Review Article:

Management of pediatric alopecia areata: A review

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Abstract

Alopecia areata (AA) is a nonscarring hair loss commonly from the scalp ranging from small patches to large areas. Though it does not cause significant physical discomfort, its visibility and disfigurement create much psychological and emotional burden on patient's quality of life. The situation is much unbearable in the case of children. In this review different established and experimental treatment modalities for children with AA are discussed.

Key word: Alopecia areata, Treatment, Children, Pediatric, Corticosteroids, Jak-inhibitors.

Introduction:

Alopecia areata (AA) is believed to be a chronic inflammation-driven disorder with autoimmune background causing acute or chronic non-scarring hair loss, with a variable presentation ranging from patchy hair loss to complete scalp and body hair loss.[1] AA having an uncertain disease course with self-regrowing of hair in 80% of cases within the first year and unexpected relapse at any time.[2-3] It is the second most common cause of hair loss following androgenetic alopecia, affects 1 person out of 1000 general population and the lifetime risk of the disease is nearly 2%.[4] The prevalence of AA is higher in the pediatric population than in adults, 40 % of cases experience their first AA attack by the age of 20.[5] Though it can appear at any age, there are two age peaks: early childhood and the third decade of life.6 Alopecia areata is the third most common cause of dermatology consultations in children.[5] It is classified as AA, alopecia totalis (AT), and alopecia universalis (AU). Approximately 5% of AA patients can progress to lose all scalp hair (AT), loss of all hair on the scalp including trunk (AU), or an overlap between the two. Other uncommon types are ophiasis pattern (OP) and sisaipho. Ophiasis is the symmetric band-like hair loss from the occipital, parietal and temporal areas of the scalp, sisaipho is the central hair loss sparing these areas.[7] Extent of involvement is more extensive in the first two decades of life; after that disease is usually less severe. Alopecia totalis and universalis occurred in 7.3% of AA cases and always occurred before the age of 30 years.[8] A poor prognosis and a higher possibility of developing refractory disease are described in kids under 6 years of age.[9] It has an unpredictable prognosis, which often includes relapses and remissions, frequently with a chronic course, contributing to the substantial psychosocial burden of AA patients.[10] So to avoid these burdens on children a standard treatment should be started timely. Treatment of AA is challenging and it is more challenging in childhood cases. Though different topical and systemic modalities are available and many new systemic agents are trying for adult AA, none is approved for children.

Diagnosis:

AA typically presents with single or multiple round or oval patches of hair loss of different shape.

Usually, AA is asymptomatic but sometimes occasional cutaneous dysesthesia may be experienced along with hair loss. The skin of the affected patches is usually normal and smooth, rarely a pinkish colouration can be detected. Nowadays trichoscopy is an essential and very helpful tool for the diagnosis and therapeutic monitoring of the disease.

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Table I: Clinical variants of alopecia areata with their characteristic manifestations[1]

Clinical variants of alopecia areata	Presentation
Patchy alopecia areata	Single or multiple circumscribed, well-demarcated patches of hair loss on the scalp
Alopecia totalis	Complete scalp hair loss
Alopecia universalis	Complete loss of facial, body and scalp hair
Ophiasis alopecia areata	Symmetric band-like hair loss from occipital, parietal and temporal areas of the scalp
Inverse-ophiasis (or sisaipho) alopecia areata	Central hair loss sparing the occipital, parietal and temporal areas
Diffuse alopecia areata/ Alopecia areata incognita	Diffuse hair loss and reduction of hair density
Alopecia barbae	Discrete circular or patchy hair loss areas in the moustache or beard, often along the jawline, rarely diffuse thinning
Alopecia areata of the nails	Nail pitting, trachyonychia, red lunula, longitudinal ridging, onychomadesis and onychorrhexis

In general, for AA diagnosis, short vellus hairs and yellow dots are the most sensitive markers, and black dots, broken hairs and tapering hairs are the most characteristic but not pathognomonic markers. Though alopecia areata can be diagnosed easily with clinical examination and with aid of trichoscopic features, in some confused situations some differential diagnoses must be considered (Table II):[1]

Table II: Differential diagnosis (DD) of alopecia in children.

DD of Patchy alopecia areata	DD of Diffuse alopecia areata
Tinea capitis	Loose anagen hair syndrome
Trichotillomania	Telogen effluvium
Temporal triangular alopecia	Congenital hypotrichosis

- Tinea capitis: the scalp is inflamed in tinea capitis and there is often scaling but the signs may be subtle.
- Trichotillomania: This is the most common confusing entity, which in some situations coexists with alopecia areata. Asymmetric bald patches are oftenly from one frontoparietal region with a bizarre or angular pattern, in which the hairs are twisted and broken to different heights from the clinically normal scalp. The broken hairs are firmly anchored in the scalp (i.e. they remain in a growing phase, anagen, unlike exclamation mark hairs) are distinguishing features.
- Anagen effluvium (drug-induced) may mimic diffuse alopecia areata.
- Loose anagen hair syndrome occasionally, alopecia areata presents as diffuse hair loss which can be difficult to diagnose. The clinical course often reveals the true diagnosis but a biopsy may be necessary in some cases.

Trichoscopy in Alopecia Areata:

Trichoscopy is a very easy rapid new technique for the diagnosis of AA. The commonest features are yellow dots, black dots, exclamation mark hairs, short vellus hairs, and coudability hairs. A therapeutic response also can be predicted by observing changes in trichoscopic features; the disappearance of black dots, broken hairs, and exclamation mark hairs indicate a favourable outcome. On the other hand yellow dots, signify chronic disease and poor therapeutic response.[11]

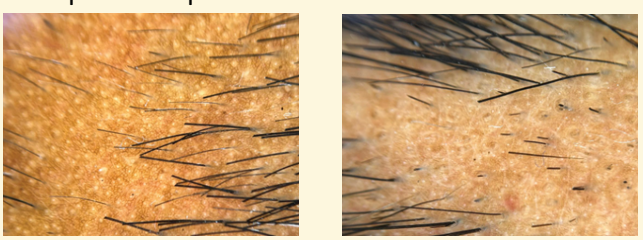

Figure 1: Trichoscopic features of alopecia areata

Biopsy:

A biopsy of the scalp for histopathological evidence is done to roll out scarring alopecia when is difficult clinically or treatment resistant single alopecic patch. Specimen better to collect from the lesional margin avoiding sites susceptible to androgenetic alopecia.

At the acute stage of AA, the principal feature is a peribulbar and intrabulbar infiltration of lymphocytes (CD4+ and CD8+ T cells) surrounding the anagen or catagen follicles- “swarm of bees”. Eosinophils, mast cells and plasma cells may also be seen. A transition to the catagen or telogen phase is occasionally noted.

At the chronic stage of AA, the degree of cellular infiltration is variable; hair follicles are mostly in the catagen/telogen phase and also miniaturized. The large number of empty follicles are also observed, corresponding to the total hair loss of the patient, as well as keratin plugs in empty follicular ostia

indicating longstanding.[1]

Comorbidities:

AA has also been associated with other autoimmune diseases, including atopic dermatitis (most common), vitiligo, and thyroid disease. The prevalence of concomitant vitiligo with AA ranges from 0.4% to as high as 16% in children.[12]Atopic dermatitis (AD) is more commonly seen in association with severe AA than in patchy AA and is a marker of poor response to treatment for AA.[12] Ikeda proposed a classification relating to aetiology and comorbidities distinguishes four AA subtypes. Type I, the 'idiopathic' form, is the most common variant. Type II and type III are associated with atopy and a familial predisposition to hypertension, respectively, whereas type IV is observed in association with autoimmune diseases or endocrinologic disorders.[13]

Prognosis:

A study aimed to see the long-term prognosis of Alopecia found that 34.7% of pediatric and adolescent patients with AA had full-hair regrowth, and 32.0% had no hair regrowth or aggravation among the 75 pediatric and adolescent patients with AA. Results suggested that the severity of the first visit is associated with long-term prognosis. In the case of children, if the hair loss area is mild but the activity is high, the disease may become worse. Therefore, the extent and disease activity should both be taken into consideration.[14]

No intervention

As the chance of spontaneous hair regrowth on small patches of short duration is high in about half of the patients, waiting and seeing is a reasonable approach if the patient is content with the situation. The patient may be asked to wait for three months for regrowth. In longstanding extensive alopecia treatment, where a reasonable treatment outcome is beyond expectation avoiding any intervention and using a wig is a better option.[15]

Table III Therapeutic options of treatment of childhood alopecia areata

Topical	Systemic
Topical and intralesional corticosteroids	Systemic corticosteroids
Anthralin	Methotrexate
Contact immunotherapy	
Cryotherapy	Janus kinase inhibitors
Minoxidil	● Baricitinib
Topical calcineurin inhibitors	● Ruxolitinib
Topical retinoids	● Tofacitinib
Prostaglandins	Hydroxychloroquine
TopicalJanus kinase inhibitors ● tofacitinib and ● ruxolitinib	Sulfasalazine and mesalazine
Laser and phototherapy	
Laser therapy: 308-nm Excimer laser	
Phototherapy	

Topical corticosteroid:

For the treatment of AA in children, super potent or ultrapotent topical corticosteroids have the highest level of evidence for the treatment of pediatric AA.[16]Highly potent topical corticosteroids such as 0.05% clobetasol propionate lotion, and subsequently, tailing down to a lower potency corticosteroid, such as 0.1% mometasone furoate or 0.1% betamethasone valerate scalp lotion to avoid skin atrophy is a reasonable approach.[17] For small patch of AA intralesional corticosteroids (ILCs), usually, triamcinolone acetonide (TAC), is often considered as a first-line therapy.[18]A recommended modality is 2.5 to 10 mg/mL may be used, but 5 mg/mL (maximum volume of 3 mL per session) is the preferred concentration for scalp at one visit. For the eyebrows and face, 2.5 mg/mL can be used (0.5 mL to each eyebrow)per month, reported outcome is greater than 50% improvement in hair regrowth in 82% of all patients younger than 20 years of age.[18-19] TriamicinoloneAcetinoide is recommended to inject intradermally with a 0.5-inch long, 30-gauge needle, as multiple 0.1-mL injections at 1-cm intervals. The TCA solute can be diluted with sterile saline which is preferred over Xylocaine as the latter stings more. Additional application of topical anaesthetic 30 to 60 minutes before the injection can be considered to minimize pain.[20]ILCs may also be

given using a painless device (Dermajet TM) it should be sterilized between patients. Treatments may be repeated every four to six weeks. Initial regrowth is often seen in four to eight weeks. If there is no improvement after six months of treatment, the ILCs should be stopped. Children younger than 10 years are not usually treated with ILCs because of pain localized at the injection sites and their fear but these can be reduced by using finer needles, distraction, or topical anaesthetic creams.[17],[20] Other adverse effects are reversible cutaneous atrophy, anaphylaxis and cataracts and increased intraocular pressure, if used close to the eyes.

Contact sensitizer:

Topical immunotherapy (squaric acid dibutylester [SADBE] and diphenylcyclopropenone [DPCP]) induces the most significant short-term hair regrowth in children with chronic and severe AA, where prolonged topical or intralesional corticosteroids injections are impractical or ineffective. Induction of allergic contact dermatitis and modulate the local autoimmune attack on the hair follicles successful in more than 30 % of severe AA case. But it is not a very common practice. time-consuming (weekly application for up to 32 months) and children are considerably impacted by the intended contact allergy.[21] The patient is first sensitized with 2% DPCP on a 2-centimeter bald patch on the scalp. This is left on for 24 hours and washed off. Patients are reviewed 2 weeks later. Sensitization to DPCP is successful if an eczematous reaction is noted over that patch. Subsequently, DPCP, starting at 0.0001% concentration, is applied weekly at increasing concentrations with to induce a mild eczematous reaction and a tolerable itch that lasts 1-2 days. The DPCP is left on for 24 hours each time and washed off. As DPCP is degraded by light, patients are advised to shield the treated areas from light for 24 hours after application.[17] Adverse effects of contact immunotherapy are occipital and cervical lymphadenopathy, vesiculation, severe contact dermatitis, secondary infection, urticaria, and hypo- or hyperpigmentation disorders but no systemic side effects except headache were reported.[17]

Anthralin:

Anthralin (dithranol), generates free radicals and induces an anti-inflammatory reaction to clear infiltrated lymphocytes. This is recommended for children who are too young to be treated with topical glucocorticosteroids. Compared with contact immunotherapy and topical corticosteroids it is less effective.

Cryotherapy:

Superficial cryotherapy refers to tissue exposure to hypothermic cryogen for a limited period of a few seconds, unlike the conventional standard cryotherapy where the exposure is prolonged till obtaining an ice crystal. With this limited exposure to the cryogen in superficial cryotherapy, neither crystal formation nor blood flow occlusion occurs. In superficial cryotherapy, after initial vasoconstriction induced by cooling, during the thaw period as the temperature reaches zero-degree Celsius, significant local vasodilatation occurs, with increased blood flow to the tissues, followed by reactive vasodilatation, improves the microcirculation by this mechanism hair regrowth is induced.22In a study 60.9% of cases considered as responders after 3 months of superficial hypothermic cryotherapy. The proportion of the responders was higher when the treatment interval was 2 weeks or less. Reported side effects were localized pain, pruritus, inflammation, and swelling.[23]

Topical Minoxidil:

Topical minoxidil (2% or 5%) is commonly used in the treatment of non-scarring alopecia such as AA. Australian dermatologists placed it as one of the first-line therapeutic options in pediatric alopecia areata.4 Moderate quality of evidence suggesting that topical 5% minoxidil is effective and safe compared to placebo in children and adults with patchy AA and that there are minimal adverse events in the short term.[24]Topical minoxidil is ineffective in alopecia totalis and alopecia universalis.24It have no proven immunomodulatory role against the autoimmune attack of the hair follicle, it acts synergistically with corticosteroids and jack inhibitors to improve outcomes in AA.25 Topical minoxidil can be systematically absorbed when used to young patients especially over large areas and cause systemic side effects including cardiovascular side effects.[25]

Topical calcineurin inhibitors:

Topical tacrolimus and pimecrolimus have been used for a long time in different dermatological conditions (atopic dermatitis, vitiligo) of children but their efficacy is not significant in AA. Experts

recommended that it can be tried for alopecia areata of the face, beard, eyebrow or scalp, but it is not considered a first line treatment.[26]

Topical bimatoprost (a prostaglandin F2α analogue normally used to treat glaucoma)
In an expert group consensus meeting topical prostaglandin analogues were recommended as the first-line topical treatment to treat eyelash alopecia areata.26 In treatment of scalp AA, topical bimatoprost 0.03% solution twice daily was found effective and better than topical mometasone furoate 0.1% cream once daily for 3 months. Bimatoprost was significantly better regarding rapidity of response in weeks, percentage of hair re-growth, and side effects compared to other areas.[27]

Systemic corticosteroid:

Systemic glucocorticosteroids are the most reliable and tested modalities with the most rapid and expected treatment outcome. Oral glucocorticosteroids are recommended in acute alopecia areata with SALT >50% and >30% in children aged 7-12 and 13-18, respectively. In the chronic form of the disease, oral glucocorticosteroids are suggested in patients between the age 13 and 18 with SALT >50%.[28] Systemic glucocorticosteroids are not approved for AA in children under 7 years of age.26 Systemic corticosteroids are used in different doses, combinations and schedules. Combination therapy with an adjunctive systemic drug including methotrexate or cyclosporine, intravenous pulse-dosed corticosteroids, oral pulse-dosed corticosteroids, oral corticosteroids maintenance or tapered therapy and intramuscular corticosteroids.[16] Doses varying from 0.5 mg-0.8 mg/kg/day of prednisone daily (for 6-weeks) to 5 mg of dexamethasone twice weekly (for a minimum of 12 weeks) may be used.[29] Pulsed oral or intravenous corticosteroids for AA are effective (complete response) in children without significant side effects and the efficacy is higher comparing with traditional corticosteroid therapy.[29] In a study on children with extensive AA or AT, the majority achieved excellent hair regrowth after taking oral prednisolone 5 mg/kg/month for 3 months in patients aged 3-11 years and 300 mg/month for 3 months in patients aged 12-18 years. Only mild epigastric burning and transient giddiness or headache were reported in two patients.[30] For pulse dosed therapy, shorter disease duration, younger age at disease onset, and multifocal disease (as opposed to AT and AU) were found to be associated with a better response.[31] Pulse therapy with the supra-pharmacological doses of corticosteroid was cumulatively less toxic than sustained corticosteroid treatment at a lower quantitative dosage.[31] Glucocorticosteroids (systemic, intralesional or topical) and JAK inhibitors (systemic or topical) may be considered as the best documented and most effective combination treatment options in alopecia areata in children. Though sufficient paediatric data to compare treatment safety and relapse rates in these therapeutic modalities are absent.[31]

Methotrexate:

Methotrexate as a single agent or combination with oral or intravenous corticosteroids or azathioprine is reasonably effective in patients with severe AA, but adults are more responsive to treatment than pediatric patients.[32] Recurrences are less common compared to systemic glucocorticosteroids, topical immunotherapy and anthralin in pediatric alopecia areata. For adult patients with AA, 5-20 mg of weekly methotrexate with a target dose of 0.4 mg/kg/week has a good steroid-sparing effect.[33] It can be considered for Acute and severe AA of children above 10 years of age when topical steroids, systemic steroids, topical minoxidil (2%) and topical squaric acid dibutylester (SADBE) immunotherapy failed to response. It has been reported to produce 64% recovery when used together with daily oral prednisolone for adult patients with AT/AU.[34] The relapse rate in children is significantly lower than that in adults.[35]

JAK-inhibitor:

Janus kinase (JAK) inhibitors are going to change the therapeutic landscape of severe alopecia areata (AA).[36] Number of publications on the efficacy of tofacitinib, baricitinib and ruxolitinib on AA in adults is increasing fast but only a few case reports are available from the pediatric population. Case series and open-label studies have demonstrated the efficacy of tofacitinib in a proportion of adults and adolescents with AA, alopecia totalis (AT) and alopecia universalis(AU).[36] Both tofacitinib and ruxolitinib cream was found effective and safe for the treatment of AA in children with good efficacy.[37-38] One pediatric patient who has been treated with ruxolitinib at dose of 10 mg twice daily for 10 months and experienced a 91% improvement in the Severity

of Alopecia Tool score with no adverse events.[39] Significant hair regrowth was achieved in children with AA with oral tofacitinib at a dose of 5-10 mg twice daily after taking 2-6 months.[40–41] Baricitinib, a JAK1/2 inhibitor, is an FDA-approved treatment modality of AA in the adult population.[42] So we have to wait to pick it in the drug list for children.

Sulfasalazine and mesalazine:

Partial response of oral sulfasalazine on AA of adolescents was reported in a paper and the efficacy of mesalazine, with or without concurrent oral or topical corticosteroids and minoxidil was reported in another case series on pediatric AA showed complete response.[43–44]

Cyclosporine:

For the adult with severe AA, cyclosporine can be considered effective as monotherapy or in combination with systemic corticosteroid but it is not a convenient modality for children as it needs frequent blood tests for monitoring.[17]

Laser and phototherapy:

The efficacy of 308-nm Excimer laser applied twice weekly for 12 weeks was studied and regrowth of hair was observed in 60% alopecia patches on the scalp.[45–46]

Narrow-band ultraviolet B therapy is ineffective in AA. Though topical PUVA is largely tried with 50-70% success, it was not considered better than the natural course of AA. In a case of refractory AA an adolescent was treated with a psoralen-soaked towel followed by sun exposure demonstrated partial response.47 PUVA can be taken as a third- or fourth-line treatment.[17]

Counseling:

Pediatric AA significantly impairs the QoL of patients as well as family members.10 Considering high visibility, the indefinite clinical course and unpredicted treatment outcome of the disease, AA imposes a significant psychosocial burden on children. When management is challenging even in the case of adults; it creates an extra burden on children as they are more vulnerable to being bullied, social withdrawal, low self-esteem, failing to achieve at school, change in behaviour.[48]

Physicians should guide their patients and family members with appropriate information and provide emotional support. A referral to a paediatric clinical psychologist, educational psychologist or social worker may be needed.[10] Parents or family members should be explained about the disease, including the nature and course, available treatments and treatment outcome. They should be practically mentally prepared for a set realistic expectation from the treatment. In discussion, it is important to consider both the positive and negative aspects of active treatment as some cases do respond well to treatment.

Conclusion:

Management of AA is still challenging and it is more challenging in the pediatric population considering the age of their physical and mental growth, many systemic agents have the potentials to hamper their growth, application and maintenance of many topical medicines (contact sensitizers, cryotherapy, intralesional injection) is impractical and frequent blood tests for monitoring are not always convenient for some systemic immune-modulators. In the management of pediatric alopecia areata, ecery single child should be judged individually. Management decisions should not be taken only on drug efficacy, but rather consider short-term and long-term adverse events of the drugs. Childs physical, mental and emotional issue should be consider with equal importance. In general a child with acute or chronic AA, a super-potent or ultra potent topical corticosteroids should be considered as the first line therapy. In limited patches of adolescents or older children, intralesional triamcinolone acetonide is recommended but pain limits its use. Contact sensitizers, anthralin and cryotherapy are effective topical therapy but practically their use in children is not convenient. Topical 2% minoxidil can be considered one of the first-line treatments in childhood alopecia areata, though it is ineffective in alopecia totalis and alopecia universalis. For recalcitrant and extensive cases systemic agents can mainly oral corticosteroids are recommended. Oral or intravenous pulsed systemic corticosteroids are more safe and more effective, particularly in patients with shorter disease duration, those who are at a younger age at disease onset, and those with multifocal disease. Systemic corticosteroids can be given in combination with other systemic immunomodulators including methotrexate, cyclosporine or JAK inhibitors. Though JAK inhibitors are not recommended yet for childhood alopecia areata, oral baricitinib has been approved for severe alopecia areata in adults. JAK

inhibitors are safely used in some pediatric conditions like atopic dermatitis, so it is logically expected that these will be proven safe and effective in pediatric AA.

Conflict of interest:

None.

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