

ABOUT THE AUTHOR

Marissa Joseph, MSc, MD, FRCPC (Pediatrics),
FRCPC (Dermatology)

Dr. Marissa Joseph graduated medical school at Dalhousie University. She is a board certified pediatrician and dermatologist after completing pediatric training at the Hospital for Sick Children, followed by dermatology residency at the University of Toronto. She completed a MSc in Community Health at the Dalla Lana School of Public Health. Dr. Joseph is full time academic faculty at the University of Toronto. She has received, and been nominated for, teaching awards in both undergraduate and postgraduate medical education. Dr. Joseph is the Medical Director of the Ricky Kanee Schachter Dermatology Centre at Women's College Hospital, with a special interest in inflammatory skin diseases and medical education of dermatology across all skin types. She also works at the Hospital for Sick Children where she manages children with complex dermatologic disease in outpatient and inpatient settings, as well as a pediatric laser treatment program. Dr. Joseph enjoys her diverse practice in general adult, pediatric, medical and surgical dermatology.



AN UPDATE ON PEDIATRIC ALOPECIA AREATA

Introduction

Alopecia Areata (AA) is a common, non-scarring autoimmune alopecia affecting both children and adults. AA is the third most common dermatosis in children¹ and has a significant emotional impact on patients, particularly children. At present, there are no universally effective treatments that guarantee low relapse rates or complete regrowth in severe disease. There is a lack of data for treatment of pediatric alopecia areata. This article provides an overview of pediatric alopecia areata and its management, including relevant peer-reviewed literature in the last 5 years.

Clinical Features

AA is classified into 3 clinical groups: 1) alopecia areata in patches, the most common form; 2) alopecia totalis (AT) complete or almost complete absence of hair on scalp and 3) alopecia universalis (AU) which includes complete loss on the scalp, face, and body.² Ophiasis pattern and sisaipho are also uncommon presentations that may confer a worse prognosis. In children, the majority of cases are localized patches and can undergo spontaneous remission. (Figure 1)



Figure 1. Patchy distribution of non-scarring alopecia in AA; photo courtesy Marissa Joseph, MD

The association of AA with other conditions such as atopic dermatitis, vitiligo, lupus erythematosus, and thyroid disease (with Hashimoto's thyroiditis being the most common in pediatric AA)³ has been reported.² In data from the National Alopecia Areata Registry, 47.0% (n=1043) of children reported comorbid disease.¹ The most common of which were atopic dermatitis, asthma, hay fever, and allergies. Other diseases present in this population, in order of decreasing prevalence, include Hashimoto's thyroiditis, vitiligo, psoriasis, Type 1 diabetes, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis.¹

Dermoscopy (Tricoscopy) in Alopecia Areata

Dermoscopy is a useful non-invasive tool to evaluate hair disorders. Biopsy can be helpful diagnostically but challenging in young patients. Dermoscopic evaluation may obviate unnecessary biopsies in pediatric patients with alopecia. Although dermoscopic findings of AA are described in the literature, studies are limited.⁴ A summary of commonly described dermoscopic features are presented in **Table 1**.

There is little data evaluating dermoscopic findings in pediatric alopecia areata. In one cross-sectional study of 126 pediatric and adult patients, the most common findings were yellow dots (84.1%), vellus hair (62.7%), black dots (48.4%), exclamation mark hairs (30.9%) and broken hairs (9.5 %).⁴

A retrospective comparative analysis of 50 children and 50 adults revealed differences in dermoscopic findings.⁶ Yellow dots were less commonly detected in children compared with adults (26/50, 52% vs 48/50, 96%) .

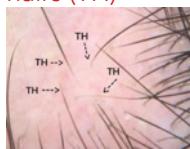
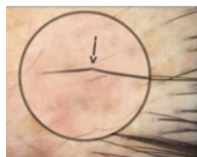
Finding	Description	Adult AA	Pediatric AA
Yellow Dots (YD) 	Round or polycyclic yellow to yellow-pink dots that represent distended follicular infundibula filled with sebum and keratin remnants	↑	↓
Black Dots (BD) 	Remnant of broken hair shafts inside follicular ostia	↑	↓
Exclamation mark hairs/ Tapering hairs (TH)  	Broken hairs that taper toward follicles	↑	↑
Pigtail hairs/Short vellus hairs 	Thin, nonpigmented hairs with length ≤10 mm may demonstrate early disease remission	↓	↑
Broken hairs (BH) 	Due to fracture of dystrophic hair shafts or rapid regrowth of hairs that formerly manifested as black dots.	↑	↓

Table 1.- Dermoscopic findings in variants of alopecia areata⁴

↑ More common ↓ Less common Photos used with permission from Dr. Jeff Donovan⁵

Pigtail hairs and empty follicular openings were more commonly observed in children compared with adults (14/50, 28% vs 2/50, 4% and 40/50, 80% vs 16/50, 32%, respectively).⁶

Differential Diagnosis

It is important to differentiate AA

from other forms of non-scarring hair loss in children. The major differential diagnoses of alopecia areata in children are presented in **Table 2**. Less common diagnoses can also be considered, such as androgenetic alopecia, lupus erythematosus, syphilis, and loose anagen syndrome.

Diagnosis	Clinical Features	Diagnostic challenge with AA Differentiating from AA
Tinea Capitis	➤ Scaling, black dot, kerion ➤ Dermoscopy: zigzag hairs, comma hairs and corkscrew hairs.	➤ Black dots on dermoscopy ➤ Absence of scaling due to application of topical products
Temporal Triangular Alopecia (Brauer Nevus)	➤ Temporal region, usually unilateral Triangular, oval or lancet-shaped ➤ Dermoscopy: vellus hairs	➤ Localized area of non scarring hair loss ➤ Dermoscopy -No yellow spots, exclamation mark hairs
Traction Alopecia	➤ Commonly frontotemporal loss ➤ Fringe sign: retention hair along the frontotemporal hairline	➤ May present with patchy hair loss over the scalp in no specific pattern of distribution depending on hair practices
Telogen Effluvium	➤ Associated with hair pull sign ➤ History of shedding, overall loss of density	➤ Diffuse loss, difficult to distinguish from diffuse alopecia areata ➤ Dermoscopy: absence of yellow spots and exclamation point hairs
Trichotillomania	➤ May admit to manipulation ➤ Patchy and non-confluent. ➤ Friar Tuck sign: May spare peripheral hairs	➤ May not admit to manipulation ➤ Dermoscopy: ➤ V-sign : two or more hairs emerge from one follicular ostium, simultaneously break at the same length above surface. ➤ Tulip hairs: short hairs with darker, tulip flower shaped ends due to diagonal fracture ➤ Hair powder: hairshafts damaged by mechanical manipulation.

Table 2. Differential diagnosis of pediatric alopecia areata

Pathogenesis

In AA, CD8⁺ T cells play a central role in the pathogenesis of disease, with an upregulation of IL-15 and IFN α causing a loss of immune privilege in the hair follicle.⁷ Recent advances in the understanding of the regulators in this pathway have led to emerging therapies and new therapeutic targets.⁸ For example, Janus Kinase (JAK) 1/2 signalling promotes IL-15 production in hair follicles, and inhibition can dampen the inflammatory response around hair follicles.⁹

Psychological and Psychosocial Support

Management of pediatric AA should include an assessment of the child's emotional well-being

and psychosocial stressors.

In one recent study, 78.1% of AA patients aged 4 to 16 years reported impairment in health related quality of life scores (CDLQI, 6.3 +/- 5.9) with feelings of self-consciousness and skin symptoms being most frequently reported.¹⁰

Christensen et al,¹¹ also demonstrated the psychological impact of alopecia areata on children and their caregivers. Sixty-nine pediatric patients with alopecia areata, as well as sixty-four parents completed an online survey to elucidate the prevalence of bullying and emotional burden associated with AA. Respondents revealed that 18% of elementary school children (6/34) had been bullied, while 13% of middle

school-aged children (2/15), and 40% of high school/college-aged adolescents (8/20) were bullied.¹¹ The types of bullying included online, physical, verbal, exclusion, rumors, and threats. Forty-eight percent of these children were embarrassed by their AA, and another thirty-three percent had stayed home at least once from school because of their AA. A multidisciplinary approach including the involvement of a pediatrician, psychologist or psychiatrist should be considered in cases of significant emotional distress. Families can be directed to patient support organizations such as the Canadian Alopecia Areata Foundation.¹²

Screening for Comorbidities

A recent retrospective chart review of 298 patients aged 0-21 years with AA who underwent thyroid testing revealed abnormalities in 20% of patients (n=59) with hypothyroidism being the most frequent abnormality detected in almost half of these patients (49%, n=29). There was no demonstrated association between age, duration of disease or pattern of alopecia and abnormal thyroid findings. Routine thyroid testing for all pediatric patients with AA is not recommended, suggesting it should be reserved for patients with risk factors such as Down syndrome, atopy, and family history of thyroid disease or clinical findings suggestive of potential thyroid dysfunction.³

Treatment Options for Pediatric Alopecia Areata

Counselling about AA should include a discussion about the natural history of the disease, available treatment options, and management of patient expectations.¹³ Therapeutic options are limited by age, temperament and lack of evidence or safety data. The quality of evidence in the peer-reviewed literature is not robust and consists mainly of case reports and case series. Recommendations for treatment and management are extrapolated from adult studies. However, clinicians should expect that children will have less tolerance for discomfort, that there may be long-term adverse effects associated with certain therapeutic agents and that the lack of approved therapies may pose treatment challenges. There are no specific guidelines for the management of pediatric alopecia areata. The British Association of Dermatologists' guidelines for the management of AA states

that "children may be treated in a similar fashion to adults".¹³

No treatment

Spontaneous remission occurs in >50% of patients with limited patchy hair loss for less than one year.^{2,12,14} This may be an option for patients with recent, localized disease, especially very young children where there are concerns about adverse effects of treatment. Families should be warned that complete regrowth is unlikely within 3 months of the development of any individual patch.¹³

Topical Treatments

Topical corticosteroids are a mainstay of treatment as they are well-tolerated, and easy to apply. Class I or II steroids are typically used with clobetasol propionate 0.05% having been shown to be superior to hydrocortisone acetate 1% (17/20 patients vs 7/21 patients showing $\geq 50\%$ improvement).¹⁴

Topical calcineurin inhibitors have been used in AA. One case series involving eleven patients in which tacrolimus 0.1% was used b.i.d. for 24 weeks, demonstrated no clinical response. Despite the lack of evidence, both tacrolimus and pimecrolimus are used in AA.^{13,14}

Topical minoxidil has been used, typically in conjunction with topical corticosteroids. The use of minoxidil is considered off-label, and there are no guidelines regarding the ideal dose, the minimum age in which to initiate treatment, or the duration of treatment in children. One small case series reported that 2% minoxidil t.i.d. helped limit post steroid hair loss in pediatric AA. Clinicians should be aware that hypertrichosis may be more common in children, especially at higher concentrations.¹⁵

Topical contact sensitizers have

been used with varying success in adult patients, but there is a paucity of data demonstrating their efficacy in pediatric AA. In one study, three out of thirty-three children with AT/AU achieved a sustained response to treatment with squaric acid dibutylester (SADBE).¹⁴ Diphenylcyclopropenone (DPCP) 2% in acetone sensitization, followed by DPCP 0.0001% two weeks later can also be used. A retrospective study of DPCP-treated pediatric patients reported that after six months of treatment 14/108 (13%) subjects showed complete regrowth, and 27/108 (25%) showed partial regrowth. The majority of patients reported adverse effects including edema, urticaria, vesicles, erosions, dermatitis and lymphadenopathy.¹⁴ Anthralin 0.5-1% has also been used as short contact therapy. It can cause stinging, burning, and brown staining of the scalp, clothing and bathtub.¹³

Topical retinoids have been used to treat adult AA, but no studies have been conducted in children.^{2,13}

Topical Janus Kinase inhibitors are novel therapeutic options for the treatment of AA. There is considerable interest in the use of topical JAK inhibitors to avoid the potential for immunosuppression with systemic use. JAK inhibitors might be most effective when delivered in a liposomal base, since small molecules are poorly soluble in water. Case reports of topical use in pediatric AA have been published. One case series of eleven patients, aged 4-16, used non-patented formulations of topical tofacitinib 2% in a liposomal base. All of the children had failed both systemic and topical steroids prior to participating in the study. Three of

eleven patients had cosmetically acceptable hair growth and eight of eleven had improvements in their Severity of Alopecia Tool (SALT) score; two patients subsequently lost response, and the patient who did not respond subsequently responded to oral tofacitinib. There were no significant side effects, with only one of eleven experiencing skin irritation.¹⁶

Topical bimatoprost use in AA is not well-established. The existing and very limited data has not shown benefit in most cases.¹⁸ The use of topical bimatoprost has typically been reserved for the eyebrows and eyelashes; areas where topical steroids should be avoided. One case report presents a 9-year-old girl who received intralesional triamcinolone, clobetasol propionate 0.05% and 5% minoxidil topically. After two months, bimatoprost 0.03% b.i.d. was started as monotherapy to the scalp, resulting in complete regrowth by two months; the treatment was discontinued at seven months with no relapse. Given the heterogeneity of the condition, the patient's previous treatment, and the possibility of spontaneous remission it is not possible to definitively attribute her response to the bimatoprost. It has a favorable safety profile, but further studies are needed.¹⁴

Intralesional Corticosteroids

Although intralesional corticosteroid injections are commonly used in adult patients with AA, their use in children is limited by tolerability and is impractical for extensive disease. It is typically used in children age 10 or older, and with limited involvement.¹⁴

Systemic Corticosteroids

Systemic corticosteroids have

long been used, but concerns remain about adverse effects of long-term use, as well relapse post-steroid withdrawal. In children with extensive patchy AA or AT/AU, high dose pulse methylprednisolone was shown to have a poor long-term outcome, with 66% of patients having less than 30% regrowth after a median of twelve months.^{13,19} Drawing conclusions using the data from trials involving systemic corticosteroids is difficult, as the studies have differing methodologies, and AA, by its very nature, has a heterogeneous and unpredictable clinical course.

Other Systemic treatments

In a retrospective study of hydroxychloroquine, nine patients with AA aged 6-16 were treated with 200 mg p.o. b.i.d. over a period of four to twenty-four months. A baseline ophthalmologic exam was done in six of nine patients, as well as baseline laboratory testing. Fifty-five percent of patients (5/9) experienced hair regrowth while on therapy. The most common adverse effects were headache and gastrointestinal intolerance, which led to treatment discontinuation in some cases.²⁰

Cyclosporine has been used as monotherapy or in combination with systemic corticosteroids in the treatment of AA.²¹ There are no specific pediatric studies evaluating the use of cyclosporine.

Methotrexate has also been used in pediatric and adult AA, with data largely coming from case reports and small case series. One retrospective chart review evaluated the efficacy of methotrexate with or without oral corticosteroids in children with AA.²² Fourteen patients aged three to sixteen years, started at 2.5 or 5 mg weekly titrating up

to between 7.5mg-15 mg weekly. Eight patients (57%) experienced good regrowth with methotrexate, including a 3-year-old child who was maintained on 2.5 mg weekly throughout the treatment course. Three children (21%) were partial responders. Twelve of the children had been treated with systemic corticosteroids and transitioned to treatment with methotrexate. Seven of the eight responders also completed a prednisone taper either before, concurrent with or overlapping with the initiation of methotrexate, suggesting that this combination approach may be more efficacious.²²

Oral *minoxidil* has been suggested as a potential treatment in pediatric AA. Originally a strong vasodilator first introduced as an antihypertensive, it has been dosed in children at 0.2 mg/kg/day. Since low-dose oral minoxidil has been used off-label for hair loss in adults, it is hypothesized that it may be a treatment option for children and adolescents. There have been no studies to date establishing dosing or safety in pediatric AA.¹⁵

Oral *Janus kinase inhibitors*, such as tofacitinib citrate have been used in AA.^{8,9,23,24} The data in pediatric AA is limited to small case series. In a retrospective cohort study of thirteen adolescents (seven of whom had AT), subjects were treated with oral tofacitinib citrate at 5 mg b.i.d. for two to sixteen months (median five months). Nine of the thirteen patients experienced clinically significant hair regrowth and achieved an overall 93% median improvement in their SALT score from baseline at an average of 6.5 months of treatment. Despite the risks associated with immunosuppression, adverse events were reported as mild.²⁵

Another study of four pediatric patients aged eight to ten years

with AT and AU who were treated with oral tofacitinib reported promising results. Three of the four initiated tofacitinib at 5 mg b.i.d. and one patient initiated tofacitinib at 5 mg o.d. and ultimately titrated to 5 mg b.i.d. at the three month mark. Three patients had significant regrowth, two with complete regrowth. One patient had scant regrowth. There were no laboratory abnormalities or adverse effects reported.¹⁷

Conclusion

Pediatric alopecia areata is a common dermatosis, with a variable and unpredictable course, that can have a significant emotional toll on patients and their families. There is variable evidence supporting even our most commonly used treatments. There is a need for future high quality studies in evaluating existing and emerging treatments for efficacy, safety and clinical outcomes.

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