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A retrospective review of paediatric alopecia areata cases seen in a tertiary institution in Singapore

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INTRODUCTION

Alopecia areata (AA) is a common benign cause of patchy hair loss seen in adults and children, affecting up to 2% of the population worldwide.[1] AA itself and the treatment can lead to psychosocial stress in patients and family, resulting in a negative quality of life.[2] Most paediatric patients with AA present with mild localised disease.[3,4] Common options for treatment include topical and oral corticosteroids, topical ciclosporin, topical minoxidil, diphencyprone therapy and intralesional corticosteroids. However, there is a paucity of randomised, double-blinded, placebo-controlled trials for treatment of AA.[5] In addition, there is a possibility of spontaneous resolution of the AA patches within one year, as reported in 34%–50% of patients.[6] Hence, conservative management is also a reasonable option and patients or parents may choose to wait. Treatment options will also need to be tailored to the needs of the paediatric population owing to their fear of pain and injections.[7]

This study aimed to evaluate AA in our local paediatric population through its prognosis, treatment options and complications, and treatment.

METHODS

This is a retrospective review of the medical records of paediatric patients with AA seen at a tertiary dermatological specialty centre (National Skin Centre, Singapore) from 2013 to 2017. The paediatric age group was defined as under the age of 21 years in our study. All cases of AA were diagnosed, managed or supervised by a team of qualified dermatologists. Biodata, information on disease presentation, treatment details, complications and follow-up duration were collected and analysed. Ethics approval was sought and obtained from the appropriate domain-specific review board.

The inclusion criteria consisted of patients aged below 21 years with a coded diagnosis of AA, seen over the course of five years from 2013 to 2017. Only patients with a disease

duration of three months or less were included. This limited disease duration was chosen, as current literature suggests that regrowth of each individual untreated AA patch starts after three months.[1] Patients who had other dermatological conditions such as eczema were also included.

Exclusion criteria included patients with concomitant diagnosis of other hair and nail disorders such as trichotillomania, telogen effluvium or scarring alopecia. Patients who had received treatment for their AA before presenting to our centre were also excluded.

Data was collected and analysed descriptively using mean ± standard deviation or median (range) for variables in the interval/ratio scale, and count with percentage for variables in the nominal scale. To assess the factors associated with treatment response, univariable and multivariable logistic regression models were obtained. All variables that were clinically relevant to the response variable were included in the logistic regression models. Crude odds ratio (OR) and adjusted OR with 95% confidence interval (CI) were reported. Significance was assessed at a level of 0.05. All data analyses were preformed using R version 3.5.3.

RESULTS

A total of 182 cases were reviewed in our study (Table I). The patients' age ranged from 0.5 to 20.0 years, with a mean age of 13.0 ± 5.4 years and no gender predisposition. The mean duration to presentation was 1.8 ± 0.9 months, with a median of two months. 51.1% (n = 93) of patients presented with a singular patch, while 14.3% of patients presented with four or more patches. 6.6% (n = 12) of patients had involvement of other body sites on presentation, namely the eyebrow, eyelash and beard areas. Exclamation point hairs were seen in only 22.5% (n = 41) of patients. Interestingly, only one patient had a personal history of vitiligo, diagnosed two years prior to the diagnosis of AA. None of our cases had a documented personal history of thyroid disease. 18 (9.9%) patients had a documented history of concomitant eczema at the

first point of contact. These patients had their eczema treated with topical medicines only. No patient had a history of psoriasis.

44.0% (n = 80) of patients received topical treatments, while 68.7% (n = 125) of patients received intralesional steroid injections (ILK). 13.7% of patients received a combination of treatments. None of our patients were treated conservatively.

Betamethasone 0.1% scalp lotion was prescribed in the majority of patients who received topical treatment (61.3%), followed by mometasone 0.1% lotion (21.3%), clobetasol 0.05% scalp lotion (17.5%), topical minoxidil (11.3%), desonide lotion (6.3%), topical calcineurin inhibitors (2.5%) and hydrocortisone cream (1.3%). The number of ILK injections varied between patients, with the majority (39.0%) of patients receiving 1–3 ILK injections prior to resolution of their AA patch.

In terms of treatment complications, 2 (1.6%) patients had scalp abscesses after ILK treatment. 9 (7.2%) patients experienced skin atrophy after ILK, which resolved completely after cessation of treatment. Patients who underwent more ILK treatments were more likely to have ILK-related treatment side effects (OR 1.17, 95% CI 1.00–1.35, p = 0.033). No patient had sustained skin atrophy or telangiectasia with topical steroid treatments.

7 (3.8%) patients received diphenylcyclopropenone immunotherapy (DCP). These patients presented either with extensive scalp involvement (four patients, range 30%–50%) or alopecia totalis/universalis (four patients). All patients were treated with a combination of topicals, ILK or oral corticosteroids with poor response, prior to initiation of DCP. The duration of DCP treatment ranged from 13 to 183 sessions over the course of our data review period. A favourable therapeutic response was observed in 176 (96.7%) patients, who showed improvement in AA. 102 (56.0%) patients had resolution of their AA at their last review, while 74 (40.7%) patients had documented improvement.

Table I. Patient demographics (n = 182).

Characteristic	No. (%)
Age (yr)	
Mean	13.0 ± 5.4
Median (range)	14.0 (0.5–20.0)
Gender	
Female	84 (46.2)
Male	98 (53.8)
Ethnicity	
Chinese	125 (68.7)
Malay	27 (14.8)
Indian	15 (8.2)
Others	13 (7.1)
Clinical characteristic	
Duration of symptoms	
Mean	1.8 ± 0.9
Median (range)	2.00 (0.25, 3.00)
No. of patches*	
Mean	2.1 ± 1.8
Median (range)	1 (1, 10)

**Excludes cases of alopecia totalis/universalis.*

Patients who presented with multiple AA patches or diffuse hair loss were less likely to have an improved clinical outcome, with an adjusted OR of 0.95 (95% CI 0.90–0.99, p = 0.027, Table II). Patients who used topicals were less likely to have their AA resolved within six months, in comparison to other treatment modalities (adjusted OR 0.23, 95% CI 0.08–0.59, p = 0.003, Table II). Patients who required more ILK treatments were also less likely to have their condition resolved within six months (adjusted OR 0.71, 95% CI 0.56–0.87, p = 0.002, Table II).

There were no statistically significant differences between treatment outcome and age, gender, race, duration of initial presentation and type of topical agent used.

All seven patients who underwent DCP for severe AA or alopecia totalis/universalis showed improvement in their condition. However, only one patient managed to achieve complete regrowth of hair with no recurrence within our study period. The three patients with alopecia totalis/universalis showed 10%–40% improvement in the scalp surface area. Two of

these patients continued with treatment beyond the collection period of our study, while the third patient defaulted follow-up. Hence, we were unable to track their clinical progress.

DISCUSSION

AA is a commonly encountered condition in the paediatric dermatology clinic. A Cochrane review published in 2008 concluded that there are no validated treatments for AA. There has been a paucity of good-quality randomised controlled trials evaluating the various treatment modalities available, rendering it a challenge for dermatologists to select an appropriate treatment option. In our study, we have attempted to breakdown the subtypes and frequency of treatment used.

No statistically significant differences were reported in our study between treatment outcome versus age, gender, duration of initial presentation and the type of topical agent used. A previous local study on AA showed a slight female preponderance, with a female-to-male ratio of 1.3:1;[8] however, our study showed a higher number of male patients than female patients. Corticosteroids were the most commonly prescribed topical agents. Topical midpotent corticosteroids are recommended in children, and may be combined with a nonsteroidal compound such as minoxidil.[5]

In our study, the remaining six patients who showed minimal or no improvement within the study period had multiple patches or a large scalp surface area of involvement on initial presentation. This is consistent with previously reported data, where risk factors for a poorer prognosis included extensive disease (more than 50% scalp involvement, ophiasis, alopecia totalis/universalis) and recalcitrance to topical or localised therapy. In addition, the severity of AA at onset of treatment is an important negative prognostic factor.[9] Interestingly, only one patient in this subgroup had a concurrent history of eczema on topical treatment. A systemic review of the association between AA and eczema showed that the odds of atopic dermatitis

were higher in patients with alopecia totalis/universalis, compared to patchy AA.[10] Further studies on the severity and chronology of AA and eczema may be warranted.

Topical immunotherapy is currently used as off-label treatment in children. It has been reported to be equally efficacious and safe as in adult patients.[11] In paediatric patients with severe AA recalcitrant to other therapy options, topical immunotherapy presents advantages of being relatively painless and easy to apply in an outpatient setting.[12] In our study, DCP treatment was used in patients who failed to respond to other treatment modalities such as topicals, ILK and oral corticosteroids. However, it is notable that studies have shown improvement rates ranging from 33% to 84%.[13,14] There is also a lack of data regarding recurrence rates after cessation of topical immunotherapy. These patients should be followed up for a long duration to determine the chronicity of disease and full efficacy of topical immunotherapy.

Anecdotally, steroid phobia remains prevalent among patients and parents locally. Patients are usually hesitant to receive topical and localised injections of corticosteroids owing to an exaggerated fear of risks or side effects. The prevalence of steroid phobia has also been shown to be moderately high in a local study, as well as internationally.[15,16] The majority of patients in our study had ILK injections for their AA. The reported risks of ILK injections include pain, haemorrhage, ulceration, skin atrophy, pigmentary changes and granuloma formation.[17] Our study showed that < 1% of paediatric patients who underwent ILK had temporary side effects of skin atrophy and infection, while none of the patients who had topical corticosteroids experienced side effects. Also, none of the patients reported any long-term persistent adverse effects from the usage of topical and locally injected corticosteroids. There are various practical considerations regarding ILK treatment in the paediatric population, and usage of a topical anaesthetic prior to treatment is recommended.[5] Otherwise, distraction

therapies and smaller needles may also be employed.[7] Our centre is also exploring the use of triamcinolone-containing microneedles for treatment of AA in special populations.

The limitations of this study include information bias associated with retrospective studies. Also, owing to the retrospective nature of the study, we were unable to employ the SALT (Severity of Alopecia Tool) scoring for an objective measure of severity. There was also a lack of standardised hair and nail clinical photos available for further objective assessment by other independent blinded physicians. Thyroid function tests were also not routinely performed in all patients. We have since harmonised our clinical workflow and suggested to include these elements in the approach to a patient with AA.

Our inclusion criteria of patients with a maximum disease duration of three months may have excluded a more severe cohort of patients, leading to selection bias. As none of our patients were conservatively treated, our retrospective review was unable to account for the possibility of spontaneous regrowth in AA. Further prospective studies with a larger pool of patients, correlating SALT scoring or a longer-term follow-up of patients may be useful. However, there may be challenges in conducting randomised controlled trials in the paediatric population owing to ethical issues and reports of spontaneous regrowth in up to 50% of patients.[7]

Newer treatments for AA include the use of Janus kinase (JAK) inhibitors such as topical or oral tofacitinib, ruxolitinib, PDE4 inhibitors such as apremilast, as well as platelet rich plasma. Various cytokine-targeted therapies are also being explored, specifically with ustekinumab and dupilumab.[18] Other treatments in the pipeline include newer JAK inhibitors (ritlecitinib and baricitinib) and cytotoxic T-lymphocyte-associated antigen 4 fusion proteins (abatacept).[19]

In conclusion, this study serves to report our experiences of treating paediatric patients with AA. Current treatment modalities appear to be safe in the paediatric population. The

variable course of AA, coupled with the multiple treatment modalities available, emphasises the need for individualised treatment in accordance with patient or parental preferences. Care must be taken to address the various psychosocial aspects of the disease in young patients. This review enables us to glean insights to management options and appropriate treatment duration for AA.

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Table II. Factors associated with clinical outcome and resolution of AA within six months from univariable and multivariable logistic regression models.

Factor	Clinical outcome (improved vs. not improved)				Resolution of AA within 6 mth (yes vs. no)			
	Univariable logistic regression		Multivariable logistic regression		Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (yr)	1.09 (0.94–1.28)	0.237	1.15 (0.90–1.52)	0.275	1.04 (0.99–1.11)	0.128	1.05 (0.96–1.14)	0.327
Gender (female vs. male)	0.85 (0.15–4.72)	0.848	0.12 (0.00–2.72)	0.241	0.86 (0.47–1.55)	0.608	0.74 (0.35–1.55)	0.430
Other past medical history (yes vs. no)	0.59 (0.11–4.35)	0.549	0.09 (0.00–1.92)	0.148	1.16 (0.57–2.33)	0.679	0.89 (0.40–1.96)	0.770
Duration of symptoms (mth)	0.92 (0.37–2.22)	0.855	0.43 (0.09–1.48)	0.213	0.98 (0.71–1.34)	0.889	0.89 (0.62–1.28)	0.530
No. of patches	0.96 (0.94–0.98)	< 0.001	0.95 (0.90–0.99)	0.027	0.93 (0.77–0.99)	0.333	0.93 (0.74–0.99)	0.363
Multiple patchy hair loss (yes vs. no)	0.18 (0.01–1.16)	0.124	0.42 (0.01–7.98)	0.563	0.65 (0.36–1.18)	0.156	1.15 (0.55–2.73)	0.717
Involvement of other body areas (yes vs. no)	0.12 (0.02–0.94)	0.022	0.41 (0.01–17.37)	0.624	0.28 (0.04–1.10)	0.106	0.32 (0.04–1.86)	0.229
Recurrence (yes vs. no)	–	–	–	–	0.47 (0.13–1.41)	0.205	0.64 (0.15–2.34)	0.516
Use of topicals (yes vs. no)	0.78 (0.14–4.30)	0.762	0.69 (0.04–10.27)	0.778	0.46 (0.25–0.85)	0.014	0.23 (0.08–0.59)	0.003
No. of ILK/DCP treatments used	1.00 (0.81–1.43)	0.989	0.77 (0.55–1.22)	0.126	0.92 (0.81–1.02)	0.137	0.71 (0.56–0.87)	0.002
Hair pull test								
Positive vs. negative	0.15 (0.02–1.25)	0.052	0.03 (0.00–2.16)	0.124	0.64 (0.16–2.25)	0.494	0.80 (0.16–4.10)	0.781
Not commented vs. negative	2.57 (0.32–52.47)	0.418	0.51 (0.02–16.51)	0.675	0.53 (0.28–0.98)	0.044	0.47 (0.23–0.94)	0.035
Treatment side effects (yes vs. no)	0.30 (0.04–6.06)	0.294	0.39 (0.01–26.60)	0.589	0.54 (0.12–1.94)	0.377	0.60 (0.11–2.67)	0.519

Recurrence was excluded from the clinical outcome model owing to collinearity. AA: alopecia areata; CI: confidence interval; DCP: diphenylcyclopropenone immunotherapy; ILK: intralesional steroid injections; OR: odds ratio