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# Alopecia Areata in Children

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*Alopecia areata (AA) is a T-cell mediated autoimmune disease resulting in partial or total non-scarring hair loss. The scalp is the predominant site of involvement, with the most common clinical pattern involving multiple areas of patchy alopecia. Childhood AA can be emotionally devastating in its worst forms. This article is a brief overview of childhood AA focusing specifically on therapeutic options.*

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**A**lopecia areata (AA) is a common disease first described in *The Papyrus Ebers* as early as the second millennium BC.<sup>1</sup> While there have only been a few large population-based studies, the incidence in Olmsted County, Minnesota, has been estimated to be 20.2 per 100,000 person-years, with a lifetime risk of 1.7%.<sup>2</sup> Most patients develop AA before 40 years of age,<sup>3</sup> with 11% to 20% of all cases occurring in children.<sup>4,5</sup> One prospective survey of 10,000 children in a pediatric dermatology clinic demonstrated a prevalence of 6.7%, with peak onset between 2 and 6 years of age.<sup>6</sup>

Alopecia areata is equally prevalent among all ethnicities. The female to male ratio is 1 to 1 until adolescence when the disease becomes more common in females.<sup>2,4,7-9</sup> In this article, we review the etiology, diagnosis, and treatment of AA in the pediatric population.

## Etiology

Alopecia areata is caused by a combination of genetic susceptibility and environmental triggers. A family history of AA is found in approximately 8% of patients.<sup>3,10</sup> Alopecia areata is commonly seen in families with multiple autoimmune diseases such as vitiligo, thyroid disease, and rheumatoid arthritis. One recent study has shown the inheritance pattern is consistent with a polygenic additive model similar to vitiligo.<sup>3</sup>

An autoimmune basis for AA has been supported by association with multiple HLA antigens including HLA-DR4, HLA-DR5, and HLA-DQ3.<sup>11</sup> HLA-DQ3 and HLA-DQB1\*03 alleles appear to be markers for general susceptibility to AA, with the latter serving as a special genetic marker for susceptibility to more severe variants.<sup>12,13</sup> A separate genetic predisposition to alopecia totalis (AT) and alopecia universalis (AU) versus patchy AA also has been identified by Colombe et al.<sup>14</sup> It has been proposed that the aberrant expression of these antigens as well as HLA-DR promotes T-cell recognition of follicular autoantigens.<sup>11,15,16</sup>

The immune process in AA is a form of antibody-mediated cellular immunity, an idea supported by the "swarm of bees" appearance of lymphocytes around the hair follicles seen on biopsy. The perifollicular lymphocytic infiltrate is made up of primarily CD4<sup>+</sup> cells, along with a CD8<sup>+</sup> intrafollicular infiltrate.<sup>17</sup> Morphologic analysis of hair follicles in AA suggests that degeneration of precortical keratinocytes and melanocytes of the hair bulb are the targets of immune attack.<sup>18</sup> Antibodies to the anagen phase hair follicle have been detected in up to 90% (9/10) of patients with AA versus 37% (3/8) of controls, with evidence that multiple structures most commonly are targeted, including the outer root sheath.<sup>19</sup>

Hair loss can be transferred to human scalp explants on severe combined immunodeficiency mice through the injection of scalp-infiltrating autologous T cells.<sup>20</sup> A helper T cell type 1 (T<sub>H</sub>1)

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immune response, marked by production of interferon- $\gamma$ , has been identified to play a role in this process.<sup>21</sup>

The indices of cellular and humoral immunity in children with AA demonstrate an increased level of activated T cells. In one cohort of 46 children, autoimmune thyroiditis was diagnosed in 47.8% (22/46) of patients with AA.<sup>9</sup> Other autoimmune diseases reported with AA include vitiligo, lichen planus, collagen vascular diseases, types 1 and 2 diabetes mellitus, and pemphigus foliaceus.<sup>7,9,22-24</sup> Furthermore, among the associated illnesses, type 1 diabetes mellitus may occur more frequently in first-degree relatives of patients with AA.<sup>4,22</sup>

Atopy does not appear more common in patients with AA than in the general population.<sup>4,6,7</sup> Furthermore, studies conflict regarding its presence as a marker for disease severity.<sup>3,5,25,26</sup>

Although family and personal history of autoimmune disease are the primary markers of AA risk, anecdotally, adults often describe severe onset of stress in their lives prior to disease onset; childhood reports of the same are few and far between.

## Diagnosis

The diagnosis of AA in children rests on a careful clinical history and physical examination. The most common presentation in children is peach- or flesh-colored patches of alopecia on the scalp in oval, round, lancet, or reticular patterns (Figure 1).<sup>4</sup> Epidermal changes such as hyperkeratosis notably are absent in AA. Hairs easily pulled out at the periphery of the patch of alopecia are a marker of disease activity. Scalp involvement usually includes annular patches but can be more diffuse. Gross or microscopic examination may reveal pathognomonic exclamation point hairs (ie, hairs tapered at the proximal end). The closest clinical mimic is tinea capitis, which rarely may present without scale. For this reason, obtaining fungal culture specimens from areas endemic for tinea capitis is a reasonable clinical approach. Examination for cervical and occipital lymphadenopathy is indicated to rule out the imitator tinea capitis.

Alopecia areata is usually categorized into 3 major patterns: AT (extensive scalp hair loss) (Figure 2), AU (extensive body hair loss), and AA (patchy disease)(Figure 1). Ophiasis (derived from the Greek word *ophis* meaning snake) refers to the pattern of AA characterized by a bandlike distribution of hair loss involving the back and sides of the scalp. The *sisaiho* (ophiasis spelled backward) pattern refers to scalp hair loss with sparing of the back and sides of the scalp. Patchy



**Figure 1.** Patch of annular hair loss on the scalp in a patient with alopecia areata.



**Figure 2.** Extensive hair loss as seen in alopecia totalis and alopecia universalis.

AA also may involve the beard, eyebrows, and less commonly other hair-bearing parts of the body. Diffuse AA is a variant that may be difficult to diagnose because it appears as a diffuse loss similar to telogen effluvium.

Nail involvement, such as nail pits, is found in up to 40% of children and may aid in the diagnosis.<sup>4,9</sup> Findings from nail examination may correlate with disease course and severity. Nail disease has been reported in infants with AA.<sup>27</sup>

The differential diagnosis of childhood AA includes tinea capitis, trichotillomania, alopecia triangularis congenitalis, and loose anagen hair syndrome; repeated episodes of telogen effluvium; and atrichia of infancy with papular lesions, vitamin D-resistant rickets, and Clouston syndrome. Generalized atrichia is an autosomal recessive genodermatosis in which hair is lost during the first 3 months of life because of a mutation of the human homologue of the murine *hairless* gene.<sup>28</sup> Vitamin D-resistant rickets appears to be an autosomal recessive trait presenting with hair loss during the first 15 months of life associated with clinical and radiologic signs of rickets and hypocalcemia with secondary hyperparathyroidism.<sup>29</sup> Finally, Clouston syndrome is an autosomal dominant hair-nail hidrotic ectodermal dysplasia characterized by hair defects, nail dystrophy, and palmoplantar hyperkeratosis.

Serology for syphilis or lupus also may be of value if the AA appears moth eaten or atypical in appearance. Occasionally, skin biopsy may be needed for atypical cases. Histopathologic features supporting the diagnosis include peribulbar and intrabulbar mononuclear infiltrates. Horizontal sectioning is helpful in demonstrating the inverted ratio of anagen to telogen stage hair follicles and degenerative changes in the hair matrix.<sup>30</sup> Testing for thyroid function abnormalities can be performed intermittently to look for the most common autoimmune condition. However, thyroid disease would not be considered the cause of AA but rather another manifestation of autoimmune diathesis.<sup>9,31</sup>

## Treatment

Childhood, particularly adolescence, is a time when the image of self develops rapidly. During this time, children with AA must deal with the psychosocial stress and feelings of rejection associated with their appearance. Major depression, generalized anxiety disorder, social phobia, and paranoid disorder all have been found to be more prevalent in patients with AA than in the general population.<sup>32,33</sup> The parents of a child with AA may feel guilt. Furthermore, siblings may develop fears that they may be affected.<sup>34</sup> Therefore, continued open dialogue with patients and their families regarding the social and emotional impact of AA is an essential part of any treatment regimen. Appropriate referrals should be made to help patients cope with the disease. Many resources, including support groups, can be found through the National Alopecia Areata Foundation. For patients with long-term AT or AU, referral to Locks of Love can be made. This not-for-profit organization has been making hair prostheses for children 18 years and younger for free since 1997.<sup>35</sup>

Because spontaneous remission occurs in up to 80% of patients with limited patchy hair loss of short duration (<1 year), active nonintervention may be a legitimate option for many patients with limited disease.<sup>31</sup> These patients can be managed with reassurance that hair growth cannot be expected until after 3 months of alopecia. However, as hair regrowth becomes less likely after 2 years of disease, patients with AA and no spontaneous hair regrowth over a 1-year period should be treated. Few treatments have been subject to randomized controlled trials, making an evidence-based approach difficult. In infants and children, topical therapies are the favored approach.

*Topical Corticosteroids*—Mid-potency topical corticosteroids have proven ineffective for adult AA; however, higher potency products may produce superior results topically.<sup>36-38</sup> Topical corticosteroids have the best risk-benefit profile of all the therapies for children. Therefore, they are first-line therapy. Several case studies have demonstrated their efficacy in limited childhood AA. In one small case series of congenital AA, the best regrowth was observed with clobetasol propionate 0.05%.<sup>39</sup> Betamethasone valerate foam 0.12% and betamethasone dipropionate lotion 0.05% have been shown to be effective and well-tolerated treatment of mild to moderate AA.<sup>40</sup>

Topical corticosteroids have been shown to be effective in hair regrowth via local, not systemic, immunomodulatory effects.<sup>41</sup> In most trials, results became evident after a minimum of 3 months, but as a rule of thumb, based on personal experience, some early regrowth should be noted by 6 weeks. The principal side effect of this treatment is folliculitis and thinning of the scalp, which is ideally covered by the newly regrown hair. Minoxidil 2% to 5% is added by some physicians to promote rapid regrowth, but it can cause redness, hyperkeratosis, or hypertrichosis. We wait until regrowth initiates and then add minoxidil as a promoter. We instruct parents to apply 1 drop per quarter-sized area once daily and continue topical corticosteroids twice daily.<sup>42,43</sup>

*Intralesional Corticosteroids*—Intralesional corticosteroid injections have been shown to stimulate hair growth in some patients with effects lasting up to 9 months.<sup>44</sup> In young adults, regrowth was likely in patients with less than 5 patches of alopecia, lesions of short durations (<1 month), and patches less than 3 cm in diameter.<sup>45</sup> Intralesional injection of AT can be successful; however, continued hair loss often results in indefinite need for injection. Patient discomfort can be minimized by usage of needleless devices.<sup>46</sup> These devices must be meticulously cleaned to avoid infection or formation of a foreign body granuloma.<sup>47</sup> Usually, triamcinolone

acetone is injected into the subcutis in an appropriate concentration (2–5 mg/mL) for the area every 4 to 6 weeks. Transient skin atrophy at the site of injection may occur if a high concentration is used or the same site is repeatedly injected.

**Topical Immunomodulators**—Topical immunomodulators such as squaric acid dibutyl ester (SADBE) and diphenylcyclopropanone (DPCP) have been used with variable success. A review of published case reports estimated the success rate to be between 50% and 60%.<sup>48</sup> Two small case report series in children with AA found response rates of 33% and 32%, respectively.<sup>31,49</sup> A case report series by Tosti et al<sup>50</sup> found similar short-term results (30.3% [10/33]); however, only a small proportion of children with severe AA in their cohort obtained a persistent benefit. One study has shown that SADBE therapy may blunt the frequency of relapses in severe AA.<sup>51</sup>

Based on a review of all known cases, Rokhsar et al<sup>48</sup> concluded that topical immunotherapy should be restricted to extensive disease involving more than 40% of the scalp.<sup>48</sup> The protocol for contact immunotherapy begins with sensitization using a 2% solution applied to a small (quarter sized) area of the scalp. Two weeks later, the scalp is painted with a weak solution (0.001%–0.1%) at weekly or biweekly intervals. The concentration is increased until a mild allergic reaction is observed.<sup>52</sup> The concentration or frequency of application (1–3 times weekly) may need to be altered every 6 to 8 weeks. After regrowth is achieved, discontinuation should be tapered to prevent relapse. One of the authors reduces frequency by once a week and then reduces concentration. This tapering proceeds over 6 months. Successful SADBE therapy will therefore take 6 to 18 months in total.

The mechanism of action of topical immunotherapy remains poorly understood; however, it appears to work through immunomodulation shifting from a T<sub>H</sub>1 to a helper T cell type 2 phenotype locally on the scalp.<sup>53</sup> Its safety profile in the past 20 years has made it an attractive option, especially in children. Rarely, urticaria has been reported. This therapy is ideal for patients who have lost their lashes, as application to the eyebrows often is associated with untreated eyelash regrowth.

Unlike dinitrochlorobenzene, neither SADBE nor DPCP have been found to be mutagenic.<sup>54,55</sup> Adverse reactions usually consist of an eczematous dermatitis; however, both hypopigmentation and hyperpigmentation (including vitiligo and dyschromia *en confetti*) may occur, especially in dark-skinned patients.<sup>31,56–58</sup> There is an absolute contraindication of usage in patients with vitiligo vulgaris because of

high risk for the Köbner phenomenon. Because topical immunotherapy is on the bulk substance list but is not specifically US Food and Drug Administration approved, patients should be informed of the nature and potential side effects of treatment.<sup>31</sup>

**Systemic Corticosteroids**—The question of systemic corticosteroid use has not been addressed with large, randomized, placebo-controlled studies. One study using alternate-day dosing of oral prednisone for varying degrees of AA in children found that the results were transient, with no substantial long-term benefits and many potentially serious side effects.<sup>59</sup>

Oral prednisone pulse therapy and oral minipulse therapy administered weekly may be useful in adults with extensive AA with fewer side effects.<sup>23,60,61</sup> Nevertheless, short- and long-term hazards of systemic corticosteroids are dangerous and cannot be supported until there is better evidence of efficacy.<sup>31</sup>

In 2005, weekly oral prednisolone pulse therapy was evaluated in a placebo-controlled trial for patients with extensive AA. The study found that 8 of 23 patients (34.8%) in the prednisolone-treated group had extensive hair regrowth versus none in the placebo group.<sup>62</sup> However, these results have been disputed based on trial design and methodology, outcome measures, presentation of results and statistical analysis, and consideration of side effects.<sup>63</sup>

Pulse therapy with methylprednisolone at 1, 3, 6, and 12 months in patients with active severe AA of less than 12 months' duration appeared to be well-tolerated and effective in patients with rapidly progressing, extensive, multifocal AA, but not patients with ophiasis alopecia and AU.<sup>64</sup>

**Dithranol (Anthralin)**—Anthralin, an anti-inflammatory anthracene derivative traditionally used in psoriasis, has not been fully evaluated in AA. Its mechanism of action is thought to be a result of the antiproliferative and immunosuppressive actions of free radicals generated by the inflammation it provokes.<sup>35</sup> In AA-affected C3H/HeJ mice, expression of tumor necrosis factor  $\alpha$  and tumor necrosis factor  $\beta$  were inhibited by anthralin with successful treatment.<sup>65</sup>

Only 2 studies have shown anthralin to be a successful treatment.<sup>66,67</sup> In one clinical trial of 68 patients, only 18% (12/68) of patients obtained adequate cosmetic response with a mean time of 23 weeks.<sup>67</sup> Anthralin generally must cause an adequate irritant contact dermatitis to regrow hair in AA.<sup>68</sup>

**Laser Therapy**—Preliminary studies using the 308-nm xenon chloride excimer laser showed effective

regrowth in all patients with limited AA but not AT or AU.<sup>69,70</sup> Although the mechanism of action is not certain in AA, it has been postulated that laser therapy results in immunosuppression via T-cell apoptosis interrupting the autoaggressive immune cascade.<sup>69</sup>

**Topical Tacrolimus**—Topical tacrolimus ointment 0.1% did not stimulate hair growth over a 24-week course in a group of 11 patients with longstanding AA.<sup>71</sup>

**Topical Psoralen Plus UVA**—Topical psoralen plus UVA (PUVA) is thought to work via a local immunomodulatory effect, but studies of PUVA have had mixed results in childhood AA.<sup>72-78</sup> In children, epidemiologic evidence suggesting sun exposure is associated with future skin cancers, photoaging, and malignant melanoma<sup>79-81</sup> raises concerns of the possibility of long-term side effects following PUVA treatment. Challenges in treating children with PUVA also include compliance with eye photoprotection and the non-child friendly atmosphere of most phototherapy units.<sup>82</sup>

**Onion Juice Extract**—A small study comparing onion juice extract to tap water demonstrated hair growth in 86.9% (20/23) of patients with AA treated with onion juice extract versus 13% (2/15) of controls treated with tap water.<sup>83</sup> Unfortunately, our own success with onion juice extract has been limited. Four of our patients aged 6 to 21 years have failed an 8-week trial of the onion juice extract.

## Conclusion

Alopecia areata is a common autoimmune disease resulting in partial or total nonscarring hair loss. While the diagnosis of AA usually is straightforward, successful treatment can be challenging. Open dialogue with patients and family members regarding the social and emotional impact of AA is an essential part of any treatment regimen. To date, evidence-based management of children is limited by the number of well-controlled, randomized studies. Initial treatment options should be tailored by the patient's age and extent for alopecia. Future research may lead to more effective immunomodulatory agents for this common autoimmune disease of the hair follicle.

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