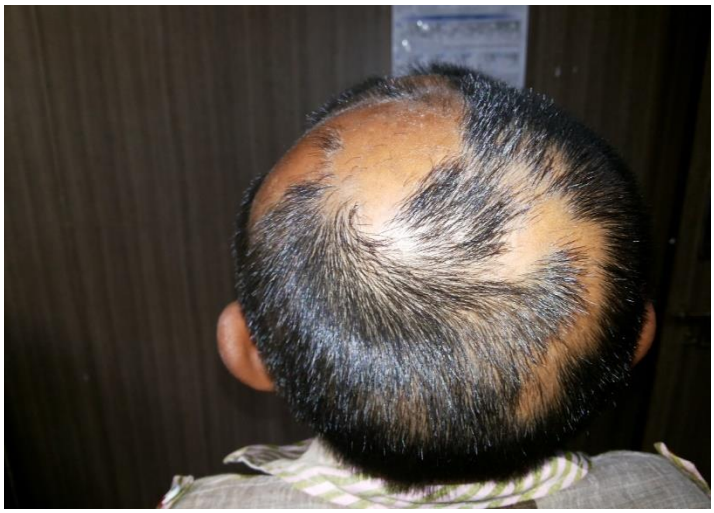


FIGURE 15: 6YEAR OLD BOY WITH RETICULAR ALOPECIA ARETA

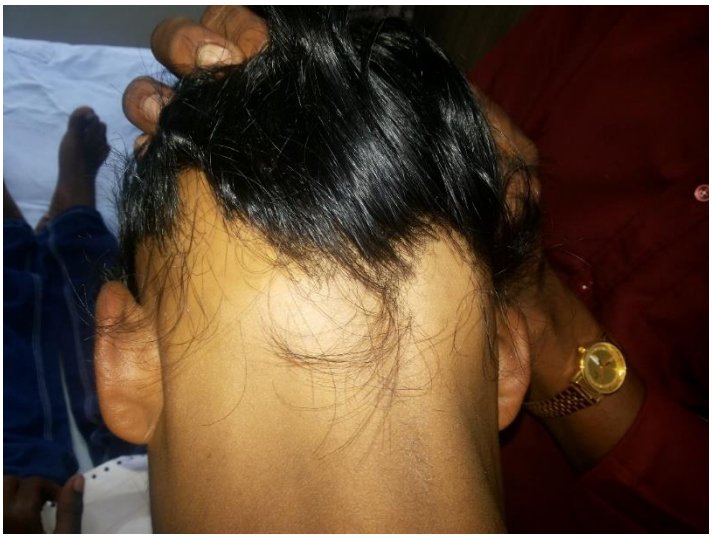


FIGURE 16: 25YEAR OLD BOY WITH OPHIASIS TYPE OF ALOPECIA AREATA

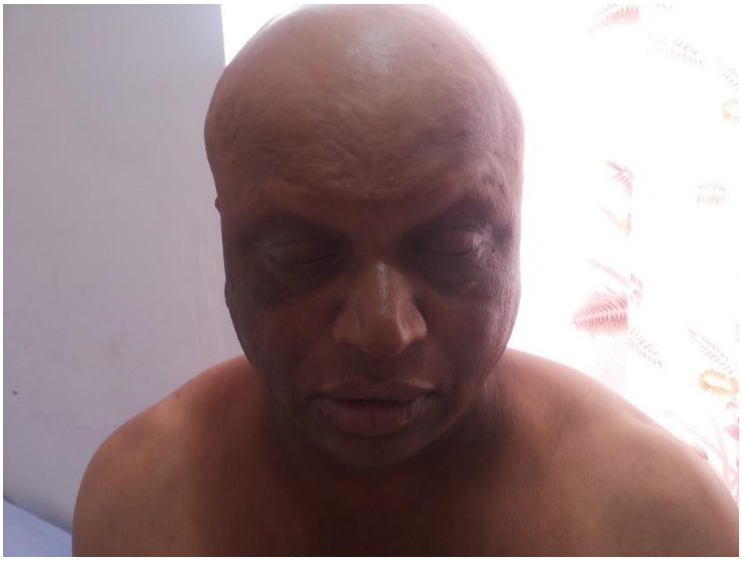


FIGURE 17: A 40YEAR OLD MALE WITH ALOPECIA UNIVERSALIS

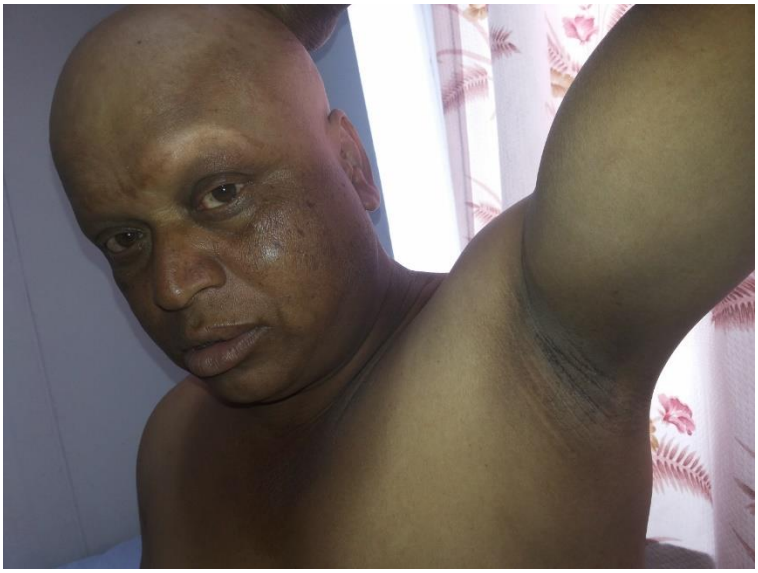


FIGURE 18: ALOPECIA OVER THE AXILLA IN ALOPECIA UNIVERSALIS

FIGURE 19: A 19YEAR OLD MALE WITH ICHTYOSIS VULGARIS

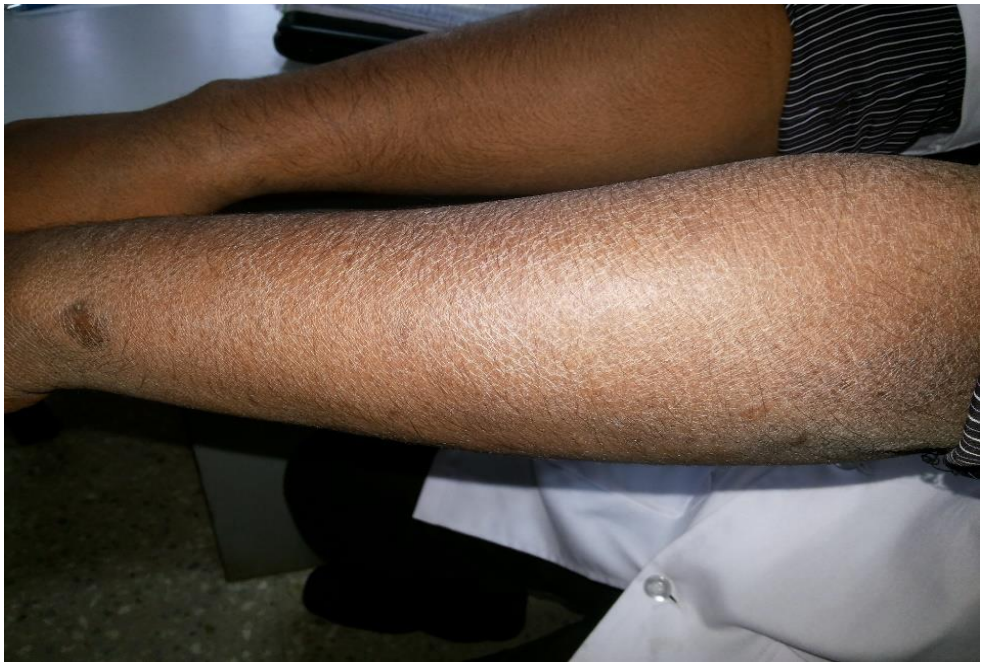
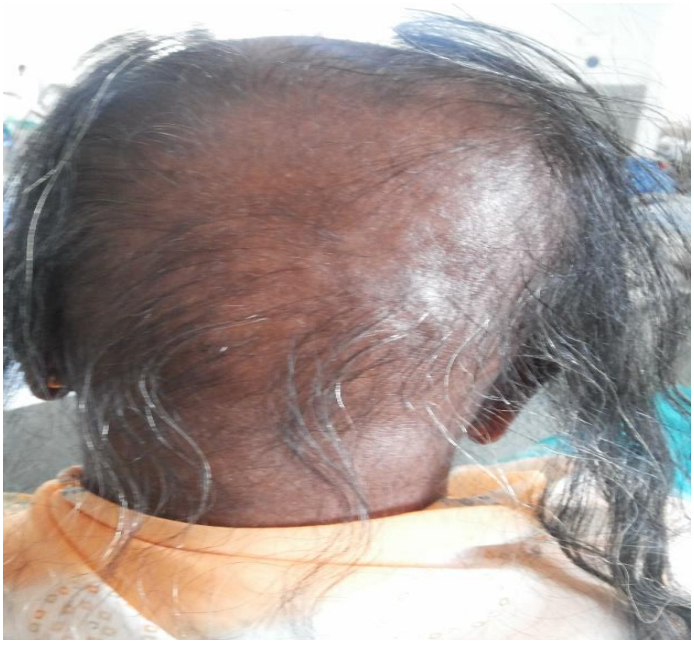


FIGURE 20: ALOPECIA TOTALIS SHOWING REGROWTH OF HAIR FOLLOWINF DEXAMETHASONE PULSE THERAPY



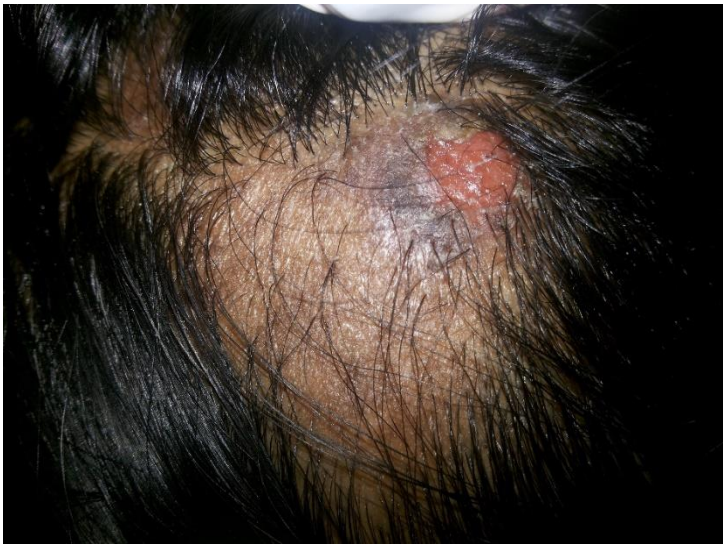


FIGURE 21: A 44YEAR OLD FEAMLE WITH PEMPHIGUS VULAGRIS AND ALOPECIA AREATA

FIGURE 22: PICTURE SHOWING MELANONYCHIA

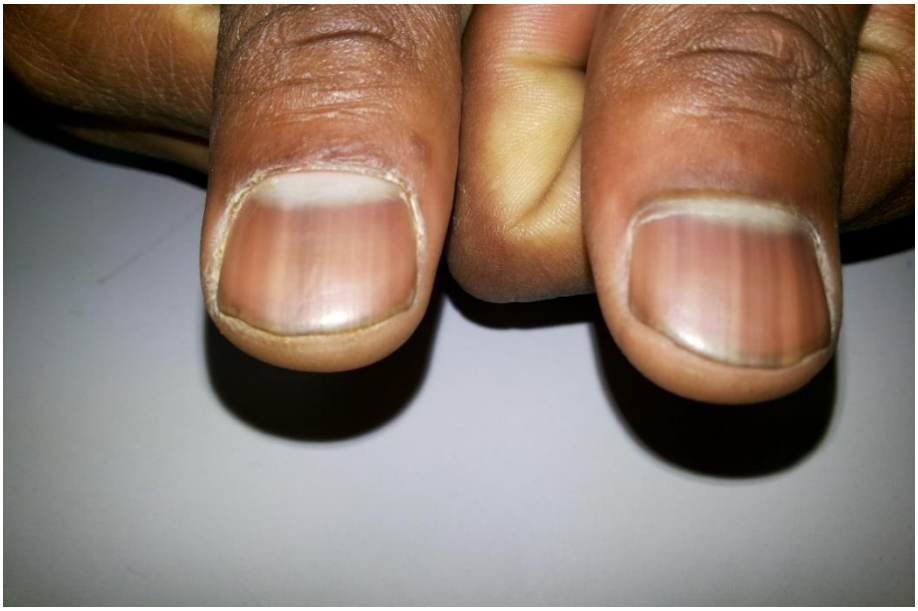


FIGURE 23: SCOTCH PLAID PATTERN OF NAIL PITTING

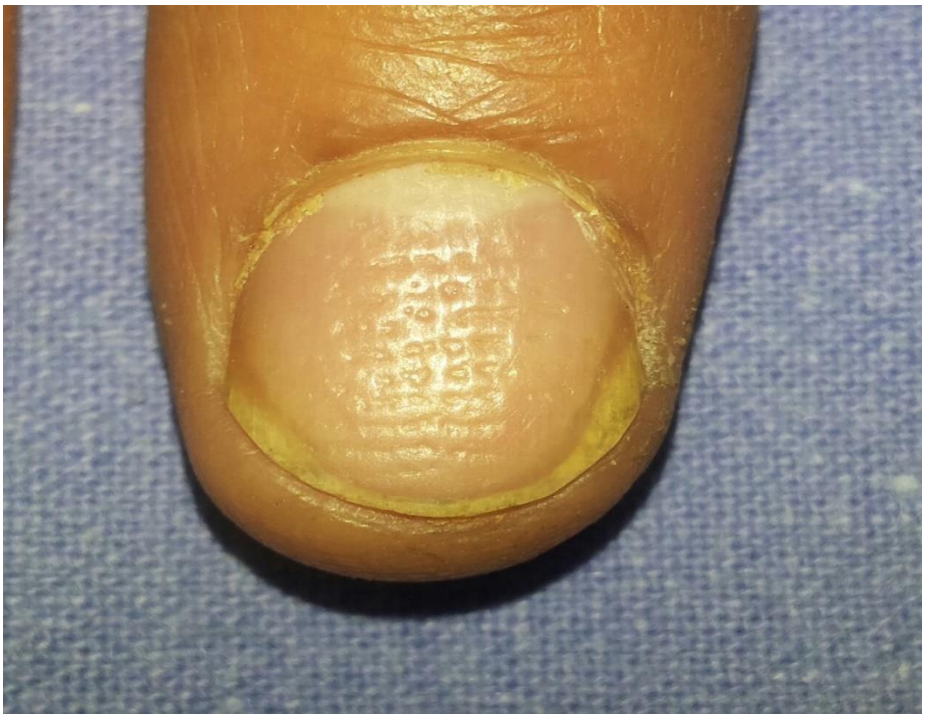
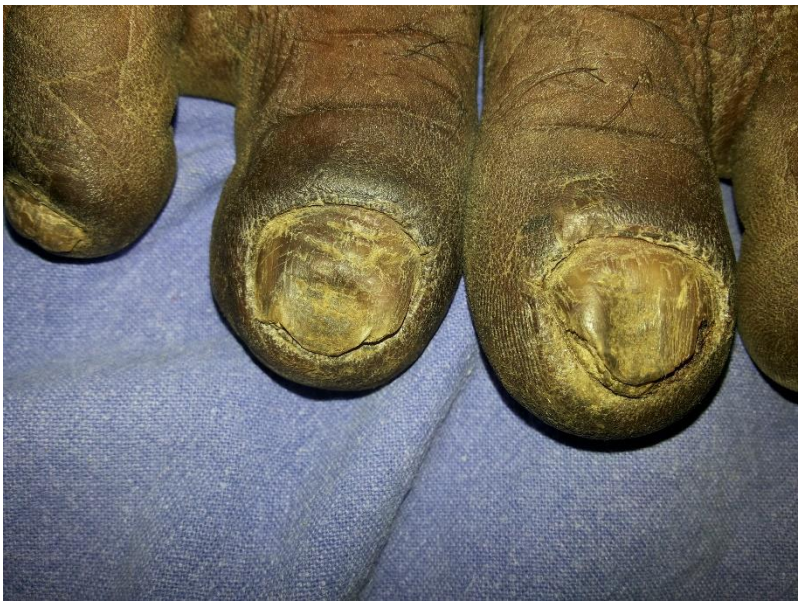


FIGURE 24: LONGITUDINAL RIDGING OF THE NAILS



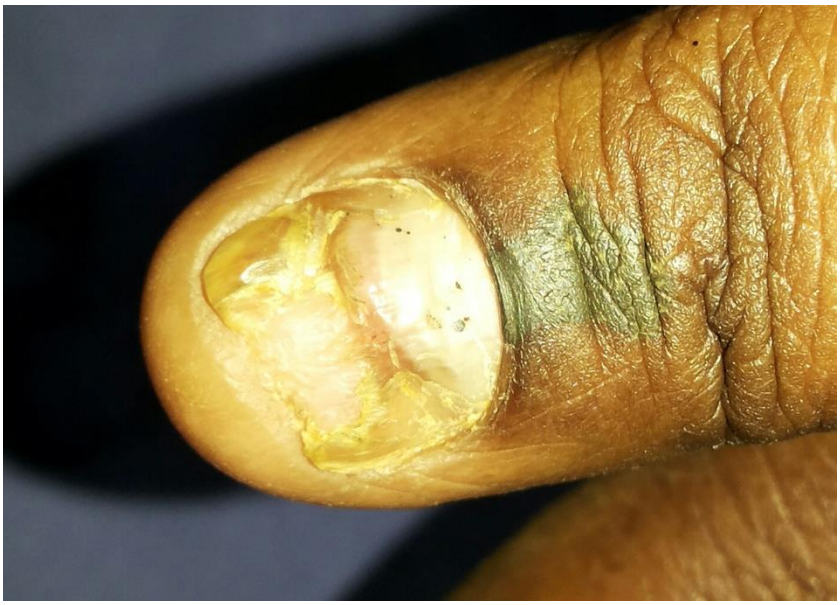


FIGURE 25: ONYCHOMADESIS OF THE NAILS

FIGURE 26: ONYCHODYSTROPHY OF THE NAILS

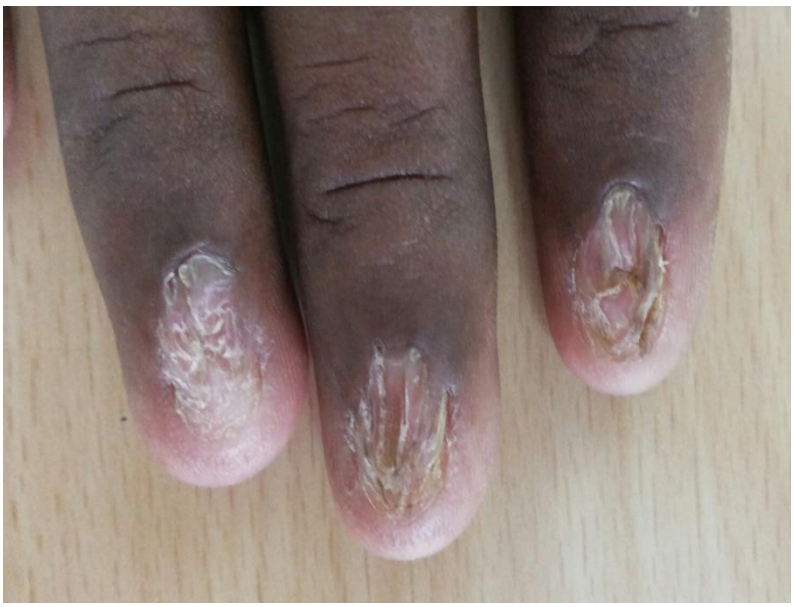
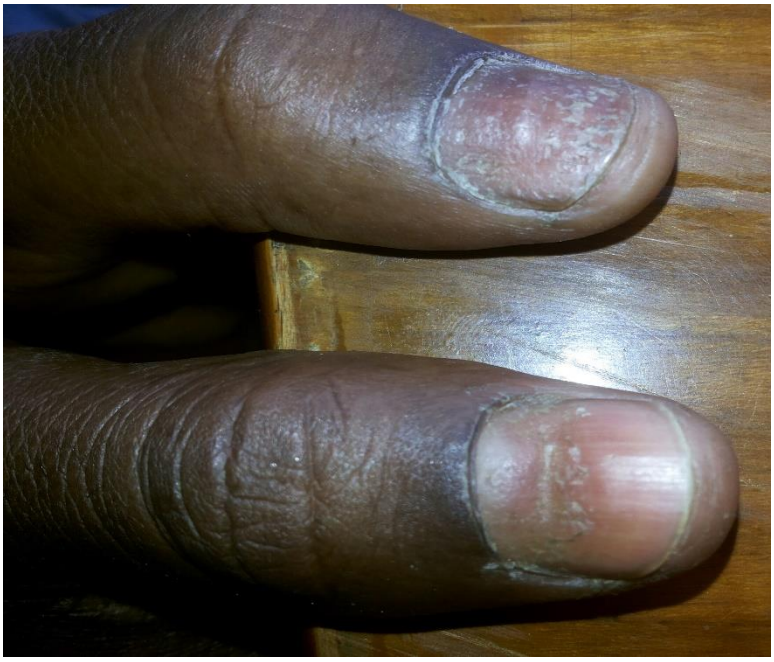


FIGURE 27: IRREGULAR PITTING OF THE NA



OBSERVATION AND RESULTS

TABLE 3: Age distribution of patients with AA

AGE IN YEARS	NO. OF CASES	PERCENTAGE
<10	5	8.3
11-20	11	18.3
21-30	18	30
31-40	16	26.6
41-50	7	11.6
51-60	3	5

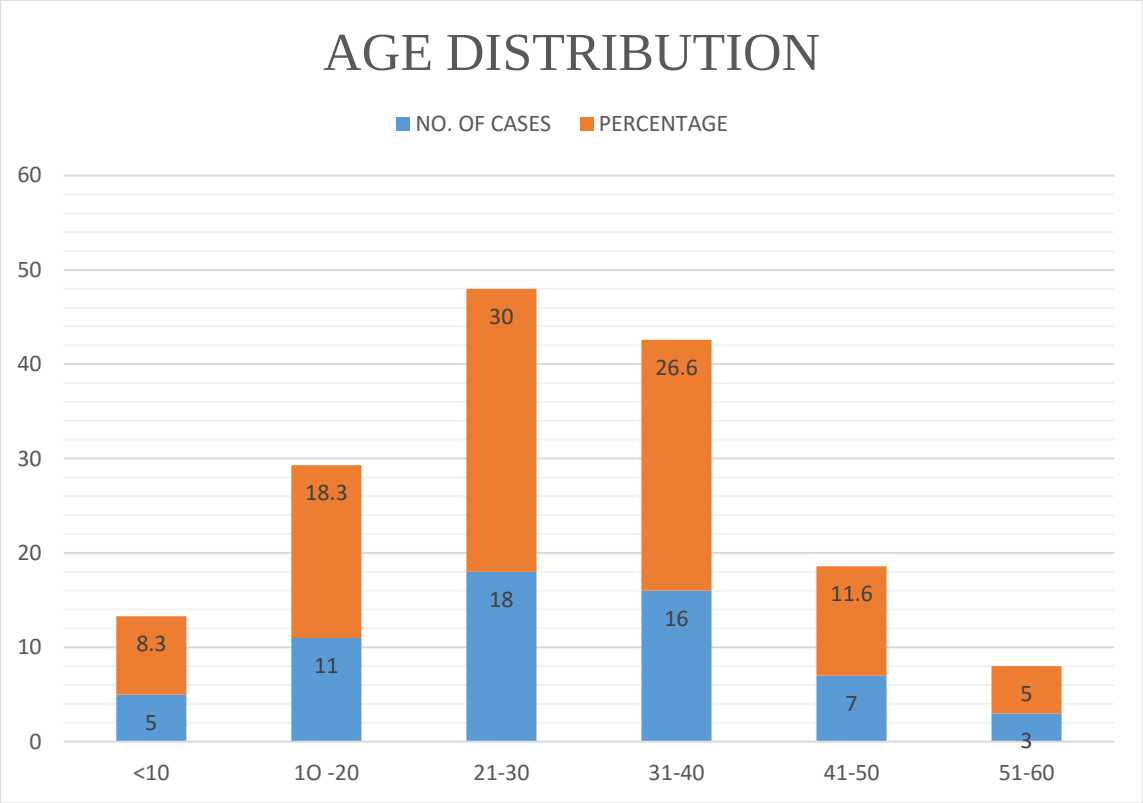


FIGURE 28: Bar chart showing age distribution in patients with AA

TABLE 4: Sex distribution of patients with AA

SEX	NO. OF CASES	PERCENTAGE
MALE	34	56.6
FEMALE	26	43.3

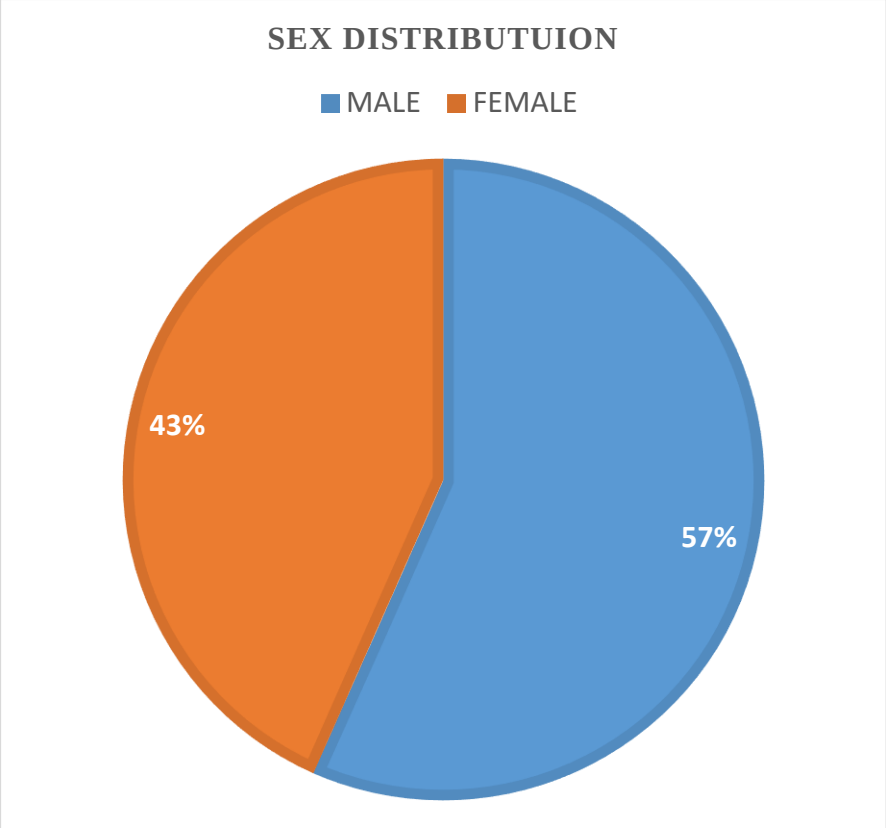


FIGURE 29: Pie diagram showing sex distribution in patients with AA

TABLE 5: Age of onset in patients with AA

AGE OF ONSET(years)	NO. OF CASES	PERCENTAGE (%)
<20	23	38.3
21-40	28	46.6
41-60	9	15

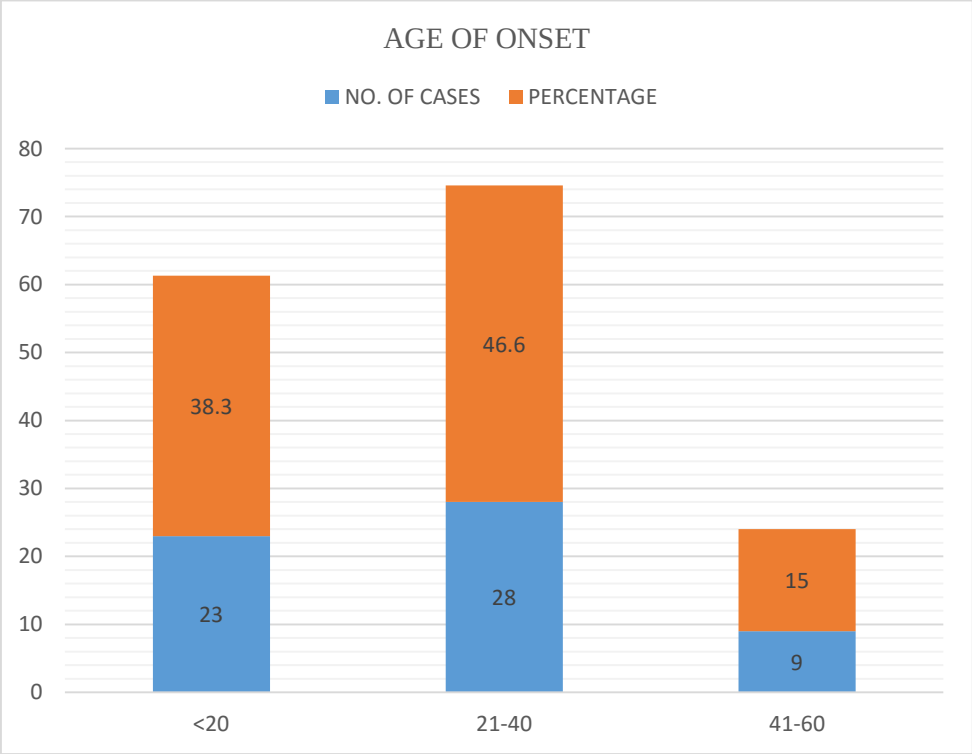


FIGURE 30: Bar chart showing age of onset in patients with AA

TABLE 6: Presentation of patients with AA

PRESENTATION	NUMBER OF CASES	PERCENTAGE
PATCHY	48	80
ALOPECIA TOTALIS	3	5
ALOPECIA UNIVERSALIS	2	3.3
RETICULAR	4	6.6
LINEAR	1	1.6
OPHIASIS	2	3.3

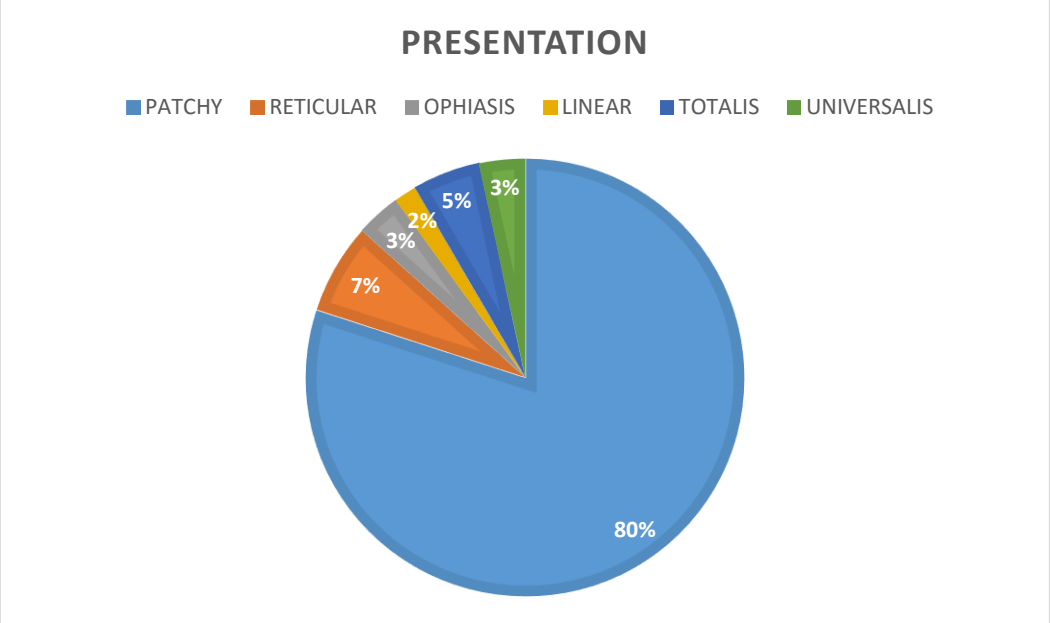


FIGURE 31: Pie diagram showing presentation in AA

TABLE 7: Number of patches in patients with AA

NUMBER OF PATCHES	NUMBER OF CASES	PERCENTAGE (%)
SINGLE	14	23.3
MULTIPLE	46	76.6

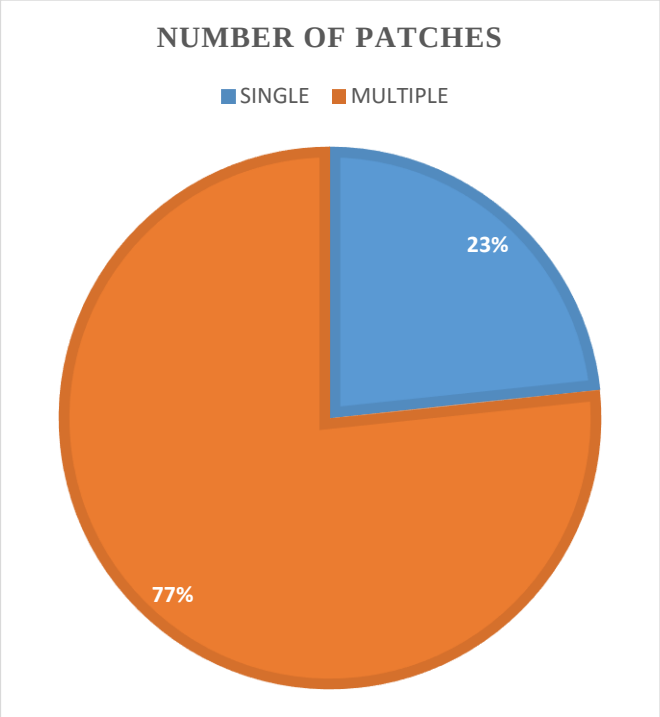


FIGURE 32: Pie diagram showing number of patches in AA

TABLE 8: Size of total number of lesions in each case

SIZE OF TOTAL NO. OF LESIONS IN EACH CASE(cm)	NO. OF CASES	PERCENTAGE (%)
<5	40	66.6
5-10	15	25
>10	5	8.3

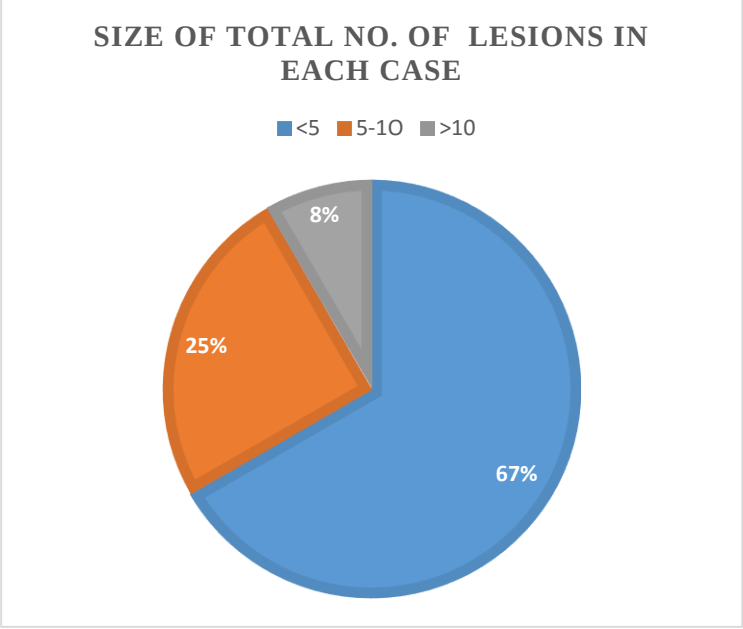


FIGURE 33: Pie diagram showing total number of lesions in each case

TABLE 9: Location of lesions in patients with AA

LOCATION OF LESIONS	NO. OF TOTAL LESIONS	PERCENTAGE (%)
FRONTAL	5	4.8
TEMPORAL	6	5.7
VERTEX	26	25
PARIETAL	14	13.4
OCCIPITAL	38	36.5
WHOLE OF SCALP	5	4.8
EYEBROWS	2	1.9
EYELASHES	2	1.9
AXILLA	2	1.9
BEARD AND MOUSTACHE	4	3.8

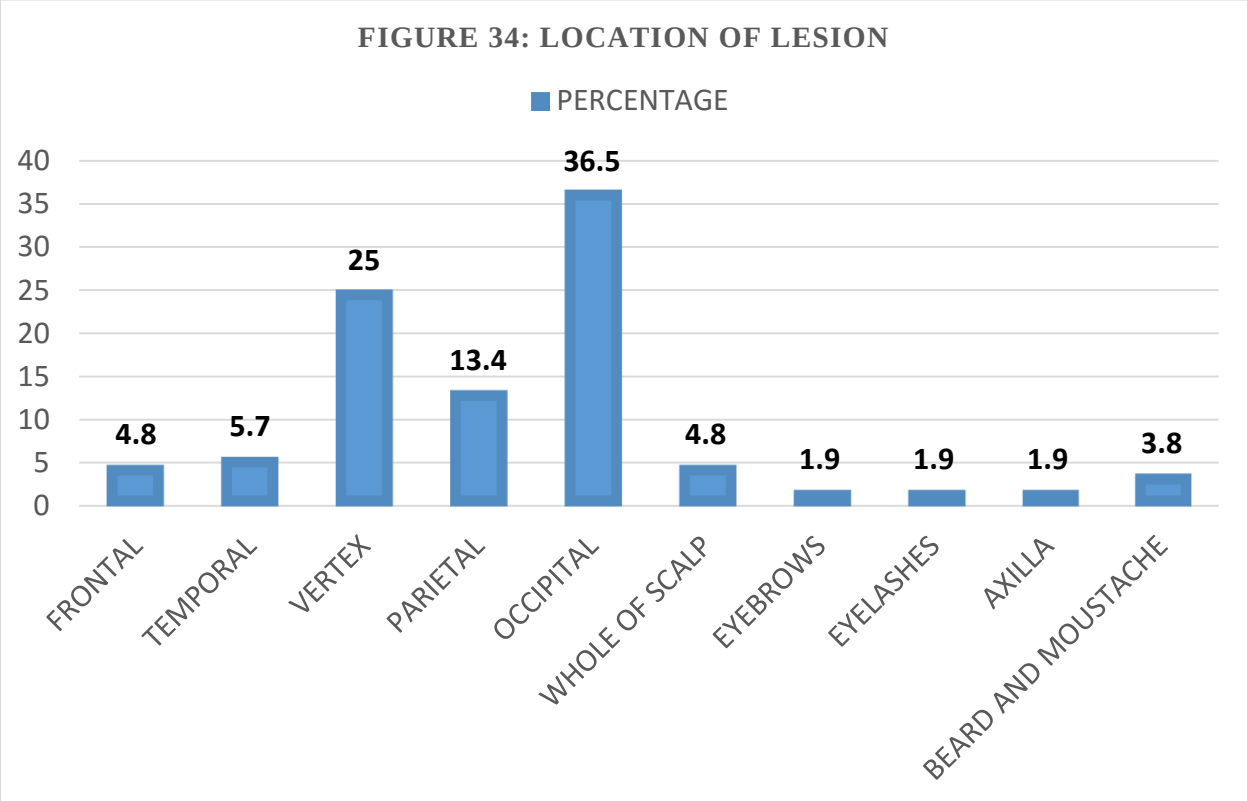


TABLE 10: Recurrence in patients with AA

H/O SIMILAR LESIONS IN THE PAST	NO. OF CASES	PERCENTAGE (%)
PRESENT	33	55
ABSENT	27	45

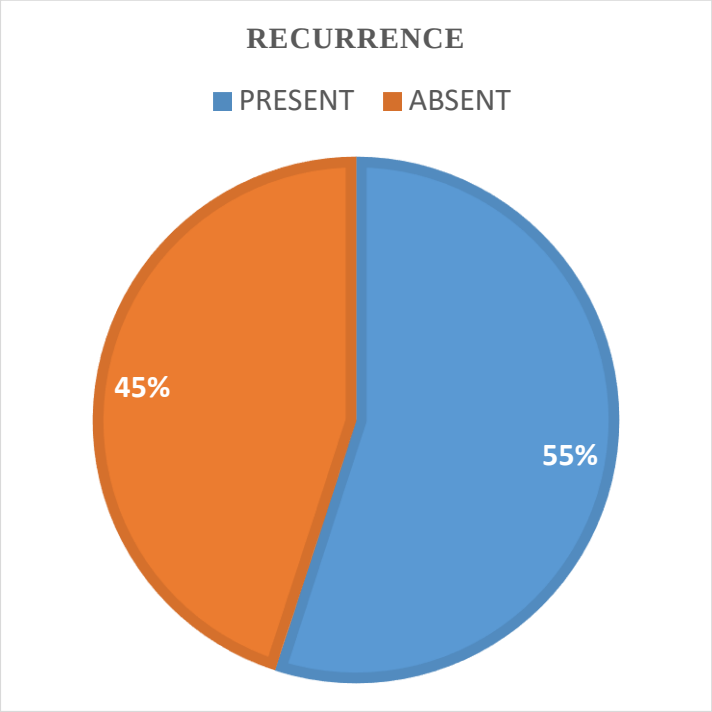


FIGURE 35: Pie diagram showing recurrence

TABLE 11: Nail changes in patients with AA

ASSOCIATED NAIL CHANGES	NO. OF CASES	PERCENTAGE (%)
PREESNT	12	20
ABSENT	48	80

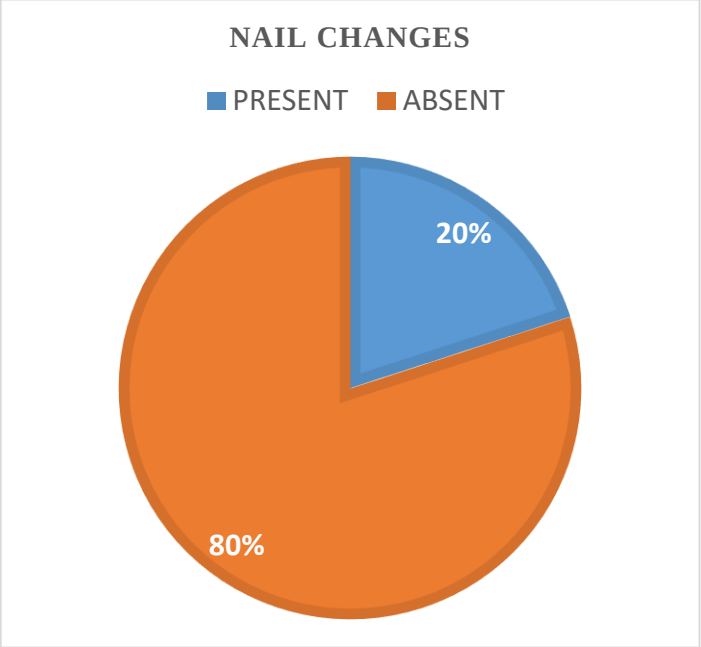


FIGURE 36: Pie diagram showing nail changes in AA

TABLE 12: Severity grading in patients with AA

SEVERITY	NO. OF CASES	PERECNTAGE (%)
MILD	52	86.6
SEVERE	8	13.3

AA investigational assessment guidelines proposed by Olsen et al was adopted for the study.

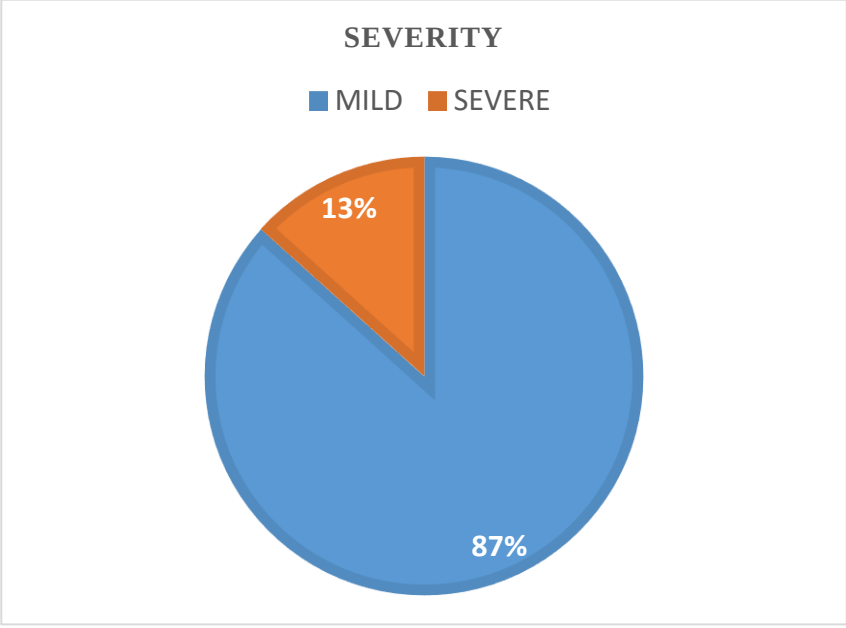


FIGURE 37: Pie diagram showing severity of AA

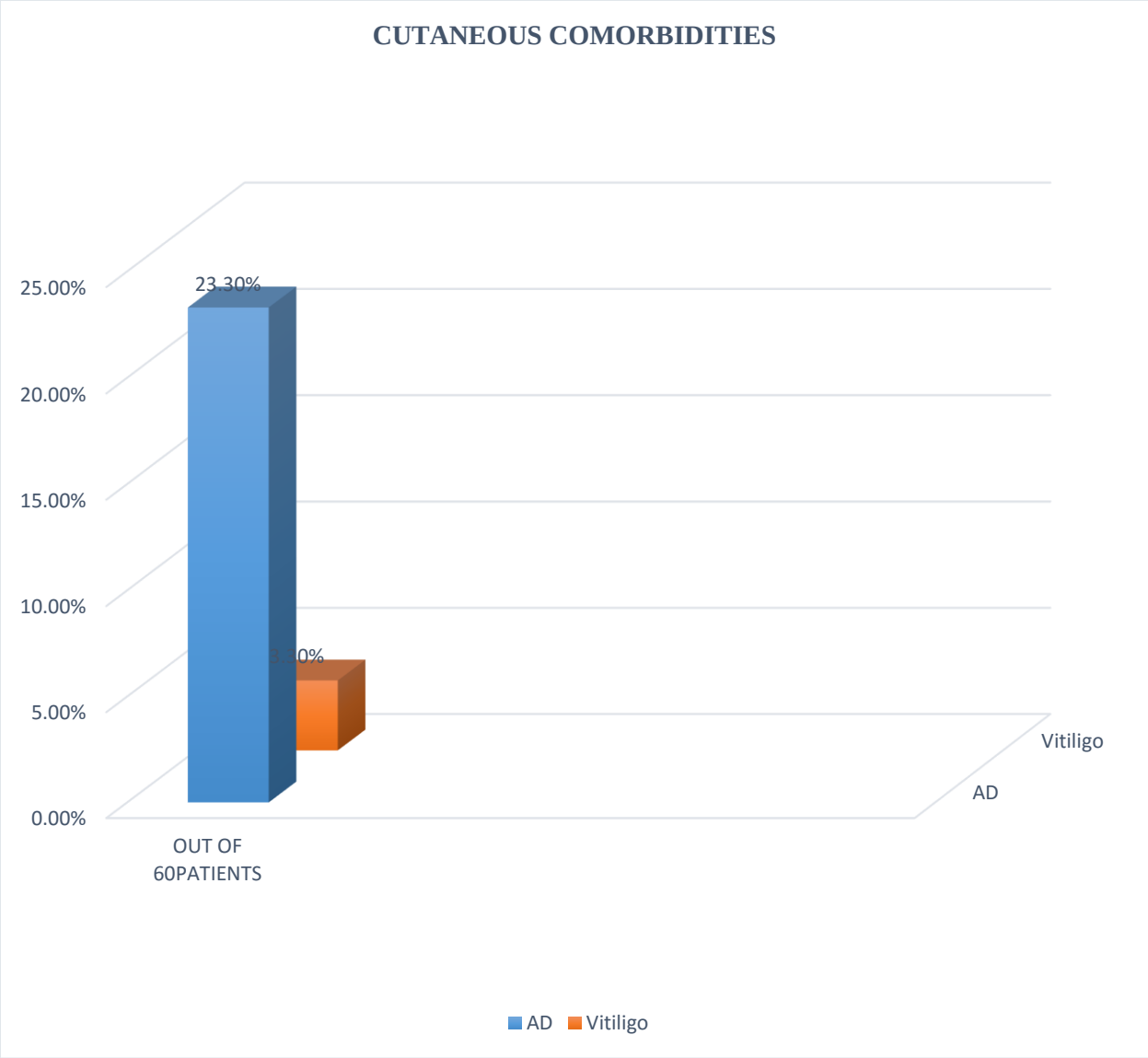


FIGURE 38: Cutaneous comorbidities in AA

Out of the 60 patients with AA, 23.3% (14patients) had atopic dermatitis and 3.3% (2patients) had vitiligo. Most atopic and autoimmune diseases were observed at ages of 11 to 30years and 41 to 50years.

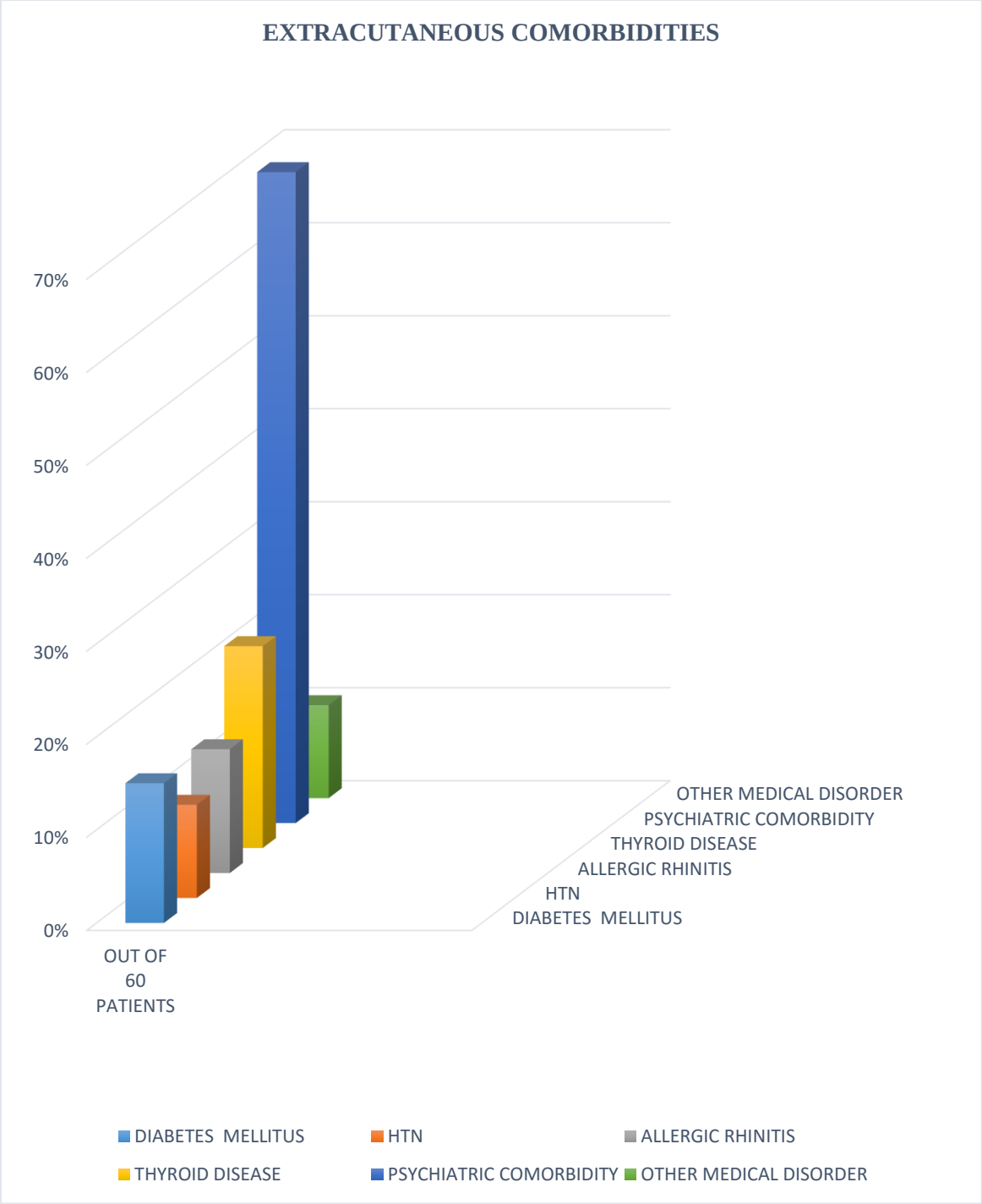


FIGURE 39: Extracutaneous comorbidities in AA

15% (9patients) in the age group 41 to 50years had diabetes mellitus. 10% (6patients) had hypertension. 13.3% (8patients) had allergic rhinitis. 10% had other conditions like rheumatoid arthritis, ichthyosis vulagris and pemphigus vulgaris. 70% (42patients) presented with psychiatric comorbidity and 21.7% had thyroid disorder

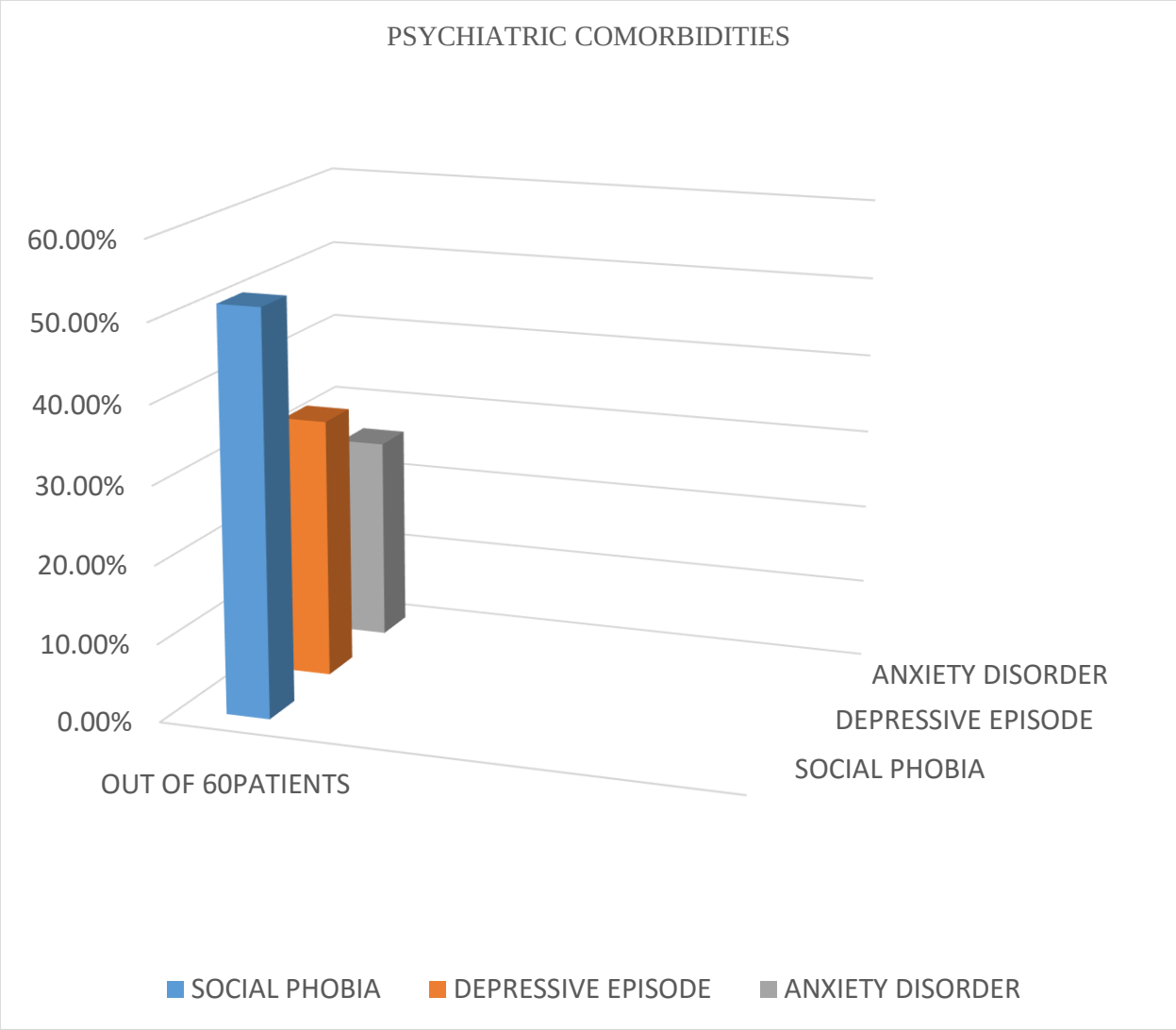


FIGURE 40: Psychiatric comorbidities in AA

70% of patients presented with psychiatric comorbidity of which 51.6%(31patients) had social phobia disorder, 33.3%(20patients) had depressive episodes and 26%(16patients) had anxiety disorder with most of them falling into the age group 11 to 30years.

DISCUSSION

DISCUSSION

AGE DISTRIBUTION: In our study most patients belonged to the age group of 21- 30(30%) closely followed by 31-40 years age group which with 26.6% patients. Similarly, the age distribution showed high incidence in the 3rd and 4thdecades as per many other observers.[52]

SEX INCIDENCE: The present study showed a slight preponderance of males (56.6%) than females (43.3 %), when compared to previous studies which showed either slightly higher incidence among males or higher incidence among females or equal incidence among both sexes.[13-17]

AGE OF ONSET: As per the previous studies age of onset varied from birth to 70 years or more. Whereas in the present study 46.6% had age of onset between 21-40 years followed by 38.3% in the age group less than 20 years. Two patients had onset at the age of 1 year, one of which had alopecia universalis thereby correlating early onset to severe disease as per other studies.[3,13,62-64]

PRESENTATION: The pattern of hair loss observed in AA can vary considerably, and less common presentations like reticular, ophiasis and totalis were observed in very few patients. In the present study patchy type was mostly seen constituting 80% followed by reticular constituting 6.6%. Similar results were obtained in studies conducted by others.[3,5,62]

SIZE OF LESION: 66% of the patients had lesions measuring less than 5cms.

NUMBER OF PATCHES AT PRESENTATION: 76.6% presented with multiple patches and 23.3% had solitary patch.

NAIL CHANGES: Nail changes were noted in 20% of patients. The commonest nail change being pitting seen in 11 patients (18.3%). Longitudinal ridging was present in 16.6% and

onychodystrophy, melanonychia and beaus lines were noted in 1.6% of patients similar to earlier studies.[3,5,13,65]

LOCATION OF LESION: It was interesting to note that 36.5% of the lesions were present in occipital region followed by vertex with 25% in this study which is similar to the studies done by others.[62]

ASSESSMENT OF SEVERITY OF AA: AA investigational assessment guidelines proposed by Olsen et al was adopted for the study. The extent of hair loss was classified as: 1 Mild: S1 (< 25% hair loss) or S2 (26–50% hair loss). 2 Severe: S3 (51–75% hair loss), S4 (76–99% hair loss) or S5 (total scalp hair loss, alopecia totalis, AT) or S5B2 (total scalp and body hair loss, alopecia universalis, AU). AA localization was defined by five anatomical areas in the scalp (occipital, parietal, frontal, vertex and temporal) in addition to beard-moustache and eyebrow-eyelash areas. Mild form of the disease was seen in 52 patients (86.6%) and severe disease was noted in 8 patients (13.3%). Mild disease is much higher in the present study similar to another study where 51.9% constituted mild disease and 48.1% constituted severe disease.[62]

RECURRENCE: Recurrence was present in 55% of patients.

ASSOCIATED DISEASES

ATOPY AND AA: Atopy has been reported to occur with an increased frequency in patients with alopecia areata. The atopic type in Ikedas classification of alopecia areata comprised 10% of 1989 patients. Similarly 11% of 736 patients of alopecia areata studied by Muller and Winkelmann had concomitant asthma or atopic dermatitis. In the present study, atopy was associated with increased frequency in patients with alopecia areata, i.e., 23.3% cases, which is in agreement with the frequency of atopic manifestations in patients with alopecia areata which

is ranging from 1-57% and 1-52% in other studies.[27,35] Huang et al noted about 38.2% of atopy whereas in the present study we found 13.3% allergic rhinitis cases.[66]

VITILIGO AND AA: In the present study vitiligo was seen in 3.3% patients which is consistent with other studies.[32-34]

PSORIASIS, LUPUS ERYTHEMATOSUS AND AA: In the present study we did not find a single case of comorbid psoriasis whereas according to a study conducted by Huang et al 6.3% had psoriasis and psoriatic arthritis.[66,67] Huang et al noted 4.3% cases of SLE whereas in the present study we did not find even a single patient with comorbid lupus erythematosus.

AA AND PSYCHIATRIC COMORBIDITY: According to a study 22.2% had generalized anxiety disorder, 7.4% had depressive episodes and 7.4% presented with social phobia. The presence of generalized anxiety or a depressive episode was also associated with worst adjustment. This shows that an integral approach to the illness is necessary, given that treatment of a depressive or anxious state, or working with the personality traits of the patients, would improve their adaptation to the disease, and perhaps its dermatologic prognosis.[38] There is a high psychiatric comorbidity in AA and therefore more systematic psychiatric evaluations of these patients are needed. A satisfactory overall adaptation to the illness in mild/moderate forms of the disease is the norm, but adaptation and psychiatric comorbidity in severe forms (totalis, universalis) are unknown. Colon and co-workers recently administered to 31 patients with alopecia areata a structured psychiatric interview using the Diagnostic Interview Schedule (DIS). They determined that 74% of patients under evaluation had one or more lifetime psychiatric diagnosis. Also noteworthy were the high lifetime prevalence rates of both major depression {39%) and generalized anxiety disorder (39%). From our study, we report prevalence rates of psychiatric disorders associated with hair loss due to alopecia areata higher than those of the

general population. 70% of patients presented with psychiatric comorbidity of which 51.6% (31patients) had social phobia disorder, 33.3% (20patients) had depressive episodes and 26% (16patients) had anxiety disorder with most of them falling into the age group 11 to 30years.

THYROID DISEASE AND AA: The prevalence of thyroid disease in patients with AA varied from 0 to 28%. These thyroid diseases include Hashimoto's thyroiditis, Graves' disease, simple goitre and others.[29] In the present study the prevalence of thyroid disease was 21.7% (13 patients), strikingly all these patients had hypothyroidism which is in contrast with other studies.[28,29,30,66]

DIABETES MELLITUS AND AA: The prevalence of DM was about 11.1% as per Huang et al which is slightly lower than the present study which had a prevalence of about 15%.[66,68]

HYPERTENSION AND AA: Huang KP et al found high prevalence of hypertension, 21.9%. This profile was different from that seen in the present study where only 10% of the patients presented with hypertension.

PEMPHIGUS VULGARIS AND AA – A single case of pemphigus vulgaris and AA was present. . Histology and immunofluorescence was consistent with PV and AA.

Scalp involvement is common in Pemphigus Vulgaris because the hair follicles contain many Pemphigus Vulgaris antigens. Different patterns of hair loss have been reported in Pemphigus Vulgaris, including anagen shedding, scarring alopecia, and tufted folliculitis.[69] The existing reports only mention about association of AA with Pemphigus Foliaceous and not AA with PV, similar to our case.

ANA AND ALOPECIA AREATA- ANA was negative in all patients.

CONCLUSION

CONCLUSION

- Patients with AA are at an increased risk of multiple comorbidities, including psychiatric comorbidity, atopic dermatitis, thyroid diseases, allergic rhinitis, diabetes mellitus, hypertension and vitiligo compared with the general population. Furthermore, severity of the disease was correlated to early age of onset thereby indicating the importance of early diagnosis. Also there was no significant association between severity and duration of the disease.
- To conclude AA is strongly related to atopic and autoimmune diseases and also there is a high psychiatric comorbidity. Since ANA is not specific for autoimmunity the presence of other autoimmune diseases in these patients can be a coexistent finding or an association due to autoimmunity etiology.

SUMMARY

SUMMARY

- Among patients who were included in the study, most of them belonged to the age group of 21- 30 years followed by 31-40years
- 2 patients had onset at the age of 1 year, one of which had alopecia universalis thereby correlating early onset to severe disease
- There was a slightly higher incidence among males which could be due to short hair length or recognition by barbers
- 8 out of 10 patients had patchy type of AA, which is important because prognosis varies in different patterns of AA
- More than half the patients presented with lesions on the occipital area which again helps in assessing the prognosis
- Almost all the patients had atleast one lesion of 1-5 cms size
- More than 3/4th of the patients presented with a single lesion
- None of the patients gave similar history among immediate family members which goes against the hereditary role in AA
- History of atopy was positive in 1 in 10 cases stressing the need for atopic history in patients presenting with AA
- Alopecia areata manifested relatively earlier in atopics than in non-atopics, which reflects the role of atopy
- Every alternate patient had recurrent disease and this emphasizes the importance of counseling patients before the initiation of therapy
- Approximately 9 out of 10 patients had mild disease and there was no significant association between severity and duration of the disease

- Two patients had ichthyosis vulgaris and one patient had rheumatoid arthritis which again strongly correlates to atopy and autoimmunity. A single case of Pemphigus Vulagris with AA was present. Though autoimmune etiology can be the cause for both AA and PV, coincidental occurrence cannot be ruled out.
- Seven in ten patients had psychiatric comorbidity which shows that AA has enormous psychological impact. Furthermore since dermatologists act as the primary care physician for patients with alopecia areata, they can recognize psychiatric comorbidity at an early stage and refer them to psychiatrics
- Approximately every 4^{th} patient had atopic dermatitis and only two patients had vitiligo
- Approximately every 5^{th} patient had thyroid disease and strikingly all these patients had hypothyroidism
- $1/6^{th}$ of the patients had diabetes mellitus and $1/10^{th}$ of the patients had hypertension
- ANA was negative in all patients

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ANNEXURES

PROFORMA

Case No. OP/IP No.

Name:

Age:

Sex:

Male Female

Occupation: Business Housewife Professional Any other

Socio-economic status:

Address with phone number:

History of presenting illness:

a. Onset b. Duration
   1. Sudden 2. Gradual
   1. Patchy 2. . Generalized

Site of the lesion:

Scalp : 1. Present 2. Absent

Beard /Moustache: 1. Present 2. Absent

Eyebrows/ Eyelashes: 1. Present 2. Absent

Axilla : 1. Present 2. Absent

Pubis: 1. Present 2. Absent

Others : 1. Present 2. Absent

Associated symptoms: Asymptomatic Itching Pain Burning Others

Aggravating/ Precipitating factors:

H/o tremors/ weight loss/ weight gain/ palpitation/ preferences to cold/ increased heat sensitivity/ sweating/ irritability

H/o recurrent pruritis / lesions involving flexures/ family H/o asthma/ dryness of skin / under eye dark circles/ light brown patches on the face and body

H/o generalized anxiety/ depressive episode / social phobia disorder

H/o white patches on the skin/ patches of white hair

H/o elevated red scaly lesions on the skin and or on the scalp

H/o recurrent itching in the nose, face and eyes/ sneezing/ watery rhinorrhoea

H/o rashes on the face and scalp/ oral ulcers/ photosensitivity

Past history:

History of similar illness: 1. Present : if so, duration_____ 2. Absent

History of Diabetes: 1. Present : if so, duration_____ 2. Absent

History of Hypertension: 1. Present : if so, duration_____ 2. Absent

History of Thyroid: 1. Present : if so, duration_____ 2. Absent

History of Atopy: 1. Present : if so, duration_____ 2. Absent

History of Pyschiatric disorders: 1. Present : if so, duration_____ 2. Absent

History of Vitiligo: 1. Present : if so, duration_____ 2. Absent

History of Psoriasis: 1. Present : if so, duration_____ 2. Absent

History of Allergic Rhinitis: 1. Present : if so, duration_____ 2. Absent

History of Lupus Erythematosus: 1. Present : if so, duration_____ 2. Absent

History of any other medical disorder:

Family History:

History of similar complaints in the family: 1. Present : if so, duration_____ 2. Absent

Treatment History: On treatment Not on treatment

Personal History:

Diet : Appetite: Bowel / Bladder: Sleep: Alcohol: Smoking:

General Physical Examination:

Built : Poor Moderate Good

Vitals: Pulse/ min BP(mm/hg) Temperature Weight

Pallor: Icterus: Cyanosis: Clubbing : Lymph nodes: Edema:

Mucocutaneous Examination:

Sites involved:

SCALP	**No. of patches**	**Uni/Bilateral**	**Surface**	**Exclamation hair**	**Scarring/Non- Scarring**	**Hair pull test**	**Coudability test**
1. Vertex							
2. Temporal							
3. Occipital							
4. Parietal							

EYEBROWS

EYELASH

BEARD/ MOUSTACHE

AXILLA

PUBIS

TOTALIS

UNIVERSALIS

OTHERS

NAIL CHANGES

Pitting Longitudinal ridges Beaus lines Onychodystrophy Onychorhexis Others

Systemic Examination:

Provisional Diagnosis:

Investigations:

1. Complete Hemogram
2. RBS
3. AEC
4. Urine Routine
5. TSH
6. ANA titre
7. Skin Biopsy

Diagnosis:

CONSENT

A CLINICAL STUDY OF COMORBIDITIES AMONG PATIENTS WITH ALOPECIA AREATA

CONDUCTED BY-DR CHAMPA.R

UNDER THE ABLE GUIDANCE OF DR. RAJASHEKAR.T.S

Respected Sir/Madam,

We invite you to participate in our study for which you are eligible. During the study you will be asked some questions in detail regarding our study.

The purpose of this study is to find out any comorbid conditions that are associated with Alopecia areata. You are being asked to participate in this study as you have been diagnosed with the above said condition.

Should you choose to participate you will be asked to give a detailed history of your disease, undergo a physical examination and consent to a few routine blood and urine investigations.

If you decide not to participate in this study you will still be receiving the usual standard care for your disease.

Your privacy will be respected and all the information collected from you during the course of the study will be kept confidential. Your identity will remain undisclosed.

You shall not be receiving any financial incentives or payment for participating in this study.

The result of this study may be published for a scientific purpose or presented to a scientific group. Your identity however will be maintained confidential at all times.

Your participation on the study is voluntary. Your decision whether or not to participate will neither affect the care of your current disease nor your future relation with doctor or hospital. You are free to discontinue participation in this study at any time and for any reason. In case you need any further information regarding your rights as a study participant you may contact Principal and Chairman of the ethical committee, SDUMC, Kolar.

STATEMENT OF CONSENT

I Mr/Ms/Mrs_____ volunteer and consent to participate in this study. I have read the consent document or it has been read to me in my vernacular language. I accept to participate in this study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

DATE:

If the participant is a minor(<18years), the parents sign the form, rather than the participants.

KEY TO MASTER CHART

1. PROFESSIONAL – PRO
2. BUSINESS – BN
3. STUDENT – STUD
4. COOLIE - C
5. AUTODRIVER – DRIVE
6. HOUSEWIFE – HW
7. MULBAGAL – MUL
8. BANGARPET – BGPT
9. KOLAR – KLR
10. MADANAPALLI – MDP
11. MALUR – MLR
12. PUNGANUR – PUGR
13. BENGALURU – BANG
14. DODDABALAPURA – DDP
15. SRINIVASAPURA – SRP
16. SIDDALGATA – SDG
17. ASYMPTOMATIC – A
18. ITCHING – I
19. FEVER – F
20. STRESS – S
21. NONE – N
22. PATCHY – P
23. RETICULATE – R
24. OPHIASIS – O
25. UNIVERSALIS – U
26. TOTALIS – T
27. LINEAR – L
28. ON TREATMENT – OT
29. NOT ON TREATMENT – NOT
30. ON TREATMENT – OT
31. OTHER MEDICAL DISORDER- MD
32. FAMILY HISTORY- FH
33. TREATMENT HISTORY- TH
34. AGE OF ONSET- OA
35. PRECIPITATING FACTORS- PF
36. ASSOCIATED SYMPTOMS- SMPT
37. YEARS- Y
38. MONTHS –M
39. WEEKS-W
40. SIMILAR ILLNESS- SI
41. LUPUS ERYTHEMATOSUS- LE
42. THYROID DISORDER- TD
43. ATOPIC DERMATITIS- ADSOCIAL PHOBIA- SP
44. ANXIETY DISORDER- ANX
45. DEPRESSIVE EPISODE- DE
46. VITILIGO- VIT
47. PSORIASIS- PSOR
48. ALLERGIC RHINITIS- AR

49. ICHTHYOSIS VULGARIS- ICTH
50. RHEUMATOID ARTHRITIS- RA
51. CHOLECYSTECTOMY- CHOL
52. ONYCHODYSTROPHY- OND
53. MELANONYCHIA- MELN
54. PITTING- PIT
55. LONGITUDINAL RIDGING- LR
56. BEAUS LINES- BL
57. RAISED AEC- AEC
58. RAISED TSH- TSH
59. ANAEMIA- ANM
60. RAISED RANDOM BLOOD SUGAR- BS

SL NO.	OP NUMBE	NAME	AGE	SEX	OCCUPATI	ADDRESS	OA (yrs	DURAT	TYPE	SMPT	PF	TD	AD	SP	ANX	DE	VIT	PSOR	AR	LE	H/O SI	H/O DM	H/o HTN	H/O TD	H/O ATOPY	H/O PD	H/O VIT	H/O PSOR	H/O AR	H/O LE	H/O MD
1	948630	Vikram	26	M	PRO	KLR	21	4W	P	A	S	NP	P	P	NP	P	NP	NP	P	NP	P- 5Y	NP	NP	NP	P- 16Y	P - 2Y	NP	NP	NP	NP	NP
2	966656	Anand	32	M	BN	BGPT	32	6M	P	A	N	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
3	999371	Zubeer Pasha	8	M	STUD	KLR	8	5days	R	A	N	NP	P	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	H/O ICHT
4	1007922	Armugam	47	M	C	KLR	47	6W	R	A	S	NP	P	NP	NP	P	NP	NP	P	NP	P-6M	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
5	1005919	Umesh	30	M	BN	SDG	30	4W	P	A	N	NP	NP	P	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
6	1005400	Arfiya Taj	17	F	STUD	BGPT	11	8W	O	A	N	NP	NP	P	P	NP	NP	NP	NP	NP	P-8Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
7	1004555	Chowdareddy	25	M	DRIVE	KLR	24	6M	O	A	N	NP	NP	P	NP	NP	NP	NP	NP	NP	P- 1Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
8	966983	Venkateshappa	50	M	BN	KLR	1	49Y	U	A	N	P	P	P	NP	NP	NP	NP	NP	NP	NP	P- 15Y	NP	NP	NP	NP	NP	NP	NP	NP	NP
9	987165	Raghavendra	29	M	BN	KLR	29	8W	P	A	N	P	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
10	989307	Salma	32	F	HW	BGPT	31	18W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
11	994082	Lalithesh	5	M	STUD	KGF	5	12W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
12	994456	Renukadevi	44	F	HW	KGF	44	4W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	H/O PV
13	996140	Sudarshan	17	M	STUD	SRP	17	4W	P	A	N	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
14	919426	Amaravathi	36	F	HW	PUGR	35	4W	P	A	N	P	NP	NP	NP	P	NP	NP	NP	NP	P-1Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
15	1008468	Nirmal	12	M	STUD	BGPT	12	12W	P	A	N	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
16	1008400	Nandini	24	F	STUD	DDP	18	6Y	U	A	N	NP	NP	P	P	P	NP	NP	NP	NP	NP	NP	NP	NP	P-15Y	NP	NP	NP	NP	NP	NP
17	38983	Sheik Hassan	30	M	BN	BANG	28	12W	P	I	N	NP	P	P	NP	NP	NP	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
18	1008668	Yashodha	36	F	HW	BGPT	33	2W	P	A	N	NP	P	NP	NP	NP	NP	NP	NP	NP	P-3Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
19	65334	Sudha	34	F	HW	KLR	33	1year	P	A	N	NP	P	NP	NP	P	NP	NP	NP	NP	NP	P- 1Y	NP	NP	NP	NP	NP	NP	NP	NP	SK
20	64709	Savithramma	55	F	HW	MUL	55	12W	P	A	N	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	P-5Y	NP	NP	NP	NP	NP	NP	NP	NP
21	935877	Shylaja	19	F	STUD	MLR	9	10Y	T	A	N	NP	P	P	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	P-10Y	NP	NP	NP	NP	NP	NP
22	998887	Chandrashekar	26	M	BN	MUL	26	8W	P	A	F	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
23	997594	Yashodha	36	M	BN	MLR	33	8W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-3Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
24	984885	Jayaraj	27	M	BN	KLR	19	8W	P	A	N	NP	NP	P	P	P	NP	NP	NP	NP	P-8Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
25	994082	Shivakumar	43	M	BN	MLR	41	6W	P	A	N	NP	NP	P	NP	NP	NP	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
26	988126	Manasa	22	F	STUD	MLR	13	4W	P	A	N	P	NP	P	NP	P	NP	NP	NP	NP	P-9Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
27	986091	Sadath	39	M	STUD	KLR	32	7W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-4Y	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP
28	984912	Mandeep	1	M		KLR	1	3W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
29	972967	Mohammed Rafi	19	M	STUD	KLR	17	1W	P	A	N	NP	NP	P	NP	P	NP	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
30	946634	Manjunath	24	M	BN	KLR	4	20Y	P	A	N	NP	NP	P	NP	P	NP	NP	NP	NP	P-20Y	NP	NP	NP	P-10Y	NP	NP	NP	NP	NP	NP
31	963649	Suresh	27	M	BN	KLR	27	3W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	H/O CHOL
32	962486	Sridhar	19	M	STUD	KLR	19	1W	P	A	N	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	ICHT
33	936703	Rajani	19	F	STUD	KLR	14	4W	P	A	N	NP	NP	P	P	P	NP	NP	NP	NP	P-5Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
34	10516	Basid Pasha	36	M	BN	KLR	35	4W	P	A	N	P	NP	P	NP	NP	NP	NP	NP	NP	P-1Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
35	63757	Khajavalli	23	F	STUD	KLR	23	8W	P	A	N	NP	NP	P	P	NP	NP	NP	P	NP	P- 8M	NP	NP	NP	NP	NP	NP	NP	P-15Y	NP	NP
36	949078	Srinivas	34	M	BN	KLR	28	1W	P	I	N	NP	P	P	NP	P	NP	NP	P	NP	P-6Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
37	955104	Parvathamma	52	F	HW	KLR	42	3W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-10Y	P- 8Y	P-6Y	NP	NP	NP	NP	NP	NP	NP	NP
38	968753	Narasimhappa	40	M	C	KLR	40	6W	P	A	N	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP
39	968485	Sadiq Khan	25	M	STUD	KLR	25	8W	P	A	N	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-20Y	NP	NP	NP	NP	NP	NP
40	61129	Suresh	27	M	STUD	MUL	27	9W	P	A	N	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
41	55146	Noor Asha	6	F	STUD	MUL	6	8W	P	A	N	NP	P	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
42	60783	Lakshmi	33	F	HW	KLR	31	10W	P	A	N	P	NP	P	NP	P	NP	NP	NP	NP	P-2Y	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP	NP
43	60596	Bharani Singh	25	M	BN	MUL	25	8W	P	A	N	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
44	28322	Muniraju	35	M	BN	KLR	34	2W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-1Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
45	59174	Narayanappa	60	M	BN	KLR	60	2W	P	A	N	NP	NP	NP	P	NP	NP	NP	NP	NP	P- 6M	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
46	21395	Zubeda begum	50	F	HW	KLR	50	8W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P- 8M	P-5Y	P-4Y	NP	NP	NP	NP	NP	NP	NP	NP
47	21341	Neha fatima	40	F	HW	KLR	39	10W	P	A	N	P	NP	P	NP	NP	NP	NP	NP	NP	P-1Y	P-7Y	P-3Y	NP	NP	NP	NP	NP	NP	NP	NP
48	101729	Anand	25	M	PRO	MLR	25	12W	P	A	N	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
49	1444	Ramesh	23	M	PRO	KLR	23	10W	P	A	N	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
50	63757	Khajavalli	19	M	STUD	MDP	19	2W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-8M	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
51	63585	Rajesh	14	M	STUD	KLR	6	2W	R	A	N	NP	NP	P	P	NP	NP	NP	NP	NP	P-8Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
52	68899	Devika	34	F	HW	KLR	19	8W	T	A	N	P	NP	P	P	P	NP	NP	NP	NP	P-15Y	NP	NP	P-10Y	NP	NP	NP	NP	NP	NP	NP
53	64308	Narayanamma	45	F	HW	BGPT	42	3W	L	A	N	NP	NP	P	P	P	P	NP	NP	NP	P-3Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	H/O RA
54	93553	Ashok	3	M		KLR	3	6W	T	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P- 6M	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP
55	93891	Shabhana	19	F	STUD	KLR	17	5W	R	A	N	NP	NP	P	P	P	NP	NP	NP	NP	P-2Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	H/O PCOD
56	113543	Manasa	23	F	STUD	KLR	22	4W	P	A	N	NP	NP	P	NP	P	NP	NP	NP	NP	P-1Y	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
57	98708	Sujoy	18	M	C	KGF	18	6W	P	A	N	NP	NP	NP	NP	NP	NP	NP	NP	NP	P-6M	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
58	99202	Lakshmi	42	M	HW	MUL	42	8W	P	A	N	NP	NP	P	NP	P	NP	NP	NP	NP	NP	P-4Y	NP	NP	NP	NP	NP	NP	NP	NP	NP
59	99249	Srinivasa	34	M	BN	BGPT	34	4W	P	A	N	NP	NP	P	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
60	871320	Kantharaj	38	M	BN	BGPT	38	4W	P	A	N	NP	NP	NP	P	NP	NP	NP	NP	NP	P-8M	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP

FH	TH	SITE	NO. PATCH	SIZE(diameter in	SEVERITY	NAIL CHANGES	INVESTIGATIONS
NP	NOT	BM	1	3	M	N	TSH
NP	NOT	BM	1	2	M	N	-
NP	NOT	O,V,P	5	2,4,4,1,2	M	N	TSH
NP	NOT	P,O	3	3,5,3	M	OND, MELN, PIT, LR, BL	TSH, TSH
NP	NOT	O	1	3	M	N	AEC
NP	NOT	O,P,T,F	6	4,6,8,7,2,9	S	PIT,, LR	ANM
NP	NOT	O,P,T,F	4	10,2,9,9,6,8	S	N	-
NP	NOT	S,A,EB,EL	7	20,6,6,8,8,3,3	S	N	ANM, TSH
NP	NOT	BM	1	3	M	N	ANM, TSH
NP	NOT	O	1	2	M	PIT,	ANM
NP	NOT	V	1	4	M	N	-
NP	NOT	P,O	3	5,3,4	M	N	BS
NP	NOT	V,O	2	3,2	M	N	-
NP	NOT	P	2	2,2	M	N	BS, TSH
NP	NOT	P,O	2	4,5	M	N	AEC
NP	NOT	S,A,EB,EL	7	18,5,5,6,6,3,3	S	N	-
NP	NOT	BM	2	2,3	M	N	-
NP	NOT	V,O	2	2,6	M	N	-
NP	NOT	V,O	2	6,2	M	PIT, LR	-
NP	NOT	V,O	4	2,3,5,2	M	N	-
NP	OT	S	1	17	S	PIT, LR	-
NP	NOT	V,O	2	2,4	M	N	-
NP	NOT	P	2	3,2	M	N	TSH
NP	NOT	P	2	1,2	M	PIT, LR	TSH
NP	NOT	V,O	2	2,4	M	N	-
NP	NOT	O	2	1,2	M	PIT, LR	TSH
NP	NOT	V,O	3	3,2,2	M	N	-
NP	NOT	T	1	2	M	N	-
NP	NOT	V,O	3	3,1,1	M	N	-
NP	NOT	O, P	2	2,4	M	N	-
NP	NOT	F	1	1	M	N	-
NP	NOT	O, P	2	2,4	M	N	-
NP	NOT	F	1	1	M	N	-
NP	NOT	P,O	2	1,2	M	PIT, LR	TSH
NP	NOT	V,O	2	1,2	M	PIT, LR	-
NP	NOT	F	1	3	M	N	TSH
NP	NOT	V,O	2	2,2	M	N	-
NP	NOT	T	1	1	M	N	-
NP	NOT	V,O	3	3,2,4	M	N	-
NP	NOT	T	1	1.5	M	N	-
NP	NOT	T	1	1	M	N	-
NP	NOT	V,O	2	2,2	M	N	-
NP	NOT	V,O	2	2,6	M	N	-
NP	NOT	F	1	3	M	LR	BS, TSH
NP	NOT	V,O	2	2,2	M	N	-
NP	NOT	V,O	2	2,3	M	N	-
NP	NOT	V,O	3	3,6,7	M	N	-
NP	NOT	V,O	4	4,5,5,3	M	N	-
NP	NOT	O	1	4	M	N	TSH
NP	NOT	O	1	2	M	N	-
NP	NOT	O	1	4	M	N	-
NP	NOT	V,O	2	2,1	M	N	-
NP	NOT	V,O	3	3,1,8	M	PIT	-
NP	NOT	S	1	17	S	PIT, LR	TSH
NP	NOT	P	1	1	M	N	-
NP	NOT	S	1	16	S	N	ANM, TSH
NP	NOT	O,V,P	4	4,4,8,9	S	N	-
NP	NOT	V,O	3	3,2,5	M	N	-
NP	NOT	V,O	3	3,1,3	M	N	-
NP	NOT	P	1	4	M	N	TSH
NP	NOT	V,O	3	3,3,8	M	N	-
NP	NOT	V,O	2	2,3	M	N	-