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The Immunological Association between Alopecia Areata and Respiratory Diseases: A Systematic Review

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Keywords
Alopecia · Immunology · Atopy · Allergic rhinitis · Asthma

Abstract
Background: While alopecia areata (AA) has been associated with atopy, the immunological relationship is unclear, with the association of specific atopic and systemic respiratory diseases not established. The relationship between T-helper (Th)1-mediated AA and Th2-mediated atopy challenges the conventional Th1/Th2 paradigm of autoimmune disease categorization. ***Objectives:*** To determine the association between AA and atopic respiratory diseases in adults and children, and respiratory diseases in general. ***Method:*** All primary literature, excluding case reports, were identified within PubMed/MEDLINE, CINAHL, and Web of Science in May 2018 using the following search terms: "(alopecia OR hair loss) AND (respiratory OR pulmonary OR lungs OR asthma OR rhinitis OR bronchitis OR COPD OR atopy OR atopic)." Information from 32 articles meeting the inclusion and exclusion criteria was reviewed. ***Results:*** Among the 32 articles identified for inclusion, the prevalence of AA was more strongly associated with allergic rhinitis compared to asthma among pediatric and adult populations. While a significant association was identified between AA, allergic rhinitis, and a late age of onset, the association of AA and asthma remains controversial despite asthma's prevalence among AA patients. No significant difference was identified with regard to the association of AA and non-atopic respiratory diseases between adult and pediatric patients. ***Conclusions:*** Adult and pediatric patients with AA warrant further workup for atopic respiratory diseases such as allergic rhinitis. AA may have an underlying Th2-mediated immunological component, which supports its association with atopic respiratory diseases and provides a new avenue for targeted therapies in select cases.

Introduction

Alopecia areata (AA) is a prevalent autoimmune disorder characterized by patchy hair loss and may be associated with medical comorbidities including atopy, thyroid, gastrointestinal, metabolic, and cardiovascular disease [1]. While AA is commonly thought to be a T-helper (Th)1 and cytotoxic T-cell-mediated nonscarring form of hair loss, it is often encountered in the presence of atopy.

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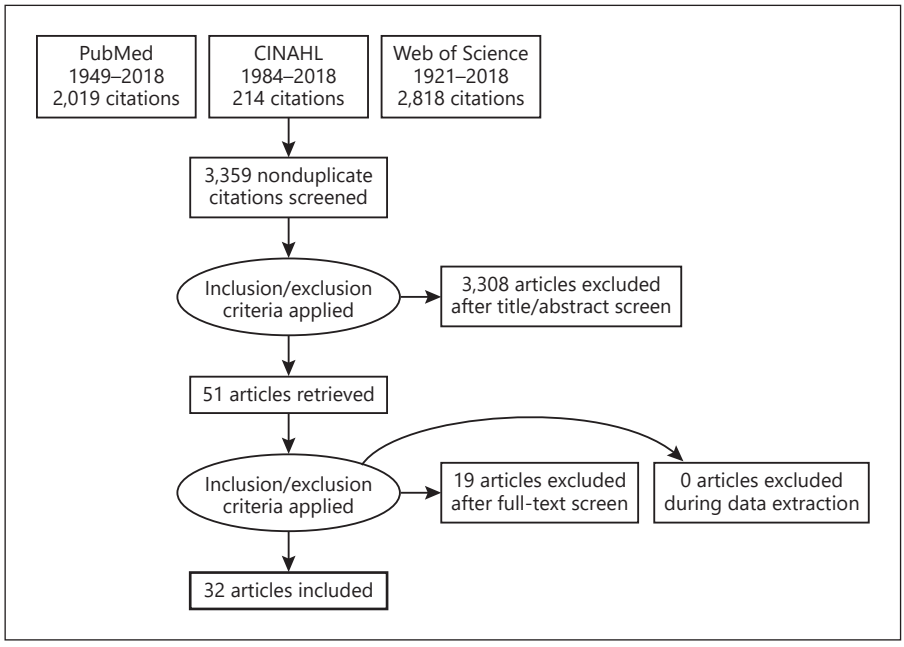

Fig. 1. PRISMA flow diagram for the literature review of AA and associated respiratory diseases.

Limited research is available to explain this immunological association with respiratory disease, including allergic rhinitis (AR) and asthma.

Conventionally, AA belongs to the Th1 axis of the adaptive immune system while atopy is a Th2-mediated process [2]. The overgeneralized underlying immunological relationship between AA and atopy calls for a revision of the traditional Th1/Th2 paradigm [3]. This review article seeks to analyze: (1) whether there is an association between AA and atopy (AR and asthma) and (2) concomitant hair loss in systemic diseases with respiratory involvement (e.g., sarcoidosis, connective tissue diseases, and systemic lupus erythematosus [SLE]). This manuscript will focus on extrapolating quantitative as well as qualitative information from pertinent studies and it will provide an immunological explanation for why AA may be significantly associated with certain respiratory diseases over others.

Materials and Methods

A primary literature search was conducted in May 2018 using the bibliographical databases PubMed/MEDLINE, CINAHL, and Web of Science with the following search terms: "(alopecia OR hair loss) AND (respiratory OR pulmonary OR lungs OR asthma OR rhinitis OR bronchitis OR COPD OR atopy OR atopic)" according to PRISMA reporting guidelines for systematic reviews [4]. All available studies prior to May 2018 were considered for inclusion. Given the clinical focus of this article, the inclusion criteria were: (1) relevant human studies on AA and its association with respiratory-related disease and (2) articles pertaining to systemic diseases with respiratory involvement and AA as a secondary manifestation. Exclusion criteria were: studies written in languages other than English, case reports, secondary articles (e.g., reviews), articles discussing atopy only in the context of eczema or atopic dermatitis (AD), and articles not pertaining to both AA and respiratory diseases. Case-control, cohort, case series, and cross-sectional studies were included. No randomized controlled trials were available. Studies included for review were graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence [5].

Results

A total of 51 nonduplicated article citations were reviewed in their entirety; 32 articles (Fig. 1) met the inclusion/exclusion criteria, with a total 17,623 patients (7,841 men and 9,782 women). Of these studies, 12 were case-control and 20 were cross-sectional (Table 1) [5].

Twenty-six (8 case-control and 18 cross-sectional) studies involved adult patients, while 6 focused on the pediatric population (4 case-control and 2 cross-sectional). Additionally, 9 studies (5 case-control and 4 cross-sectional) stratified patients based on the type of atopic respiratory disease (i.e., AR vs. asthma), and 7 studies (1 case-control and 6 cross-sectional) reported hair loss in patients with systemic disease with pulmonary manifes-

Table 1. Summary of the studies included in a systematic review of AA and respiratory disorders

Study	Type of study (evidence level)	Patients, *n*	Male/female ratio	Controls, *n*	Patient description	Prevalence of patients vs. controls (OR; 95% CI)
Prevalence of atopy in adult AA patients						
Sharma et al. [19]	Case-control (3)	808	532/276	572	North Indian patients with AA	18 vs. 20% (0.89; 0.67–1.16, $p = 0.39$)
Huang et al. [14]	Cross-sectional (4)	2,115	811/1,304		Boston, MA, USA, tertiary hospital AA patients	38.20%
Tan et al. [13]	Cross-sectional (4)	219	97/122		Singaporean patients with AA	27.8 (limited alopecia) vs. 32.9% (severe alopecia)
De Waard-van der Spek et al. [16]	Cross-sectional (4)	209	94/115		Dutch patients with AA	34%
Sukhjot et al. [2]	Cross-sectional (4)	100	76/24		North Indian patients with AA, aged >12 years	23%
De Weert et al. [15]	Cross-sectional (4)	100	66/34		Belgian patients with AA	22%
Late-Onset AA						
Lyakhovitsky et al. [17]	Cross-sectional (4)	29	4/25		Israeli patients with late-onset AA (onset age >50 years)	6.90%
Wu et al. [18]	Cross-sectional (4)	73	24/49		Northern Taiwan patients with late-onset AA (onset age >50 years)	0%
Prevalence of asthma and AR in adult AA patients						
Chu et al. [21]	Case-control (3)	4,334	2,123/2,211	784,158	Taiwanese patients with AA	Asthma: 5.7 vs. 5.6% (1.07; 0.93–1.22, p = 0.90) AR: 14.3 vs. 11.1% (1.29; 1.18–1.41, $p < 0.01$)
Barahmani et al. [28]	Case-control (3)	2,055	579/1,476	558	Patients from the National AA Registry	Asthma: 10.3 vs. 7.7% (1.36; 1.00–1.85, $p = 0.064$) AR: 18.7 vs. 14.2% (1.14; 0.90–1.44, $p = 0.013$) Atopy: 30.5 vs. 20.8% (1.22; 0.99–1.50, $p < 0.001$)
Magen et al. [27]	Case-control (3)	1,751	865/886	3,502	Israeli patients with AA	Asthma: 9.9 vs. 6.5% ($p < 0.001$) (1.57; 1.28–1.93, $p < 0.001$) AR: 24.3 vs. 12.9% ($p < 0.001$) (2.15; 1.85–2.49, $p < 0.001$)
Miller et al. [29]	Case-control (3)	584	184/400	172	Cleveland, OH, USA, tertiary hospital AA patients	Asthma: 13.5 vs. 8.14% (1.77; 0.97–3.20, $p = 0.06$) AR: 17.12 vs. 11.62% (1.57; 0.94–2.6, $p = 0.083$)
Ghaffari et al. [30]	Case-control (3)	50	37/13	150	Iranian patients aged <18 years with AA	Asthma: 22 vs. 12.5% ($p = 0.109$) (1.95; 0.85–4.43, $p = 0.11$) AR: 20–22 vs. 8–10% ($p = 0.046$) (2.64; 1.07–6.46, $p = 0.03$)
Ro. [12]	Cross-sectional (4)	905	512/393		Korean patients with AA	Pulmonary diseases: 3.8%
Shellow et al. [31]	Cross-sectional (4)	800	224/576		AA patients via Help Alopecia International Research (HAIR)	Asthma: 14.50% AR: 24.90%
Goh et al. [32]	Cross-sectional (4)	513	132/381		Patients in New York, NY, USA, with AA	Asthma: 23.11% AR: 25.10% Atopy: 46.41%
Cho et al. [20]	Cross-sectional (4)	287	154/133		Korean patients with alopecia totalis or alopecia universalis	Asthma: 1.34% AR: 9.40%
Prevalence of atopy in pediatric AA patients						
Nanda et al. [23]	Case-control (3)	215	62/153	100	Children (aged <12 years) in Kuwait with AA	20 vs. 34% (0.49; 0.29–0.83, $p = 0.008$)
Sharma et al. [19]	Case-control (3)	201	84/117	100	Children aged <16 years with AA	17.5 vs. 18% (0.96; 0.51–1.80, $p = 0.90$)
Kakourou et al. [24]	Case-control (3)	157	83/74	100	Children aged <16 years with AA	11.4 vs. 18% (p =0.14) (0.59; 0.29–1.20, $p = 0.14$)
Al-Khawajah [22]	Case-control (3)	92	45/ 47	88	Saudi Arabian patients with AA of different severities	13.04 vs. 1.14% ($p < 0.05$) (13.05; 1.66–102.65, $p = 0.015$)
Tan et al. [13]	Cross-sectional (4)	392	231/161		Singaporean children with AA diagnosed before age 16 years	26.60%
Alzolibani et al. [40]	Cross-sectional (4)	114	54/60		Pakistani children aged <15 years with AA	20%
Prevalence of atopy comparing adult and pediatric AA patients						
Serarslan et al. [25]	Case-control (3)	124	69/55	114	Turkish patients with AA; 43 children aged <18 years and 81 adults	Adults: 27.2%, children: 34.9% (total: 29.8%) vs. adults: 35.5%, children: 26.3% (total: 32.5%) (0.89; 0.51–1.53, $p = 0.66$)
Muller et al. [26]	Cross-sectional (4)	736	324/412		Patients in Rochester, NY, USA, with AA; 158 children aged <16 years and 578 adults	Adults: 18%, children: 9% (total: 11%)

Table 1 (continued)

Study	Type of study (evidence level)	Patients, *n*	Male/female ratio	Controls, *n*	Patient description	Prevalence of patients vs. controls (OR; 95% CI)
Prevalence of alopecia in patients with pulmonary disease						
Buechner et al. [56]	Case-control (3)	213	213/0	255	Hair patterns in patients with diffuse obstructive pulmonary emphysema	Diffuse obstructive pulmonary emphysema group: 41% fronto-coronal-occipital baldness, 41% frontal baldness, 18% complete baldness Control group: 22% fronto-coronal-occipital baldness, 50% frontal baldness, 28% complete baldness; the greatest number of severe emphysema patients was found in the group with pure frontal baldness, suggesting a greater susceptibility of noncoronally bald individuals to obstructive pulmonary diseases
Boddaert et al. [11]	Cross-sectional (4)	161	21/140		Pulmonary involvement and alopecia in French tertiary hospital SLE patients stratified by onset age	Late-onset SLE: 24% with alopecia, 21.2% with pulmonary involvement Early-onset SLE: 44% with alopecia and 11.3% with pulmonary involvement
Zhang et al. [10]	Cross-sectional (4)	108	88/20		Pulmonary involvement and alopecia in Chinese Han patients with SLE stratified based on the presence of ES	SLE patients with ES: 40.7% with alopecia, 25.9% with pulmonary involvement SLE patients without ES: 29.6% with alopecia, 16% with pulmonary involvement
Fiorentino et al. [9]	Cross-sectional (4)	77	26/51		Interstitial lung disease and alopecia in Stanford, CA, USA, tertiary hospital dermatomyositis patients	34% (22 patients) had alopecia and 25% (16 patients) had interstitial lung disease in addition to dermatomyositis
Prystowsky [8]	Cross-sectional (4)	46	7/39		Pulmonary involvement and alopecia in patients with high-titer serum antibody to ribonucleoprotein and mixed connective tissue disorder	46% with alopecia, 59% with pulmonary involvement
Mosam and Morar [7]	Cross-sectional (4)	30	5/25		Pulmonary involvement and alopecia in Black South African patients with cutaneous sarcoidosis	3.33% (1 patient) with alopecia and 10% (3 patients) with pulmonary involvement
Chong et al. [6]	Cross-sectional (4)	25	15/10		Pulmonary involvement and alopecia in Singaporean Asians with cutaneous sarcoidosis	4% (1 patient) with alopecia and 32% (8 patients) with pulmonary involvement

tations (e.g., sarcoidosis [6, 7], mixed connective tissue disease [MCTD] [8], dermatomyositis [DM] [9], SLE [10, 11], and emphysema) [12].

AA, Atopy and Asthma

Seven cross-sectional studies reported that the prevalence of both AA and personal history of atopy in adults ranges from 22 to 38% when confounding variables are considered [2, 13–18]. Results regarding the association of AA and atopy in adults is controversial, with some studies suggesting that patients with atopy also present more frequently with severe AA [2, 16] and other studies reporting a lack of an association between patients with AA and a personal history of atopy [13, 19].

Of note, a late age of AA onset (>50 years) is a major confounding variable associated with a significantly reduced prevalence of AA and atopy [17, 18, 20, 21]. For example, one cross-sectional study of Taiwanese late-onset AA patients ($n = 73$) reported no association with currently active disease or personal or family history of atopy [18], while another Israeli study ($n = 29$) reported a prevalence of atopy in 6.90% of late-onset AA patients [17], Interestingly, juvenile AA (<16 years) may be associated with a more severe disease course than that of patients with disease onset after 16 years of age [16].

Four case-control studies discussed atopy in the context of pediatric AA populations, with contradictory results. One study (92 AA patients and 88 control patients) reported a statistically significant positive association between AA and atopy ($p = 0.015$) [22], while another ($n = 215$) described a significant negative association ($p = 0.008$), with non-AA patients having a higher prevalence of atopy (34%) than AA patients (20%) [23]. However, 2 other studies failed to identify any significant relationship [19, 24].

In one case-control study, no significant differences were reported in the severity or pattern of AA between pediatric and adult patients based on personal or family history of atopy. In adults, 27.2% of AA patients had atopy compared to 35.5% of controls while 34.9% pediatric AA patients had atopy compared to 26.3% of controls. In addition, no statistically significant difference was identified in terms of disease duration between adult and pediatric AA patients [25]. Furthermore, one cross-sectional study reported that the prevalence of atopy and AA in the total population, adults, and children was 11, 18, and 9%,

respectively [26]. A Korean cross-sectional study identified a 3.8% prevalence of pulmonary disease among AA patients (n = 905), although the specific nature of pulmonary disease was unspecified [12].

A statistically significant association between asthma and hair loss was identified in one case-control study (3,806 AA patients and 4,060 control patients) [27]. The prevalence of asthma in hair loss patients ranged from 9.9 to 10.3%, compared to 6.5–7.7% for controls ($p \leq 0.001$–0.064) [27, 28]. No statistical association was identified in 4 other case-control studies (4,918 AA patients and 784,330 control patients) [21, 28–30]. The nationwide study of Chu et al. [21] derived from the Taiwanese National Insurance Registry identified a statistically significant association between AA and several autoimmune diseases including AD, AR, psoriasis, thyroid disease, vitiligo, SLE, and diabetes mellitus. However, there was no statistical association between AA and asthma; furthermore, no statistically significant differences were identified upon stratification between men and women [21]. The case-control study of Ghaffari et al. [30] (50 Iranians with AA and 150 control patients) described significant differences in both mean eosinophil levels (38% of the AA group had high eosinophils vs. 12% of controls; p = 0.004) and mean IgE levels (36% of the AA group vs. 15% of the controls; p = 0.046).

A significant association was found between family history of atopy and allergic disorders and AA, with 28% of AA patients reporting a positive family history compared to 4% of controls (p = 0.046) [21, 27–30]. Three cross-sectional studies regarding asthma and hair loss with a total 1,600 patients reported the prevalence of asthma among AA patients of 1.34–14.5%; however there was no reported association with early onset of AA or development of alopecia totalis or universalis [20, 31, 32].

AA and AR

Three case-control studies (6,135 AA patients and 787,810 controls) demonstrated a statistically significant associated between AR and hair loss, with a prevalence in AA patients ranging from 14.3 to 24.3% compared to 8–12.9% in controls ($p < 0.01$–0.05) [21, 27, 30]. However, 2 further case-control studies (2,639 AA patients and 730 controls) did not report a statistically significant association between AR and AA [29, 28]. Two cross-sectional studies (n = 2,915) reported a prevalence of AA and AR ranging from 24.9 to 38.2% [14, 31].

Alopecia and Pulmonary Disease

Six cross-sectional studies analyzed the association of sarcoidosis (n = 2), SLE (n = 2), MCTD (n = 1), and DM (n = 1) with AA. In 2 studies in Singaporean Asian and Black South African sarcoidosis patients (n = 55), 3.33–4% of patients had AA while 10–32% had sarcoid-associated pulmonary disease [6, 7]. Evans syndrome (ES) is a rare hematological manifestation of autoimmune hemolytic anemia or immune thrombocytopenia in the presence of SLE. Out of 108 patients with SLE, those with ES demonstrated a 40.7% prevalence of alopecia, while 25.9% had pulmonary disease, which represents an increase compared to those without ES (alopecia in 29.6% of patients and 16% with pulmonary disease) [10]. A further study of 161 SLE patients (114 with early onset, i.e., <50 years, and 47 with late onset, i.e., >50 years) reported that those with early-onset disease had a greater prevalence of alopecia (44%) compared to those with late-onset disease (24%), but they had less pulmonary disease (11.3% of early-onset patients compared to 21.2% of late-onset patients) [11]. Patients with MCTD (n = 46) have a high prevalence of alopecia and abnormal pulmonary function, including restrictive and diffusion defects (i.e., 46 and 59%, respectively) [8]. The reported prevalence of alopecia in DM patients (n = 77) is slightly lower (34%), while the prevalence of interstitial lung disease is significantly lower (25%) than that of MCTD [9].

Discussion

The strength of the association between AA and atopic respiratory disease varies. Case-control and cross-sectional studies report a much higher correlation between AA and AR than AA and asthma. However, based on the nature of these studies, evidence must be carefully interpreted. Nonetheless, the authors of this review postulate that AA, and hair loss in general, should be evaluated as a medical disease with the possibility of existing comorbidities. This hypothesis holds particularly true for diseases where hair loss precedes primary cutaneous, endocrine, immunological, infectious, oncologic, psychological, or other systemic manifestations [21].

Limited research exists linking alopecia to nonatopic respiratory disease. Patterns of alopecia have been associated with the severity of obstructive pulmonary disease, and multiple autoimmune diseases that manifest with pulmonary disease also demonstrate an association with AA including sarcoidosis, SLE, MCTD, and DM [6–11]. Immunologically, active MCTD, sarcoidosis, and SLE favor CD4+/interleukin (IL)-4/Th2 pathways, while AA is considered a Th1 disease state [33–35]. However, the Th1/Th2 paradigm alone may underscore the complexity

of the immune system, as Th17 cells have been demonstrated to suppress regulatory T cells, which is associated with SLE pathogenesis [36]. Thus, the Th1/Th2 paradigm used to describe the relationship between respiratory diseases and AA should be used as a reference point. Further research has shown that MCTD and sarcoidosis pathogenesis may involve a complex balance between Th1 and Th2 cells, which may explain their association with AA [3]. In SLE, the finding of increased alopecia and pulmonary involvement in younger patients may be better understood due to increased SLE severity compared to the elderly [11]. However, based on the current literature, no association can be extrapolated with regard to the relationship between alopecia and respiratory disease in sarcoidosis, SLE, MCTD, and DM.

The atopic triad conventionally alludes to the following 3 diseases associated with defects in the adaptive immune system: (1) AR, (2) AD, and (3) asthma [37]. While the current literature alludes to a casual association between AA and atopy, it should be noted that atopy is broadly defined as bronchial allergy, asthma, and AD. The symptoms of atopy decline with age, so many studies use a personal or family history of atopy, as opposed to current signs/symptoms of atopy, to account for a possible discrepancy in the time of presentation of atopy versus AA.

Atopy is also generally classified as a Th2-associated disease. This again raises an important discussion regarding the traditional Th1/Th2 disease paradigm and their mutual exclusivity, thus creating the erroneous conclusion that atopy and AA are also therefore mutually exclusive [3, 38]. While AR and asthma are both atopic diseases, their underlying immunological pathophysiology differs. Asthma has a relatively robust Th1-mediated response relative to the Th2-mediated AR. The conventional Th1/Th2 association thus fails to explain why AA, a Th1- mediated process, would be more closely associated with AR than asthma [39]. This supports the role of Th2/IL-4, in addition to Th1/IFNγ, in the pathogenesis of both AA and AR [40–47].

A history of atopy and allergic disease has been identified as factors increasing AA susceptibility [38]. A strong genetic links exists between AA and atopy (AR and asthma) through the IL-13 and KIAA0350/CLEC16A susceptibility loci which have been identified in AA, as well as other autoimmune diseases [27, 48]. Additionally, AA and atopy share a Th2 cytokine pattern with increased levels of IgE, antibodies, mast cells, and eosinophils [49, 50]. Notably, Th2/IL-4 stimulates IgE production and eosinophil activation indirectly by promoting IL-5 production [51]. The role of Th2 in AA may be further elucidated after experimental treatment with targeted therapies, in select individuals with concomitant atopy, with anti-Th2 (anti-IL-4/IL-13) therapies such as dupilumab, currently approved for AD and a possible novel therapy for asthma [52].

AA is associated with late-onset atopic diseases among adult patients with disease occurring between 21 and 60 years [21]. Late-onset AA is characterized by a marked female predominance, and disease severity is inversely proportional to age [17, 18], which is supported by the clinical consensus that young patients are often afflicted with a rapid disease progression, more extensive involvement, and a worse prognosis [53]. The association between AA and atopy among the pediatric population is controversial considering that an early disease onset often signifies a worse prognosis, while an increased age of onset is associated with a more mild disease course [16]. Children with AA and a family history of autoimmune disease usually present with a short (<6 month) episode of AA before the age of 5 years, and up to 60% will present of AA prior to 20 years of age [16, 24]. However, no significant difference was identified with regard to the severity, pattern, or duration of disease or gender between adult and pediatric patient groups [25], highlighting the robust underlying immunological association between AA and atopy.

Age of atopy onset and disease severity are independent factors whose association with AA should be explored further, in addition to the mere presence of atopy [54]. Stratification of atopy and AA prevalence by population demographics should also be undertaken given that the reported prevalence of atopy differs significantly depending on the patient population being studied, especially since atopy is more common in industrialized versus developing nations [2, 14, 16, 19, 55]. Of note, an increased frequency of AA is associated with more severe atopy [2–4].

Conclusions

Results regarding the association of AA with asthma are controversial; however, it is well-established that AA and AR occur more frequently together than AA and asthma. There is no established association between AA and systemic autoimmune disease involving the pulmonary system including sarcoidosis, SLE, MCTD, or DM.

Further research from an immunological standpoint is necessary to better understand the association between AA and respiratory diseases, as well as the other associated medical comorbidities beyond determining statistical significance. Elucidation of the involvement of Th2 cytokines in AA pathogenesis may even lead to the pos-

sibility of utilizing therapeutics specifically targeting IL-4/IL-13 pathways to temporarily treat patients with severe concomitant AA and atopy.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interests to declare.

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Author Contributions

The authors contributed equally to this paper.

References

1 Lee S, Lee H, Lee CH, Lee WS. Comorbidities in alopecia areata: A systematic review and meta-analysis. J Am Acad Dermatol. 2018 Jul;S0190-9622(18)32285-0.
2 Sukhjot S, Sharma VK, Kumar L, Kumar B. Atopy and alopecia areata in North Indians. Indian J Dermatol Venereol Leprol. 2001 Sep-Oct;67(5):231–3.
3 Romagnani S. The Th1/Th2 paradigm. Immunol Today. 1997 Jun;18(6):263–6.
4 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009 Jul;6(7):e1000100.
5 University of Oxford Center for Evidence-Based Medicine [Internet]. OCEBM Levels of Evidence [cited 2018 Jun 20]. Available from: https://www.cebm.net/2016/05/ocebm-levels-of-evidence/.
6 Chong WS, Tan HH, Tan SH. Cutaneous sarcoidosis in Asians: a report of 25 patients from Singapore. Clin Exp Dermatol. 2005 Mar;30(2):120–4.
7 Mosam A, Morar N. Recalcitrant cutaneous sarcoidosis: an evidence-based sequential approach. J Dermatolog Treat. 2004 Dec;15(6):353–9.
8 Prystowsky SD. Mixed connective tissue disease. West J Med. 1980 Apr;132(4):288–93.
9 Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. J Am Acad Dermatol. 2011 Jul;65(1):25–34.
10 Zhang L, Wu X, Wang L, Li J, Chen H, Zhao Y, et al. Clinical Features of Systemic Lupus Erythematosus Patients Complicated With Evans Syndrome: A Case-Control, Single Center Study. Medicine (Baltimore). 2016 Apr;95(15):e3279.
11 Boddaert J, Huong DL, Amoura Z, Wechsler B, Godeau P, Piette JC. Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. Medicine (Baltimore). 2004 Nov;83(6):348–59.
12 Ro BI. Alopecia areata in Korea (1982-1994). J Dermatol. 1995 Nov;22(11):858–64.
13 Tan E, Tay YK, Goh CL, Chin Giam Y. The pattern and profile of alopecia areata in Singapore – a study of 219 Asians. Int J Dermatol. 2002 Nov;41(11):748–53.
14 Huang KP, Mullangi S, Guo Y, Qureshi AA. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. JAMA Dermatol. 2013 Jul;149(7):789–94.
15 De Weert J, Temmerman L, Kint A. Alopecia areata: a clinical study. Dermatologica. 1984;168(5):224–9.
16 De Waard-van der Spek FB, Oranje AP, De Raeymaecker DM, Peereboom-Wynia JD. Juvenile versus maturity-onset alopecia areata – a comparative retrospective clinical study. Clin Exp Dermatol. 1989 Nov;14(6):429–33.
17 Lyakhovitsky A, Gilboa S, Eshkol A, Barzilai A, Baum S. Late-Onset Alopecia Areata: A Retrospective Cohort Study. Dermatology. 2017;233(4):289–94.
18 Wu MC, Yang CC, Tsai RY, Chen WC. Late-onset alopecia areata: a retrospective study of 73 patients from Taiwan. J Eur Acad Dermatol Venereol. 2013 Apr;27(4):468–72.
19 Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. Int J Dermatol. 1996 Jan;35(1):22–7.
20 Cho HH, Jo SJ, Paik SH, Jeon HC, Kim KH, Eun HC, et al. Clinical characteristics and prognostic factors in early-onset alopecia totalis and alopecia universalis. J Korean Med Sci. 2012 Jul;27(7):799–802.
21 Chu SY, Chen YJ, Tseng WC, Lin MW, Chen TJ, Hwang CY, et al. Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. J Am Acad Dermatol. 2011 Nov;65(5):949–56.
22 Al-Khawajah M. Alopecia areata and associated diseases in Saudi patients. Ann Saudi Med. 1991 Nov;11(6):651–4.
23 Nanda A, Al-Fouzan AS, Al-Hasawi F. Alopecia areata in children: a clinical profile. Pediatr Dermatol. 2002 Nov-Dec;19(6):482–5.
24 Kakourou T, Karachristou K, Chrousos G. A case series of alopecia areata in children: impact of personal and family history of stress and autoimmunity. J Eur Acad Dermatol Venereol. 2007 Mar;21(3):356–9.
25 Serarslan G, Savaş N, Yenin JZ. Is atopy and autoimmunity more prevalent in patients with alopecia areata? A comparative study. J Eur Acad Dermatol Venereol. 2012 Jun;26(6):720–3.
26 Muller SA, Winkelmann RK. Alopecia Areata. An Evaluation of 736 Patients. Arch Dermatol. 1963 Sep;88(3):290–7.
27 Magen E, Chikovani T, Waitman DA, Kahan NR. Association of alopecia areata with atopic dermatitis and chronic spontaneous urticaria. Allergy Asthma Proc. 2018 Mar;39(2):96–102.
28 Barahmani N, Schabath MB, Duvic M; National Alopecia Areata Registry. History of atopy or autoimmunity increases risk of alopecia areata. J Am Acad Dermatol. 2009 Oct;61(4):581–91.
29 Miller R, Conic RZ, Bergfeld W, Mesinkovska NA. Prevalence of Comorbid Conditions and Sun-Induced Skin Cancers in Patients with Alopecia Areata. J Investig Dermatol Symp Proc. 2015 Nov;17(2):61–2.

30 Ghaffari J, Rokni GR, Kazeminejad A, Abedi H. Association among Thyroid Dysfunction, Asthma, Allergic Rhinitis and Eczema in Children with Alopecia Areata. Open Access Maced J Med Sci. 2017 Jun;5(3):305–9.
31 Shellow WV, Edwards JE, Koo JY. Profile of alopecia areata: a questionnaire analysis of patient and family. Int J Dermatol. 1992 Mar; 31(3):186–9.
32 Goh C, Finkel M, Christos PJ, Sinha AA. Profile of 513 patients with alopecia areata: associations of disease subtypes with atopy, autoimmune disease and positive family history. J Eur Acad Dermatol Venereol. 2006 Oct;20(9): 1055–60.
33 Bodolay E, Aleksza M, Antal-Szalmás P, Végh J, Szodoray P, Soltész P, et al. Serum cytokine levels and type 1 and type 2 intracellular T cell cytokine profiles in mixed connective tissue disease. J Rheumatol. 2002 Oct;29(10):2136–42.
34 Inui N, Chida K, Suda T, Nakamura H. TH1/TH2 and TC1/TC2 profiles in peripheral blood and bronchoalveolar lavage fluid cells in pulmonary sarcoidosis. J Allergy Clin Immunol. 2001 Feb;107(2):337–44.
35 Chen S, Hu D, Shi X, Shen N, Gu Y, Bao C. The relationship between Th1/Th2-type cells and disease activity in patients with systemic lupus erythematosus. Chin Med J (Engl). 2000 Oct;113(10):877–80.
36 Chen M, Chen X, Wan Q. Altered frequency of Th17 and Treg cells in new-onset SLE patients. Eur J Clin Invest. 2018;48(11):e13012.
37 Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. Allergy Asthma Immunol Res. 2011 Apr;3(2):67–73.
38 Barahmani N, Lopez A, Babu D, Hernandez M, Donley SE, Duvic M. Serum T helper 1 cytokine levels are greater in patients with alopecia areata regardless of severity or atopy. Clin Exp Dermatol. 2010 Jun;35(4):409–16.
39 Rogala B, Bozek A, Gluck J, Jarzab J. Prevalence of IgE-mediated allergy and evaluation of Th1/Th2 cytokine profiles in patients with severe bronchial asthma. Postepy Dermatol Alergol. 2015 Aug;32(4):274–80.
40 Alzolibani AA, Al Robaee AA, Al Shobaili HA, Bin Saif G, Al-Saif F, Ali A, et al. Interleukin-4 -590 T[{GT}]C and interleukin-4 receptor Q551R A[{GT}]G gene polymorphisms in Saudi cases with alopecia areata. J Egypt Public Health Assoc. 2015 Mar;90(1): 20–3.
41 Song T, Pavel AB, Wen HC, Malik K, Estrada Y, Gonzalez J, et al. An integrated model of alopecia areata biomarkers highlights both Th1/Th2 up-regulation. J Allergy Clin Immunol. 2018;142(5):1631–4.
42 Czarnowicki T, He HY, Wen HC, Hashim PW, Nia JK, Malik K, et al. Alopecia areata is characterized by expansion of circulating Th2/Tc2/Th22, within the skin-homing and systemic T-cell populations. Allergy. 2018 Mar;73(3):713–23.
43 Ma X, Chen S, Jin W, Gao Y. Th1/Th2 PB balance and CD200 expression of patients with active severe alopecia areata. Exp Ther Med. 2017 Jun;13(6):2883–7.
44 Renert-Yuval Y, Guttman-Yassky E. The Changing Landscape of Alopecia Areata: The Therapeutic Paradigm. Adv Ther. 2017 Jul; 34(7):1594–609.
45 Renert-Yuval Y, Guttman-Yassky E. A novel therapeutic paradigm for patients with extensive alopecia areata. Expert Opin Biol Ther. 2016 Aug;16(8):1005–14.
46 Sadeghi S, Sanati MH, Taghizadeh M, Mansouri P, Jadali Z. Study of Th1/Th2 balance in peripheral blood mononuclear cells of patients with alopecia areata. Acta Microbiol Immunol Hung. 2015 Sep;62(3):275–85.
47 Suárez-Fariñas M, Ungar B, Noda S, Shroff A, Mansouri Y, Fuentes-Duculan J, et al. Alopecia areata profiling shows TH1, TH2, and IL-23 cytokine activation without parallel TH17/TH22 skewing. J Allergy Clin Immunol. 2015 Nov;136(5):1277–87.
48 Jagielska D, Redler S, Brockschmidt FF, Herold C, Pasternack SM, Garcia Bartels N, et al. Follow-up study of the first genome-wide association scan in alopecia areata: IL13 and KIAA0350 as susceptibility loci supported with genome-wide significance. J Invest Dermatol. 2012 Sep;132(9):2192–7.
49 Elston DM, McCollough ML, Bergfeld WF, Liranzo MO, Heibel M. Eosinophils in fibrous tracts and near hair bulbs: a helpful diagnostic feature of alopecia areata. J Am Acad Dermatol. 1997 Jul;37(1):101–6.
50 McElwee KJ, Hoffmann R. Alopecia areata – animal models. Clin Exp Dermatol. 2002 Jul; 27(5):410–7.
51 Nakajima H, Iwamoto I, Tomoe S, Matsumura R, Tomioka H, Takatsu K, et al. CD4+ T-lymphocytes and interleukin-5 mediate antigen-induced eosinophil infiltration into the mouse trachea. Am Rev Respir Dis. 1992 Aug; 146(2):374–7.
52 Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018 Jun; 378(26):2486–96.
53 Uchiyama M, Egusa C, Hobo A, Irisawa R, Yamazaki M, Tsuboi R. Multivariate analysis of prognostic factors in patients with rapidly progressive alopecia areata. J Am Acad Dermatol. 2012 Dec;67(6):1163–73.
54 Kaur S, Sharma VK, Kumar L, Kumar B. Atopy and alopecia areata in North Indians. Indian J Dermatol Venereol Leprol. 2002 Sep-Oct;68(5):267–9.
55 Thomsen SF. Epidemiology and natural history of atopic diseases. Eur Clin Respir J. 2015 Mar;24:2.
56 Buechner HA, Brown M, Tretola RJ. Baldness and emphysema. J La State Med Soc. 1964 Sep; 116:329–32.