Atopic diseases and the risk of alopecia areata among pre-teens and teenagers in Taiwan

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Abstract

Background: Alopecia areata (AA), a disorder of non-scarring hair loss with a variable relapsing and remitting course, is a common autoimmune disease in children. Although it often presents as several focal small patchy bald lesions, early onset AA can lead to a total loss of scalp hair, even body hairs, a severe subtype. Atopic diseases are common concurrent disorders in AA, especially among those with early onset severe type of hair loss. Whether atopic diseases increase the risk of AA in the paediatric population of Taiwan, remains unclear.

Objective: To identify if atopic diseases increase the risk of AA among pre-teens and teenagers in Taiwan.

Methods: From Taiwan National Health Insurance Database 2010, we used the claims data to clarify the risk of AA in pre-teens and teenagers with atopic diseases (atopic dermatitis, allergic conjunctivitis, asthma, allergic rhinitis and food allergy) as compared to the general population. Cox proportional hazards model yielded hazard ratios (HRs) to address the impact of atopic diseases, sex and age on AA risk after adjusting for covariates and subsequent stratified analyses.

Results: Overall, 21,070 children (10,535 patients with atopic diseases and 10,535 normal cohort) aged over nine years were recruited. During a follow-up of 15 years, 39 (0.37%) cases were identified to have AA in the atopic diseases group, while 11 (0.10%) had developed AA in the normal cohort. As compared with the normal population, the paediatric population with atopic diseases had a 9.66-fold higher risk of developing AA. The risk was greater for boys and increased with advanced age. In the atopic diseases group, pre-teens and teenagers with food allergies and Sjogren's syndrome were more likely to have AA.

Limitations: Only one ethnic group.

Conclusion: All atopic diseases enhanced the risk of developing AA in Taiwan pre-teens and teenagers. Children with atopic diseases should be monitored to look for the development of AA.

Key words: Alopecia areata, atopic diseases, cohort, risk

Introduction

As a common non-scarring disorder of hair loss, alopecia areata (AA) carries a lifetime risk of approximately 2.1%.[1,2] AA is a polygenic, complex, immune-mediated disease occurring due to the lack of immune privilege of the hair follicle.[3] AA often manifests as a sudden onset of several

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oval patchy bald lesions in the hair-bearing area and has an unpredictable course with frequent remissions and relapses. No curable therapy exists for AA, and most treatments have variable or poor efficacy.[4] Early onset AA may have severe course, with total hair loss on the scalp (alopecia totalis, AT) or all body hair loss (alopecia universalis, AU) with frequent recurrences and chronic course.[5] Paediatric patients are particularly susceptible to adverse psychosocial outcomes.[2] AA is often associated with thyroid disease, vitiligo, lupus erythematous, psoriasis and other autoimmune diseases.[6,7] Familial autoimmunity is usually associated with poor outcome.[8,9]

An immunoglobulin (Ig) E-mediated type I hypersensitivity reaction is termed as atopy. Atopic diseases have a high prevalence, with approximately 20% of the population involved worldwide. Childhood atopic diseases include atopic dermatitis, allergic conjunctivitis, asthma, allergic rhinitis, and food allergy, the symptoms of which occur in the skin, eye, respiratory, and gastrointestinal tract.[10] These atopic diseases share similar immunological responses and are closely related throughout life, with temporal progression as atopic march. Previous studies have suggested that patients with atopic diseases often have AA.[11] Israeli AA patients have a higher prevalence of food allergy (odds ratio [OR] = 2.79), allergic rhinitis (OR = 2.15), asthma (OR = 1.57) and atopic dermatitis (OR = 4.17)[12], reflecting the association of AA with atopic comorbidities. In addition, a US cohort study reported that people with atopic diseases tend to have a twofold risk of AA.[9] Comorbid atopic diseases and high IgE levels were considered poor prognostic factors of AA.[13]

Since early-onset AA has comorbid allergic diseases and whether atopic diseases increase the risk of AA in Taiwan paediatrics remains unclear, we aimed to conduct a large-scale population-based study to estimate the risk of AA in Taiwan pre-teens and teenagers with atopic diseases.

Methods

Data source

Taiwan national healthcare system established the National Health Insurance Research Database (NHIRD), a large-scale, population-based database. The database covered more than 99% of residents in Taiwan and contained all beneficiaries' records for medical services and enrolment data. We utilised the NHIRD Longitudinal Health Insurance Database (LHID) 2010 coded by ICD-9-CM in the study, which represented one million insurance beneficiaries randomly sampled from NHIRD in 2010. The study was performed according to the Declaration of Helsinki guidelines and approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB No. 202300974B0). Since all data from NHIRD were deidentified and personal information traced was anonymised before data analysis, informed consent was not required to perform analysis.

Ascertainment of patients

After excluding the missing data from the LHID 2010 database and to estimate the risk of AA in Taiwan pre-teens and teenagers with atopic diseases, 10,535 patients aged between 9 years and 18 years with atopic diseases (one of following diseases including atopic dermatitis [ICD-9-CM code 691.8], allergic conjunctivitis [ICD-9-CM codes 372.05, 372.10, 372.14], asthma [ICD-9-CM code 493], allergic rhinitis [ICD-9-CM code 477], and food allergy [ICD-9-CM code 693.1]) during 1996–2010 were recruited in the experiment. Only the diagnoses of atopic disease confirmed by a dermatologist at more than three outpatient/inpatient attendances were identified. The date of the first clinical diagnosis for atopic diseases was established as the index date. For each patient with atopic diseases, one non-atopic disease normal control (referring to one who didn't suffer from any atopic diseases mentioned earlier) was pair-wise matched by sex and age. A total of 10,535 normal cohorts were recruited. Both cohorts were followed up from the index date to the date of diagnosis of AA (ICD-9-CM code 704.01) confirmed by a dermatologist at more than three outpatient/inpatient attendances or at the end of 2010 during the follow-up of 15 years.

Assessment of comorbidities and confounders

Besides demographic characteristics (sex and age), potential comorbidities and confounders such as atopic dermatitis (ICD-9-CM code 691.8), allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10, 372.14), asthma (ICD-9-CM code 493), allergic rhinitis (ICD-9-CM 477), food allergy (ICD-9-CM code 693.1), vitiligo (ICD-9-CM code 709.01), autoimmune thyroid disease (ICD-9-CM codes 244, 244.9, 245.2), lupus erythematosus (ICD-9-CM codes 695.4, 711), psoriasis (ICD-9-CM code 696.1) and Sjogren's syndrome (ICD-9-CM code 710) were included in the experiment, since they may influence the development of AA.

Statistical analysis

To match each atopic diseases cohort with age, age group and sex, a propensity analysis through logistic regression to obtain a five-digit match of the propensity score was conducted. The Student *t*-test and $\chi 2$ tests were used to compare the distribution of demographic characteristics between the atopic diseases cohort and the normal cohort. Wilcoxon rank-sum test was employed in comparing the period of developing AA between the atopic diseases cohort and the normal cohort. Based on the verified assumption by score process (Kolmogorov-type Supremum test, $p = 0.9110$), the primary objective was to assess the AA incidence densities for both cohorts as per 1000 person-years and the hazard ratios (HRs) and their 95% confidence intervals (CIs) of AA using Cox proportional hazards models after adjusting for covariates (age, age groups, sex and related comorbidities such as vitiligo, autoimmune thyroid disease, lupus erythematosus, psoriasis and Sjogren's syndrome). The second objective was to address the impact of sex and age on AA risk by arranging

subsequent stratified analyses. The SAS statistical software (Version 9.4) was used to calculate all statistical analyses in which the statistical significance level was established at 0.05.

Results

Demographic profile and comorbidities of atopic disease cohort and normal cohort

Over the study period, 10,535 patients aged more than nine years diagnosed with atopic diseases were matched to 10,535 patients identified as the control group. Age (mean 13) and sex (62.27% girls) were distributed similarly in both groups [Table 1]. More pre-teens and teenagers with atopic diseases had psoriasis (0.63 vs 0.29, $p = 0.0004$), Sjogren's syndrome (2.97 vs 0.22, $p < 0.0001$) and autoimmune thyroid diseases (0.93 vs 0.19, $p < 0.0001$).

Atopic disease cohort pre-teens and teenagers have an increased risk to develop AA

The occurrence of AA was significantly higher in the pre-teens and teenagers with atopic diseases (0.37 %, $n = 39$) than in the normal cohort (0.10 %, $n = 11$). Also, pre-teens and teenagers with atopic diseases were prone to have AA faster (5.7 years after recruitment) than the normal cohort (10.9 years after recruitment) [Table 1].

During a follow-up of 15 years, pre-teens and teenagers with atopic diseases had a 9.66-fold higher risk of having AA (0.41 vs. 0.07 per 1000 person-years, separately) after adjustment for covariates. The statistical power reached above 99% with an incident AA event of 39 out of 10,535 (0.37%) versus 11 out of 10,535 (0.10%) to detect a HR of 9.66. The stratified analysis also showed that pre-teens and teenagers with atopic diseases had a higher risk of having AA. In the sex-specific analyses of atopic diseases in pre-teens and teenagers, the AA incidence was higher in girls than that of boys (0.46 vs 0.34 per 1000 person-years, separately); besides, the impact of atopic diseases on AA risk in pre-teens and teenagers was larger in boys than that in girls (adjusted HR = 15.16, 95% CI = 1.98–116.10 for boys; adjusted HR = 8.67, 95% CI = 3.39–22.16 for girls). In the age-specific analysis of atopic diseases in pre-teens and teenagers, AA incidence increased with age. The impact of atopic diseases on AA risk was larger in older aged teenagers (adjusted HR = 12.10, 95% CI = 3.13–46.79) than that in younger aged pre-teens (adjusted HR = 6.66, 95% CI = 2.09–21.20) [Table 2].

The impact of different atopic diseases on the risk of AA

In a comorbidities-specific analysis of atopic diseases in pre-teens and teenagers, AA incidence increased with food allergy, atopic dermatitis, asthma and allergic rhinitis, not allergic conjunctivitis [Table 3].

Table 1: The development of AA events, demographic profiles and comorbidities between atopic diseases cohort and normal cohort.

Variables	Atopic diseases cohort (n = 10,535)	Normal cohort (n = 10,535)	*P* value
AA patients, n (%)	39 (0.37)	11 (0.10)	<0.0001[a]
Period of developing AA, median, IQR (years)	5.7 (3.7-9.1)	10.9 (6-13.9)	<0.0001[b]
Age of AA onset, SD (years)	13.6 (2.8)	16.9 (2.9)	<0.0001
Age, SD (years)	13.0 (2.7)	13.0 (2.7)	1.0000
Age groups, n (%)			1.0000
9–12 years	4693 (44.55)	4693 (44.55)	
12–15 years	2922 (27.74)	2922 (27.74)	
15–18 years	2920 (27.72)	2920 (27.72)	
Sex, n (%)			1.0000
Boys	3922 (37.23)	3922 (37.23)	
Girls	6613 (62.27)	6613 (62.27)	
Comorbidities, n (%)			
Lupus erythematosus	10 (0.09)	17 (0.16)	0.1777
Psoriasis	66 (0.63)	31 (0.29)	0.0004
Sjogren's syndrome	313 (2.97)	23 (0.22)	<0.0001
Vitiligo	15 (0.14)	12 (0.11)	0.5635
Autoimmune thyroid disease	98 (0.93)	20 (0.19)	<0.0001
Food allergy	60 (0.60)	0	<0.0001
Atopic dermatitis	1370 (13.00)	0	<0.0001
Asthma	1634 (15.51)	0	<0.0001
Allergic rhinitis	6426 (61.00)	0	<0.0001
Allergic conjunctivitis	10,482 (99.50)	0	<0.0001

SD: Standard deviation, IQR: Interquartile range, [a] $\chi 2$-value = 15.7173, $\chi 2$ tests, [b] Z-value = 134.224, Wilcoxon rank-sum test

Table 2: Stratified analysis of AA events between atopic diseases cohort and the normal cohort.

Variables	Atopic diseases cohort			Normal cohort			Compared to atopic diseases cohort	
	AA (n)	PY	Rate (95%)	AA (n)	PY	Rate (95%)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
All	39	94,239.60	0.41(0.41-0.42)	11	157,943.88	0.07 (0.07-0.07)	10.07 (4.38-23.16)*	**9.66 (4.18–22.39)***
Sex								
Boys	12	35,257.02	0.34 (0.33-0.34)	2	58,813.50	0.03 (0.03-0.03)	15.67 (2.08-118.01)*	**15.16 (1.98–116.10)***
Girls	27	58,982.58	0.46 (0.45-0.46)	9	99,130.38	0.09 (0.09-0.09)	9.12 (3.59-23.17)*	**8.67 (3.39–22.16)***
Age group								
9–12 years	12	41,714.24	0.29 (0.28–0.29)	5	70,358.74	0.07 (0.07–0.07)	6.89 (2.17–21.92)*	**6.66 (2.09–21.20)***
12–15 years	13	26,000.80	0.50 (0.49–0.51)	3	43,809.43	0.07 (0.07–0.07)	12.40 (3.22–47.86)*	**11.78 (3.04–45.64)***
15–18 years	14	26,524.56	0.53 (0.52–0.53)	3	43,775.70	0.07 (0.07–0.07)	13.00 (3.39–49.81)*	**12.10 (3.13–46.79)***

CI: Confidence interval, HR, Hazard ratio, PY, Person-year, Rate, the incidence rate in per 1000 person-years. *, $P < 0.05$.
[a] Model adjusted for relevant diseases (vitiligo, autoimmune thyroid disease, lupus erythematosus, psoriasis and Sjogren's syndrome).

Table 3: Stratified analysis of AA events in atopic diseases cohort by different type of atopic diseases

Comorbidities	AA (n)	PY	Rate (95%)	Adjusted HR[a] (95% CI)
Food allergy				
No	36	156,909.29	0.23 (0.22–0.23)	Reference
Yes	3	404.87	7.41 (6.72–8.17)	**15.16 (4.61–49.81)***
Atopic dermatitis				
No	33	137,316.96	0.24 (0.23–0.24)	Reference
Yes	6	8558.67	0.70 (0.69–0.72)	**3.86 (1.27–11.72)***
Asthma				
No	33	133,364.82	0.25 (0.24–0.26)	Reference
Yes	6	12,754.33	0.47 (0.46–0.48)	**3.09 (1.14–8.39)***
Allergic rhinitis				
No	15	59,762.93	0.25 (0.24–0.25)	Reference
Yes	24	86,356.21	0.28 (0.28–0.29)	**3.37 (1.47–7.69)***
Allergic conjunctivitis				
No	1	785.38	1.27 (1.19–1.37)	Reference
Yes	38	86,424.56	0.44 (0.43–0.44)	**0.44 (0.05–3.83)**

CI: Confidence interval, HR: Hazard ratio, PY: Person-year, Rate, incidence rate in per 1000 person–years. *, $P < 0.05$. [a] Model adjusted for age, sex and relevant diseases (vitiligo, autoimmune thyroid disease, lupus erythematosus, psoriasis and Sjogren's syndrome).

Table 4: Significant predictors of AA after atopic diseases diagnosis in pre-teens and teenagers

Variables	Adjusted HR[a] (95% CI)	*P*-value
Food allergy	11.986 (3.680–39.036)	<0.0001
Sjogren's syndrome	3.059 (1.084–8.639)	0.0347

CI: Confidence interval, HR: Hazard ratio. [a] The adjusted HR and 95% CI were assessed using a backward elimination method; model adjusted for age, sex and relevant diseases (atopic dermatitis, allergic conjunctivitis, asthma, allergic rhinitis, food allergy, vitiligo, autoimmune thyroid disease, lupus erythematosus, psoriasis and Sjogren's syndrome).

Predictor of AA in atopic diseases

In pre-teens and teenagers with atopic diseases, those with concomitant d food allergy (p <0.0001) or Sjogren's syndrome (p = 0.0374) had significantly higher risk of AA, after excluding other covariates (vitiligo, p = 0.9975; lupus erythematosus, p = 0.9970; psoriasis, p = 0.9944; autoimmune thyroid disease, p = 0.9890; atopic dermatitis, p = 0.8153; asthma, p = 0.5577; allergic rhinitis, p = 0.3928; allergic conjunctivitis, p = 0.1261) [Table 4].

Discussion

In this research, we observed that pre-teens (9–12 years) and teenagers (12–18 years) with atopic diseases were prone to develop AA. AA developed in 0.37% of patients with atopic diseases and only 0.10% of normal cohorts. As compared with the normal population, pre-teens and teenagers with atopic diseases had a 9.66-fold higher risk of having alopecia. This is the first large-scale research to elucidate the association between atopic diseases and AA in pre-teens and teenagers. The impact of atopic disease increased with advancing age and was more in boys. In the atopic diseases group, pre-teens and teenagers with concomitant food allergy or Sjogren's syndrome were more likely to have AA.

The possible causes underlying the association between atopic diseases and AA are multifactorial. Both atopic diseases and AA have similar immune dysregulation. AA is a well-known aberrant T-cell-mediated disorder directed against targeting hair follicles[14] and is traditionally considered a TH1 disease. However, recent studies show that high TH2 profiles are detected in blood and scalp specimens of AA patients.[15] Besides, some AA patients have increased IgE levels, even in the absence of associated atopic diseases. [16] Dupilumab, a newly IL-4R inhibitor against TH2 signals, improved the clinical severity of AA coupled with suppression of cell infiltrates around a hair follicle and changes of transcriptomes towards those of non-lesional scalp, which was pronounced in atopic AA patients.[17] Moreover, circulating Treg cells cannot maintain normal function[18] while infiltrates of TH17 cells activate the surrounding hair follicle, leading to an imbalance between TH17 cells and Treg cells in AA patients. The Janus Kinase-signal transducer and activator of transcription (JAK-STAT) family is also enhanced in AA patients.[19] After three- to five-month use of JAK inhibitors, hair regrowth developed with decreased perifollicular infiltrates and inflammation.[20] Atopic diseases are also regarded as biphasic T-cell-medicated diseases.[21] During acute phases, atopic diseases initiate TH2 inflammatory responses triggered by an allergen, which produces IL-4, IL-13 cytokines, high IgE and

eosinophil.[22] TH1 response and Treg/TH17 imbalance lead to sustained inflammatory reactions in atopic diseases.[23,24] These cytokines promote T cell infiltrates surrounding hair follicles, skin, conjunctiva, airway and intestinal epithelium, and in turn, stimulate inflammation and hair loss. Allergy may also trigger local immune reaction around hair follicles.[25]

A recent study proposed that atopy and AA have genetic susceptibility in common. Since family history has a significant impact on the development of AA, numerous genomic regions, and human leukocyte antigen (HLA) regions that are high risk for AA were identified. The larger the area of scalp involvement, the higher the genomic dysregulation. Jagielska *et al.* identified that IL-13 was the susceptibility gene in AA patients through the genome-wide association study (GWAS).[26] Betz RC, *et al.* reported that some single nucleotide polymorphisms (SNPs) involving the IL-4 and JAK-STAT signalling pathway occur in AA.[27] Suarez-Farinas *et al.* showed that AA has signatures of both TH1 (*IFNG, CXCL10/CXCL9*) and TH2 cytokines (*thymic stromal lymphopoietin [TSLP], CCL26, CCL18, IL13* and *periostin*) signature. Transcriptomes related to T-cell activation (*JAK1/3*) and general inflammation (*phosphodiesterase 4B, PDE4B*) are highly expressed in AA and atopic dermatitis.[28] In addition, mutation of filaggrin genes is seen to be involved in both atopic dermatitis and AA.[29] These genes might stop follicular regeneration and maturation in AA and create a barrier defect by suppressing epidermal differentiation.[30] In our research, the impact of atopic diseases on AA risk was larger among older teenagers than in pre-teens, suggesting that the high genetic susceptibility significantly contributed to the development of AA in atopic diseases teenagers who had longer and protracted courses.

In our research, food allergy in the atopic diseases cohort was a high-risk predictor of developing AA compared to the non-food allergy group. In a Taiwan adolescent cohort study, patients with food allergies were prone to have atopic dermatitis (HR = 2.49). The food allergen may possibly initiate allergen sensitization in the gut, triggering sequential inflammation in the skin.[31] In atopic diseases, atopic dermatitis is regarded as a causative initiator in the atopic march. Therefore, food allergy might induce a series of inflammatory cascades in atopic diseases, further enhancing perifollicular inflammation in AA.

In addition, the presence of concomitant Sjogren's syndrome in the atopic diseases cohort had a higher risk of developing AA as compared to those without Sjogren's syndrome. Sjogren's syndrome is a chronic disease with lymphocytic infiltrate into exocrine glands, and alopecia is common among patients with Sjogren's syndrome.[32] In Sjogren's syndrome, interferon-γ, IL-1β and high-mobility group box 1 protein (HMGB1) can serve as an alarmin to promote inflammation.[33] Activated HMGB1 also mediates cellular response to release proinflammatory cytokines in AA.[34] Thus, chronic inflammation can trigger autoimmunity in Sjogren's syndrome and AA through the release of HMGB1.

One of the powerful strengths is that this was a large-scale longitudinal study, including reliable diagnoses of atopic diseases and AA made by appropriate specialists.[35] Besides, it enabled us to determine the temporal relationship between AA and atopic diseases. Our findings were not only consistent with the previous data, which revealed that AA easily occurs in atopic dermatitis patients,[9] but also offered more information regarding the effect of allergic conjunctivitis, asthma, allergic rhinitis and food allergy on AA, which was not spotlighted before.

Limitations

However, some limitations in the experiment also need to be addressed. First, incidences of AA and atopic diseases may be miscalculated since only those who sought help were included in the study. The small sample size of the identified AA cases might introduce a potential bias, which might be mitigated by conducting a large-scale longitudinal experiment. Second, the family history, degree of severity of AA and atopic diseases cannot be identified. Also, laboratory data such as IgE level or specific IgE were not available; thus, the association between disease severity or IgE level could not be evaluated. As this study included only Taiwanese residents, the findings cannot be extrapolated to other ethnic populations, and global studies are required.

Conclusion

Taken together, all atopic diseases can enhance the risk of developing AA in Taiwanese pre-teens and teenagers. All pre-teens and teenagers with atopic diseases should be closely monitored for the development of non-scaring alopecia, which might help in early intervention.

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Ethical approval: The research/study was approved by the Institutional Review Board at Chang Gung Medical Foundation, number 202300974B0, dated 20230715.

Declaration of patient consent: The data used was anonymised, therefore informed patient consent was not required.

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