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Case Report

Successful treatment of three cases of pediatric alopecia areata using a combination of corticosteroids, minoxidil, immunomodulator and light-emitting diode therapy

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Abstract We report three pediatric patients with alopecia areata and high seropositive immunoglobulin G of rubella, toxoplasmosis, cytomegalovirus, and herpes simplex virus. We treated the patients with a combination of topical and intralesional injections of corticosteroids, topical minoxidil 5%, inosine pranobex, valacyclovir, and light-emitting diode therapy with excellent results.

Key words
Alopecia areata, combination therapy, corticosteroid, minoxidil, immunomodulator, antiviral, light-emitting diode.

Introduction

Following androgenetic alopecia, alopecia areata (AA) is the second most frequent cause of hair loss.[1] It is distinguished by acute or chronic non-scarring hair loss, with clinical manifestations that could vary starting at patchy to complete hair loss on the body and scalp, and it can also affect nails and, in rare cases, the retinal pigment epithelium.[1-3] AA could affect any area that could grow hair, however, the scalp, beard area, and brows are the most common.[3] AA has a lifetime incidence of 1.7-2%, affects both sexes equally, and is more frequent in children than in adults.[1-8] In the Asian population, about 85.5% of AA patients acquire the disease preceding the fourth decade,[2] and up to 60% of AA cases begin within the first twenty years of life.[4] As known by many, the pathophysiology of AA is not fully comprehended, but the most widely accepted idea is that it is caused by complicated interactions that happen between genetic or epigenetic framework and undefined triggering circumstances such as viral infections, trauma, or stress arising from a physical or psychological condition.[2]

The course of AA is unexpected, and relapse is frequent. Most treatment suggestions are based on three important aspects: age, severity (the size of the impacted area), and disease phase (acute or chronic).[2] Many therapy modalities, including topical, systemic, and injectable modalities with different efficacy and safety profiles, are available for the treatment of AA; however, data on pediatric AA patients is insufficient.[5,6] The management of these cases in children is a common occurrence that must consistently consider the child's life stage and level of development.[4]

We present three cases of pediatric patients with AA who were effectively treated with a combined application of topical and intralesional

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corticosteroid injections, topical minoxidil 5%, inosine pranobex, valacyclovir, and light-emitting diode (LED) treatment. The purpose of this case series was to highlight different established treatments that have been shown to be beneficial in the treatment of pediatric AA.

Case Description

Case 1

A 10-year-old boy presented with a 3-year history of scalp hair loss. Without any reported family history of the disease or history of allergic rhinitis, atopic dermatitis (AD), thyroid disease, lupus erythematosus, and vitiligo. Physical examination revealed multiple well-demarcated alopecia patches in the vertex, parietal, and occipital regions **(Figures 1a,1b)**. Dermoscopy examination revealed yellow dots and exclamation hairs. There was no nail involvement. The results of the Woods lamp and 10% KOH examinations were negative. Blood serology test revealed a high seropositive immunoglobulin (Ig)-G titer each for rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV)-1.

The patient was diagnosed with AA and was treated with triamcinolone acetonide 10 mg/ml injection and LED therapy on the scalp every 2-4 weeks intervals, topical 0.1% hydrocortisone 17-butyrate scalp lotion once daily (morning), and 5% minoxidil once daily (night), inosine pranobex 4x320 mg (4x10 mg/kg/day) twice a week for three weeks, and valacyclovir 2x320 mg (2x10 mg/kg/day) for 10 days of a month. The lesions respond favorably after six months of treatment **(Figures 1c,1d)**.

Case 2

An 11-year-old boy presented with a 6-month history of scalp and eyebrow hair loss. Without any reported family history of the disease or history of allergic rhinitis, AD, thyroid disease, lupus erythematosus, or vitiligo. Physical examination revealed multiple well-defined alopecia patches in the vertex, temporal, and brow regions **(Figures 2a,2b)**.

Dermoscopy examination revealed yellow dots and exclamation hairs. There was no nail involvement. Woods lamp and 10% KOH examination results were negative. Blood serology test titers revealed a high seropositive IgM titer for HSV-1 and IgG titers for rubella and CMV.

The patient was diagnosed with AA and was treated with triamcinolone acetonide 10 mg/ml injection and LED therapy on the scalp every 2-4 weeks intervals, topical 0.1% hydrocortisone 17-butyrate scalp lotion once daily (morning)

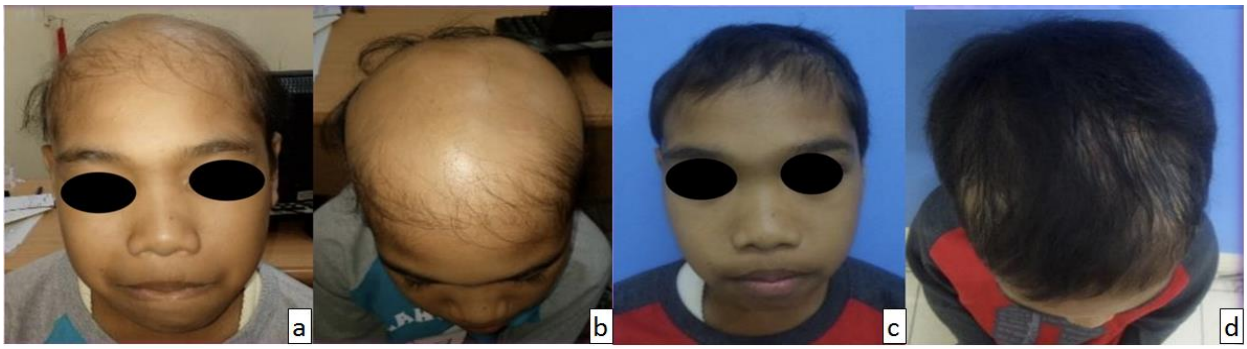

Figure 1 (a-b) Physical examination initial visit showed multiple well-demarcated hair loss patches of alopecia were present in the vertex, parietal, and occipital before treatment. (c-d) Physical examination on the latest visit showed significant regrowth of scalp hair after 6 months of combination treatments.

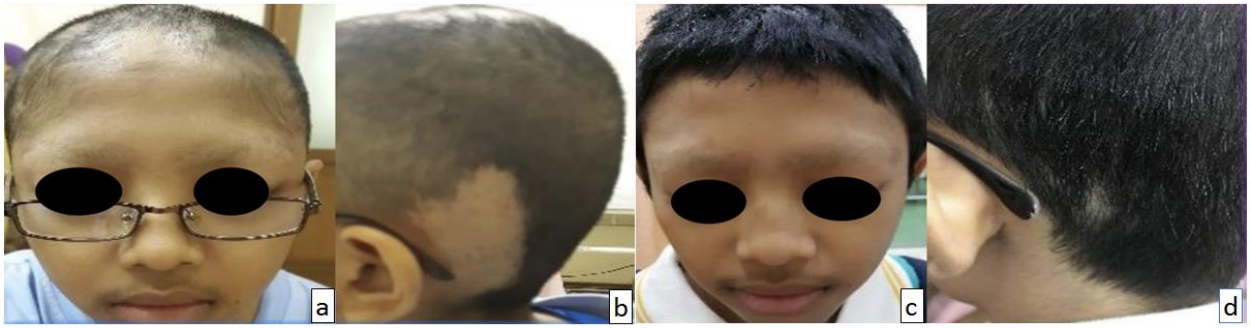

Figure 2 (a-b) Physical examination initial visit showed multiple well-demarcated hair loss patches of alopecia were present in the vertex, temporal, and eyebrow areas before treatment. (c-d) Physical examination on the latest visit showed significant regrowth of scalp and eyebrow hair after 6 months of combination treatments.

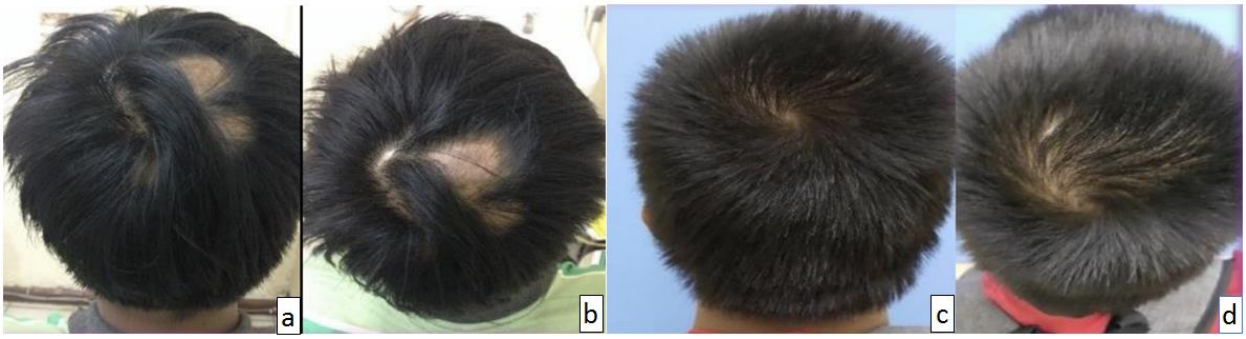

Figure 3 (a-b) Physical examination initial visit showed multiple well-demarcated hair loss patches of alopecia were present in the vertex before treatment. (c-d) Physical examination on the latest visit showed significant regrowth of scalp hair after 6 months of combination treatments.

and 5% minoxidil once daily (night), 0.5% desonide cream twice daily at the eyebrow, inosine pranobex 4x400 mg (4x10 mg/kg/day) twice weekly for three weeks, and valacyclovir 2x400 mg (2x10 mg/kg/day) for 10 days of a month. The lesions respond adequately to treatment after 6 months of therapy **(Figures 2c,2d)**.

Case 3

A 12-year-old boy presented with a 1-month history of scalp hair loss. Without any reported family history of the disease, nor was there a history of allergic rhinitis, AD, thyroid disease, lupus erythematosus, or vitiligo. On physical examination, many well-demarcated alopecia patches were seen in the vertex **(Figures 3a,3b)**. Dermoscopy examination revealed yellow dots and exclamation hairs. There was no nail involvement. Blood serology test revealed high IgG titers for toxoplasma and rubella.

The patient was diagnosed with AA and was treated with triamcinolone acetonide 10 mg/ml injections and LED therapy on the scalp every 2-4 weeks intervals, topical 0.1% hydrocortisone 17-butyrate scalp lotion once daily (morning) and 5% minoxidil once daily (night), inosine pranobex 4x400 mg (4x10 mg/kg/day) two times a week for three weeks, and valacyclovir 2x400 mg (2x10 mg/kg/day) for 10 days of a month. The lesions respond favorably to treatment after six months of therapy **(Figures 3c,3d)**.

Discussion

With a lifetime risk of 1-2%, AA is a moderately frequent non-scarring hair loss disorder and the third-most frequent reason for pediatric

dermatology consultations. It is distinguished by an autoimmune reaction to anagen HFs.[2,5,6] Evidence shows that the collapse of the HF immune privilege following triggering circumstances, such as viral infection, results in an autoimmune reaction wherein exposed HF autoantigens are the primary target of autoreactive cytotoxic CD8+NKG2D+ T cells.[2]

The management of pediatric AA is still problematic.[5,6] There seems to be currently a scarcity of evidence-based medicine for AA.[2] A multitude of treatment methods, comprised of topical and systemic medications, have been utilized to treat AA, with varying effectiveness and safety profiles based on age, disease severity, and activity.[2] Because the children's population is more vulnerable to the psychosocial ramifications of AA, proper management is crucial to prevent further morbidity related to this illness.[5]

A couple of literature (strongest level of evidence, LoE 1) support the use of topical corticosteroids, particularly high-potency corticosteroids, as a safe and effective first-line therapeutic option for children with patchy AA.[5,8] In a randomized controlled trial with 41 pediatric patients, high-potency topical corticosteroids were shown to be more effective than low-potency topical corticosteroids.[5] In contrast, 33% of children receiving therapy of 1% hydrocortisone cream showed a 50% decrease in impacted scalp surface area.[7] In general, children have a good tolerance towards topical corticosteroids, but skin atrophy, telangiectasias, and folliculitis were among the negative effects of topical corticosteroids.[5] It is recommended to wash the application site after 12 hours to limit the occurrence of folliculitis, and restricting the usage up to five times per week appears to prevent the occurrence of atrophy.[4] In our center, pediatric cases of AA are initially treated with a topical corticosteroid as a first-line treatment choice, because of its simplicity of application, comfort, and absence of pain. To avoid skin atrophy, we recommend starting with a highly potent topical corticosteroid for instance 0.05% clobetasol propionate lotion, and gradually decreasing to a lower strength corticosteroid, such as 0.1% hydrocortisone 17-butyrate scalp lotion once daily.

While intralesional corticosteroid (triamcinolone acetonide/ TA) injection is indicated as first-line therapy for patchy AA in adults, its usage in children is not favored due to discomfort.[5] A meta-analysis consisting of 12 trials found that injection of TA is beneficial for patients with limited-type AA, with response rates varying from 60-95%. This mode of delivery bypasses the epidermal barrier delivering the medication directly to the inflamed region. As a result, it reduces the potential side effects of systemic corticosteroid treatment while increasing drug penetration in comparison to the topical route.[4] Patients who have isolated alopecia patches that are small in size (<3 cm), have a brief period, or occupy less than 25% of the scalp are the most suitable candidates for intralesional injection.[4] We use TA 10 mg/ml for scalp lesions, injecting 0.05-0.1 ml per site, separated about 1 centimeter apart on affected the scalp area every 2 - 4 weeks.

A 0.05-0.1 mL injection will result in a tuft of hair growth roughly 0.5 cm in diameter.[9] Children's use of intralesional corticosteroids is not favored due to their dread of needles and discomfort. There are several pain relief methods that could be used such as smaller gauge needles (30 G or 32 G), cold or ice compresses, ethyl chloride spray, diversion technique, and use of topical anesthetic creams.[11] To reduce pain and promote patient acceptability, we utilize smaller gauge 30 G needles and topical anesthetic creams such as

EMLA (eutectic combination of local anesthetic including 2.5% lidocaine and 2.5% prilocaine).

Topical minoxidil is a hair growth promoter that is primarily used to treat androgenetic alopecia. Minoxidil, as opposed to immunomodulatory drugs and corticosteroids which work on inflammation, functions primarily to increase hair growth.[1,3] Some of the hypothesized mechanisms of action by which it stimulates the hair follicle are including vasodilation, angiogenesis, potassium channel opening, and boosting the proliferation of follicular dermal papilla cells. Based on these principles, it has the potential to lengthen the anagen phase of the hair cycle.[4] The efficacy of Minoxidil in children is inconclusive for adult AA and the supporting literature available to date of writing this manuscript are only case reports (strongest LoE 4) which evaluated its use in 9 children.[5] Minoxidil is frequently used as adjuvant therapy in conjunction with other therapeutic options. The concentration used varies between 1% and 5%, with one to two applications each day.[3-5,7] Generalized hypertrichosis and arrhythmia were observed as adverse effects of topical minoxidil in pediatric AA.[5,7,8] We do not recommend utilizing excessive topical minoxidil administration, and subsequently, we used it mainly in localized form with a concentration of 5% once daily to minimize systemic absorption (manifesting as palpitations, hypotension, etc.).

Although immunogenetics is regarded to be the most important factor influencing patient vulnerability to AA, environmental factors such as viral infections are also likely to have a role. Interferon (IFN)-γ, a crucial T helper (Th)-1 effector cytokine in AA pathogenesis, has been linked to the development of AA. Th1 immune responses after viral infection result in supraphysiologic IFN production.[11] The patient in case 1 had anti-rubella IgG, anti-CMV IgG, and anti-HSV-1 IgG; the patient in case 2 had anti-HSV-1 IgM, anti-rubella IgG, and anti-CMV IgG; and the patient in case 3 had anti-toxoplasma IgG and anti-rubella IgG. These data might point to the role of viruses as one of the triggering factors. As a result, oral antiviral administration might be considered. Valacyclovir is the L-valyl ester prodrug of acyclovir with higher oral absorption and bioavailability than acyclovir.[12] Acyclovir and valacyclovir are primarily used to treat HSV and VZV infections; however, valacyclovir is preferable for CMV disease prevention. Chronic suppression is quite efficient at preventing clinical and viral recurrence. The combination of valacyclovir and immunomodulator drugs improved their therapeutic impact.[13]

Inosine pranobex is an immunomodulator with antiviral properties that boost cell-mediated immunity.[10,14] There has been little prior experience with inosine pranobex in the treatment of AA. Georgala *et al*. randomized 32 participants with recalcitrant AA into two separate groups of 16 participants, each receiving either inosine pranobex (group 1) or placebo (group 2). Five of the 15 (33.3%) patients that were available to be evaluated in group 1 achieved complete remission, eight patients (53.3%) responded partially, and two patients (13.3%) did not respond. In group 2, none of the 14 evaluable patients had complete remission, four patients (28.5%) responded partially, and ten patients (71.4%) did not respond. In comparison to the placebo, inosine pranobex demonstrated statistically significant efficacy with negligible adverse effects.

Existing evidence suggests that inosine pranobex has several key roles including as a potentiator of both T lymphocyte and phagocytic cell function, as an enhancer in mitogen-dependent and antigen-dependent lymphocyte DNA

synthesis, as an appearance inducer of the phenotypic markers of differentiation on immature precursor T cells, as an augments helper or suppressor T cell functions, and increases lymphotoxin production. Because cell-mediated immune abnormalities have been implicated in the etiology of AA, the repair of these shortcomings may explain the effectiveness of inosine pranobex in AA.[10] More and larger trials are needed to clarify its role as a therapeutic option in AA.

Laser and light therapies are a non-invasive and effective treatment alternative to AA.[15] Photo-biomodulation (PBM) is the use of visible red (600-700 nm) or near-infrared (NIR) (700 nm-1400 m) light generated by a laser or LED source. Several published studies including in vitro, animal, and human investigations measuring PBM utilizing laser in comparison to LED (an incongruous light source) found that both are uniformly beneficial in aspects of wound healing, inflammation reduction, and pain relief. PBM is considered to stimulate hair growth in AA via an anti-inflammatory mechanism. The activation of the electron transport chain converts the activated macrophage in AA from a pro-inflammatory M1 to an anti-inflammatory M2, lowering the inflammation that otherwise damages the hair follicle and causes hair loss.[16]

AA has an uncertain course.[3,5,7] Due to its autoimmune element, AA is likely to be a chronic and recurring illness.[3] A spontaneous remission is feasible. Some individuals have recurrent episodes, progress to a significant loss, and extended courses with little to no regrowth. 7 Poor prognosis markers include the onset preceding puberty, a confirmed record of AA in the family, involvement in the nail area, and longer than a year of chronic lesion.[2,7] Patient in case 1 had onset before puberty, but none of the three patients had a family history of AA or nail involvement. Two of the three cases described here had short courses, while one in case 1 had a three-year AA course. Furthermore, the existence of AA has been linked to a number of comorbidities such as Alzheimer's disease, allergic rhinitis, thyroid illness, lupus erythematosus, and vitiligo.[2] Extensive hair loss, a history of Alzheimer's disease, and concurrent autoimmune illness are also risk factors for poor hair regrowth.[8] The comorbidities or concurrent autoimmune illness were not present in any of the patients documented in this case series. These many elements indicate that all three cases had a favorable prognosis factor.

Conclusion

AA is a substantial dermatological problem with unmet needs and a negative social impact on hair loss that should not be disregarded, especially in children. It is critical to assess the disease's influence on the child's body and mind well-being, including concerns such as self-confidence, self-image, and peer acceptability. Many therapy modalities, including topical, systemic, and injectable modalities with different efficacy and safety profiles, are available for the treatment of AA; however, data on pediatric AA patients is insufficient. In general, topical corticosteroids are the chosen first-line therapy, and combination treatments have shown to be promising and efficacious in the treatment of pediatric AA. More clinical study, comparative research, and international study collaborations are imperative to better guide pediatric AA management and better understand its prognostic indicators.

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