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Autoimmune, Atopic, and Mental Health Comorbid Conditions Associated With Alopecia Areata in the United States

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Objective: To evaluate the prevalence of comorbid conditions among patients with alopecia areata (AA) seen at tertiary care hospitals in Boston, Massachusetts, during an 11-year period.

Design: Retrospective cross-sectional study.

Setting: Tertiary care hospitals in Boston, including Brigham and Women's Hospital and Massachusetts General Hospital.

Participants: We identified 3568 individuals with AA seen in the Partners health care system in Boston between January 1, 2000, and January 1, 2011. We performed comprehensive searches of the Research Patient Data Repository using *International Classification of Diseases, Ninth Revision* code 704.01. We randomly selected 350 patients and manually reviewed their medical records to train and validate a novel artificial intelligence program. This program then used natural language processing to review free-text medical records and confirm a diagnosis of AA. To confirm the algorithm, we manually reviewed a subset of records and found 93.9% validity.

Main Outcomes and Measures: The prevalence of comorbid conditions was assessed.

Results: Common comorbid conditions included autoimmune diagnoses (thyroid disease in 14.6%, diabetes mellitus in 11.1%, inflammatory bowel disease in 6.3%, systemic lupus erythematosus in 4.3%, rheumatoid arthritis in 3.9%, and psoriasis and psoriatic arthritis in 2.0%), atopy (allergic rhinitis, asthma, and/or eczema in 38.2% and contact dermatitis and other eczema in 35.9%), and mental health problems (depression or anxiety in 25.5%). We also found high prevalences of hyperlipidemia (24.5%), hypertension (21.9%), and gastroesophageal reflux disease (17.3%). This profile was different from that seen in a comparison psoriasis and psoriatic arthritis group.

Conclusions and Relevance: We found a high prevalence of comorbid conditions among individuals with AA presenting to academic medical centers in Boston. Physicians caring for patients with AA should consider screening for comorbid conditions.

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ALOPECIA AREATA (AA) IS AN autoimmune disease that presents with nonscarring hair loss from some or all hair-bearing areas of the body, typically the scalp. Its reported prevalence in the United States is in the 0.1% to 0.2% range, but it can be as high as 0.7% to 3.8% in dermatology patients.^{1,2} It has a tremendous effect on patients' quality of life, but characterization of the patients affected by it has been limited.

Hypotheses regarding the pathogenesis of AA include a lymphocyte-mediated inflammation that suggests an underlying autoimmune etiology, an association with HLA class II antigen alleles, and contribution from environmental factors such as hormonal fluctua-

tion, infectious agents, vaccinations, and stress.^{1,3-18} Common treatment modalities include intralesional steroids and topical immunosuppressants.^{13,19-23}

See Invited Commentary

Alopecia areata has been reported to be associated with multiple comorbid conditions, including vitiligo, lupus erythematosus, psoriasis, atopy, thyroid disease, and mental health problems.^{1,3,5,12,13,24-31} Most of these studies are limited by small population size, homogeneous populations, or patient self-reported data. In this study, we used a novel algorithm to collate data on disease associations in a large retrospective patient cohort, allowing us to compre-

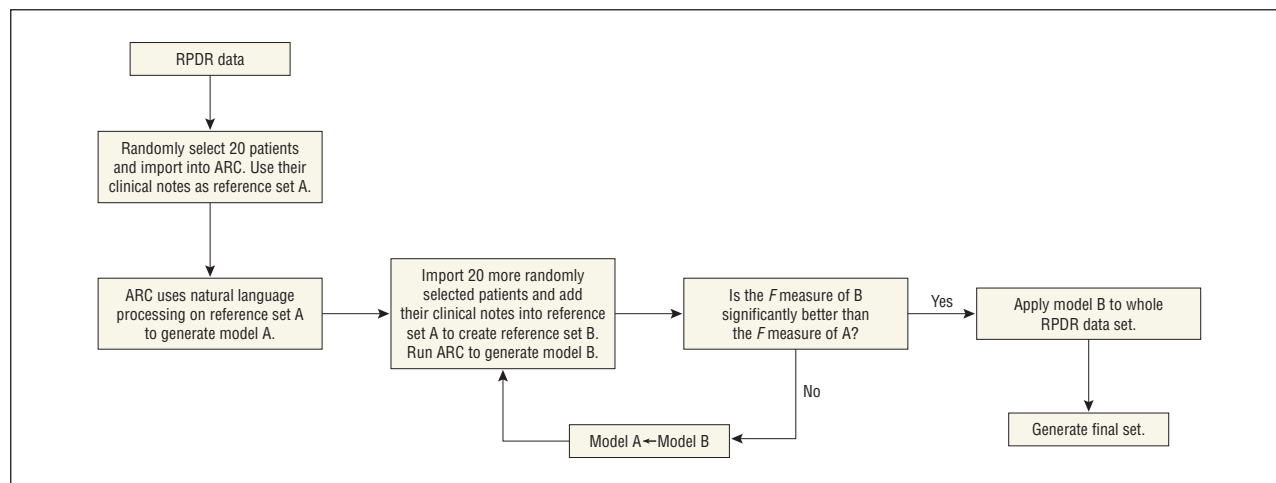


Figure. Automated Retrieval Console (ARC) training algorithm. RPDR indicates Research Patient Data Repository.

hensively evaluate the comorbid conditions among all individuals with AA seen at tertiary care hospitals in Boston, Massachusetts, during an 11-year period.

METHODS

STUDY POPULATION

After Institutional Human Research Committee approval, we identified 3568 individuals with AA seen between January 1, 2000, and January 1, 2011, performing comprehensive searches of the Research Patient Data Repository (RPDR) for *International Classification of Diseases, Ninth Revision (ICD-9)* code 704.01. The RPDR is an institutional review board–approved centralized clinical data registry that combines information from more than 1.8 million patients, mainly from Brigham and Women's Hospital and Massachusetts General Hospital. The collected information included demographics, diagnoses, medications, pathology reports, and the complete longitudinal medical record notes.

For comparison, we evaluated the same comorbid conditions in the Psoriasis and Psoriatic Arthritis Follow-up Study (PAFS) cohort, comprising patients in the RPDR who were evaluated at Brigham and Women's Hospital or Massachusetts General Hospital in Boston between January 1, 2005, and October 31, 2012, and who consented to be followed up prospectively. Diagnosis of psoriasis or psoriatic arthritis was obtained initially by ICD-9 code 696.1 or 696.0.

ASCERTAINMENT OF RESULTS

After using ICD-9 codes to select 3568 patients with a diagnosis of AA from a centralized clinical data registry, we used an artificial intelligence program, the Automated Retrieval Console (ARC), which performed natural language processing and machine learning technology to review free-text medical records and select for the diagnosis of AA (**Figure**). We randomly selected 350 patients, manually reviewed all their medical records, and used all the records to train ARC to generate a validation model using the following criteria: mention of AA in the history of present illness or medical history; presence of clinically diagnostic features of AA in the medical record, such as rapid patchy hair loss; and detailing of treatment for AA in the assessment and plan. We then randomly selected another 40 patients to validate this model and found 93.9% validity. After applying this model in the 3568-patient set, ARC identi-

Table 1. Demographic Characteristics of 2115 Patients

Characteristic	Value
Sex, No. (%)	
Female	1304 (61.7)
Male	811 (38.3)
Race, No. (%)	
White	1052 (49.7)
Hispanic	485 (22.9)
Black	249 (11.8)
Asian	122 (5.8)
Native American	2 (0.1)
Multiracial	1 (0.05)
Other	204 (9.6)
Age, mean, y	42

fied 2115 patients with AA. Comorbid conditions, such as obesity (body mass index [calculated as weight in kilograms divided by height in meters squared], ≥ 30), hypertension, hyperlipidemia, thyroid disease, eczema, allergies, psoriasis, systemic lupus erythematosus, and depression, were documented in patients' electronic records by a health care professional at Brigham and Women's Hospital or Massachusetts General Hospital. Laboratory results were also available in the electronic medical record system, and we extracted data results for thyroid peroxidase antibody, antinuclear antibody, free thyroxine, thyrotropin, and rheumatoid factor.

For the PAFS group, diagnoses were initially identified by screening for ICD-9 code and then confirmed by the study coordinator through manual review of the medical records. The cohort included 416 patients, with complete data in 402. Comorbid conditions for these patients were documented in the patients' electronic records by health care professionals at their respective hospitals.

Descriptive statistics were performed with Stata software, version 11 (StataCorp).

RESULTS

In our study population of 2115 patients with AA, 61.7% were women (**Table 1**). Approximately half were white (49.7%), with Hispanics the next largest group (22.9%). The mean age in the AA population was 42 years.

Table 2. Summary of Comorbid Conditions

Comorbid Condition	Prevalence, No. (%) ^a	
	AA Group (n = 2115)	PAFS Group (n = 402)
Atopy (allergic rhinitis, asthma, and/or eczema)	808 (38.2)	112 (27.9)
Contact dermatitis and other eczema	759 (35.9)	155 (38.6)
Mental health problems (depression or anxiety)	539 (25.5)	131 (32.6)
Hyperlipidemia	518 (24.5)	131 (32.6)
Hypertension	463 (21.9)	178 (44.3)
Anemia	415 (19.6)	98 (24.4)
Gastroesophageal reflux disease	365 (17.3)	28 (7.0)
Thyroid disease	309 (14.6)	62 (15.4)
Diabetes mellitus	234 (11.1)	52 (13.0)
Inflammatory bowel disease	133 (6.3)	11 (2.7)
Systemic lupus erythematosus	92 (4.3)	21 (5.2)
Rheumatoid arthritis	83 (3.9)	130 (32.3)
Vitiligo	59 (2.8)	7 (1.7)
Psoriasis and psoriatic arthritis	42 (2.0)	...

Abbreviations: AA, alopecia areata; PAFS, Psoriasis and Psoriatic Arthritis Follow-up Study.

^aPearson χ^2 test revealed significant differences in the associated comorbid conditions between the AA and PAFS groups ($\chi^2 = 448.8$; $P < .001$).

The most common comorbid conditions in these patients are shown in **Table 2**. The prevalence of atopy (including allergic rhinitis, asthma, and/or eczema) was high at 38.2%, as was the prevalence of contact dermatitis and other eczema at 35.9%. The prevalences of hyperlipidemia, hypertension, and gastroesophageal reflux disease were 24.5%, 21.9%, and 17.3%, respectively. Twenty-five percent of the population had a documented history of mental health problems, including depression or anxiety. Anemia was also common, affecting 19.6%. Previously reported associations with autoimmune diseases were also seen, including thyroid disease (14.6%), diabetes mellitus (11.1%), inflammatory bowel disease (6.3%), systemic lupus erythematosus (4.3%), rheumatoid arthritis (3.9%), vitiligo (2.8%), and psoriasis and psoriatic arthritis (2.0%).

Of the 107 patients who underwent antinuclear antibody testing, 100 (93.5%) had a positive result (**Table 3**), and 142 (10.9%) of 1302 patients tested had abnormal thyrotropin levels.

For comparison, the same comorbid conditions were evaluated in the PAFS cohort (Table 2). Of the 402 patients in that cohort, 204 (50.7%) were male and 198 (49.3%) were female, with a mean age of 56 years (range, 21-90 years); 305 patients (75.9%) were white, 25 (6.2%) Hispanic, 18 (4.5%) black, 7 (1.7%) Asian, and 1 (0.2%) Native American, with no ethnicity recorded in 44 patients (10.9%). Several comorbid conditions had similar prevalences in the 2 cohorts, with some notable differences in the PAFS cohort, including atopy (allergic rhinitis, asthma, and/or eczema) (27.9%), rheumatoid arthritis (32.3%), and hypertension (44.3%). Analysis with Pearson χ^2 test revealed significant differences in the associated comorbid conditions between patients with AA and the PAFS cohort ($\chi^2 = 448.8$; $P < .001$).

Table 3. Investigation of Laboratory Values of Patient Population

Marker	Patients, No. (%)
Thyroid peroxidase antibody (n = 206)	
Positive	72 (35.0)
Negative	134 (65.0)
Antinuclear antibody (n = 107)	
Positive	100 (93.5)
Negative	7 (6.5)
Free thyroxine (n = 331)	
Elevated	21 (6.3)
Normal	302 (91.2)
Decreased	8 (2.4)
Thyrotropin (n = 1302)	
Elevated	130 (10.0)
Normal	1160 (89.1)
Decreased	12 (0.9)
Rheumatoid factor (n = 224)	
Positive	25 (11.2)
Negative	199 (88.8)

DISCUSSION

Our descriptive study aimed to characterize the comorbid conditions associated with AA in the Boston patient population seen at the Partners institutions during an 11-year period. The ARC program, which harnessed properties of artificial intelligence and systematic natural language processing, allowed us to select a group of 2115 patients with AA. These patients were initially screened on the basis of their ICD-9 codes, and their diagnosis was confirmed by using our innovative program, which created a model based on manual review of records.

In our study, significant comorbid conditions were identified in a large percentage of patients with established diagnoses of AA in the population screened at the Partners hospitals. Many of these associations confirmed findings of multiple previous studies, but levels of association between AA and some comorbid conditions were slightly different than previously reported. Many of the prior studies were performed in smaller patient populations or homogeneous cohorts. The National Alopecia Areata Registry is a centralized database of patients with AA, from which valuable insights into disease associations have emerged.^{3,24,25,32} Our database differs in that we used medical records to collate patient data from a comprehensive sweep of patients seen in the major hospitals of Boston, an approach that can avoid confounding data from self-reported history.

For comparison, we also obtained the prevalences in the PAFS group for the comorbid conditions found in the AA group. Both groups were treated at the same medical institutions. One benefit of using the PAFS group for comparison is that the comorbidity profile for psoriasis and psoriatic arthritis has been defined. Psoriasis is also an autoimmune T-cell-mediated disease that has been found to be associated with other medical comorbid conditions, including obesity, metabolic syndrome, cardiovascular disease, autoimmune disease, psychiatric ill-

ness, malignant neoplasms, and chronic obstructive pulmonary disease.²⁶⁻²⁹

There were some notable differences between the 2 groups, including significantly increased prevalences of atopy, vitiligo, and gastroesophageal reflux disease in the AA group. The PAFS group had higher prevalences of hyperlipidemia, hypertension, anemia, and rheumatoid arthritis. Both groups had substantial prevalences of mental health problems, thyroid disease, and diabetes. Because psoriasis and AA are distinct conditions, we expected differences in the comorbidity profiles between these 2 groups.

We found a high prevalence of autoimmune diseases in our AA cohort compared with previous studies. For example, we found that 4.3% of our patients with AA also had a diagnosis of systemic lupus erythematosus compared with 0.6% in a previous report by Goh et al.³⁰ Thyroid autoimmunity has been described elsewhere as the main association for AA, ranging in prevalence between 8% and 28%.^{1,33} We found a prevalence of 14.6% for thyroid disease among our patients. Although we could not delineate the breakdown of hypothyroidism and hyperthyroidism and other nonautoimmune causes of thyroid disease, we were able to extract laboratory data in many of these patients. Among patients whose thyrotropin levels were measured, 10% had elevated levels, suggesting hypothyroidism, and 1% had decreased levels, suggesting hyperthyroidism (Table 3).

It has also been suggested that the presence of thyroid autoantibodies has no clinical correlation with AA severity.⁴ Of the 206 patients with laboratory data for thyroid peroxidase antibodies, 35.0% had positive results. This rate is higher than expected, but these tests were performed only in a subset of patients when clinically indicated, which might cause selection bias. Further prospective studies with a control population are needed to evaluate the true prevalence of positive autoimmune thyroid markers. Moreover, 93.5% of patients tested had positive antinuclear antibody results, although this data point may also reflect selection bias. Further studies using a control group would be necessary to evaluate whether this finding is significant.

Our results are consistent with previous findings of an increased prevalence of other immune-mediated diseases in patients with AA. We showed very high associations with atopy (including allergic rhinitis, asthma, and/or eczema) at 38.2% and contact dermatitis (and other eczema) at 35.9%. Comorbid association with atopic disease has been reported previously in a severe form of AA,^{30,34} and findings of molecular studies suggested that this effect is driven by the presence of filaggrin mutations affecting the integrity of the epidermal barrier.³⁵ Barahmani et al³ submitted compelling evidence from the National Alopecia Areata Registry to suggest that atopy or autoimmune disease is associated with increased risk for AA. Our study therefore corroborates these prior findings.

We found high psychiatric comorbidity among our patients with AA at 25.5%; this category included depression and anxiety, consistent with findings of previous studies that surveyed the most common psychiatric disorders in adult patients with AA.³⁶ The prevalence of mental health problems among adult dermatology patients has

previously been characterized; Bashir et al³⁷ reported a 34.11% prevalence of depression among 114 men with dermatologic disorders in Pakistan. Ghanizadeh³⁸ reported a depression rate of 78% among children with AA. In fact, the evidence for the role of stress in precipitating or augmenting this disorder has triggered debates about whether AA should be considered a psychosomatic disorder.³⁹ Ruiz-Doblado et al⁴⁰ found a 66% prevalence of psychiatric comorbidity among 32 patients with AA—mostly adjustment disorders, generalized anxiety disorders, and depressive episodes. Although these authors demonstrated that overall adaptation to AA was satisfactory, showing few repercussions in family or social life, work, or sexual adjustment, they recommended that treating depression or anxiety would improve patients' adaptation to the disease and, importantly, their dermatologic prognoses. This highlights the importance of addressing mental health problems in patients with AA because they may be interrelated and their treatment can enhance patient care.

We also found associations with conditions such as hyperlipidemia, hypertension, and gastroesophageal reflux disease, which may be attributable to both the nature of our screen and our much larger than average sample size and heterogeneous patient population. One could speculate that these associations are related to steroid use in the treatment of AA, but without a control group, the significance of the associations is unknown.

Our study benefits from a large heterogeneous population seen over a long period and the multiple tiers of scrutiny used in patient selection, which included both the artificial intelligence program and manual record review. The major limitation of the study is that it was retrospective. However, the true prevalence of associations in AA may be underestimated with the use of case records alone. Physicians caring for patients with AA should be aware of the associated comorbid conditions, especially autoimmune-related disease, atopic diathesis, and mental health problems, so that we can screen for them when clinically indicated. Future studies should include a control group to evaluate the significance of these associations. Further studies can also help elucidate the sequence of development for these comorbid conditions, and it would be clinically relevant to see whether any of them might precipitate alopecia.

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